Tetrahedron 65 (2009) 7422–7428

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Versatile synthesis of epicatechin series procyanidin oligomers, and their antioxidant and DNA polymerase inhibitory activity☆

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ARTICLE INFO

Article history:
Received 2 June 2009
Received in revised form 4 July 2009
Accepted 6 July 2009
Available online 9 July 2009

Keywords:
Proanthocyanidin
Condensed tannin
Epicatechin
Catechin
Antioxidant
Radical scavenging activity
DNA polymerase inhibitory activity

ABSTRACT

Proanthocyanidins, known as condensed tannins or oligomeric flavonoids, exist in many edible plants and show various interesting biological activities. We have developed a simple and versatile method of synthesizing procyanidin oligomers consisting of (−)-epicatechin and (+)-catechin. This method is applicable to the synthesis of various 3-*O*-substituted oligomers. We report here the stereoselective and length controlled synthesis of [4–8]-condensed (−)-epicatechin series procyanidin oligomers. We described the details of the synthesis of an two tetramers, (−)-epicatechin-(−)-epicatechin-(−)-epicatechin-(−)-epicatechin and (−)-epicatechin-(−)-epicatechin-(−)-epicatechin-(+)-catechin (arecatannin A1), (−)-epicatechin pentamer and two 3,3″,3‴-tri-*O*-galloyl trimers, (−)-epicatechin-(−)-epicatechin-(−)-epicatechin-3,3″,3‴-tri-*O*-gallate and (−)-epicatechin-(−)-epicatechin-(+)-catechin-3,3″,3‴-tri-*O*-gallate with the condensation method using TMSOTf as a catalyst. The ability of DPPH radical scavenging activity and DNA polymerase inhibitory activity of these oligomeric compounds were investigated.

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1. Introduction

Oxygen is biologically important for energy production, but active oxygen and free radicals in the body can injure cells and genes. They are also thought to be a cause of cancer, a lifestyle-related disease, and to contribute to aging. Therefore, there is currently great interest in the research and investigation into compounds that have strong anti-oxidation activity and superior ability to scavenge radicals. Thus, food and ingredients that can eliminate active oxygen and free radicals have recently received increased attention.

Proanthocyanidins (condensed tannins or oligomeric flavonoids)[1,2] are known to be extremely strong antioxidants: investigating them has become increasingly important because of various strong biological activities. In many cases, however, proanthocyanidins are obtained as a mixture of various analogues, making purification of each compound difficult. An elegant contribution by Kozikowski et al.,[3] reported the synthesis of oligomeric catechin and epicatechin derivatives.[4] We also developed and reported a simple, versatile, and stereoselective method of synthesizing procyanidin oligomers consisted with (−)-epicatechin (**1**) and (+)-catechin (**2**) (Fig. 1).[5–15] Our synthetic methodology is applicable to various procyanidin oligomers, such as the 3-*O*-substituted oligomer.[13–15] In particular, numerous galloyl-substituted flavan-3-ols and proanthocyanidins have been also isolated from plants, and demonstrated strong bioactivity.[1,2] For example, epigallocatechin-3-*O*-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

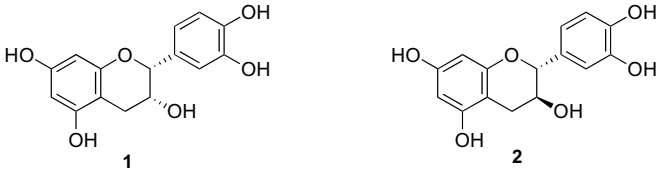

Figure 1. The structure of (−)-epicatechin (**1**)and (+)-catechin (**2**).

☆ This report is Part 12 in the series 'Synthetic studies of proanthocyanidins'. See Ref. 5–15.

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doi:10.1016/j.tet.2009.07.018

effect against a variety of cancers, such as that of the lung, prostate, and breast.[16] Furthermore, the receptor that mediates the anticancer activity of EGCG was identified,[17] but the effect of the galloyl group in proanthocyanidins is poorly understood.

Our study aimed at synthesizing various pure proanthocyanidins and measuring activity systematically. We previously reported the stereoselective synthesis of procyanidin dimers (B1,[9] B2,[9] B3,[5,6] B4,[9] *cis*-diastereomer of B3[7] and their galloyl derivatives[13–15]) with intermolecular condensation[5,6,8,13–15] and intramolecular[7,8,11] condensation using TMSOTf as the catalyst. Using this same condensation method, we synthesized procyanidin trimers stereoselectively in good yields.[10,12] We also reported their antioxidant activities, the Maillard reaction inhibitory activity and DNA polymerase inhibitory activities. Here, we describe the stereo, regio, and oligomerization degree controlled synthesis of two epicatechin series tetramers, epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin (**3**) and epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-catechin (arecatannin A1) (**4**), a epicatechin pentamer, epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin (**5**) and two galloyl-substituted epicatechin series trimers, epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin, 3,3″,3‴-*O*-trigallate (**6**) and epicatechin-(4β-8)-epicatechin-(4β-8)-catechin 3,3″,3‴-*O*-trigallate (**7**) (Fig. 2). Their antioxidant and DNA polymerase inhibitory activities were also described.

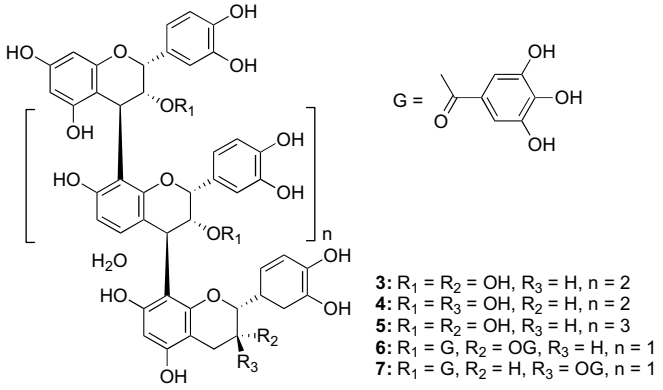


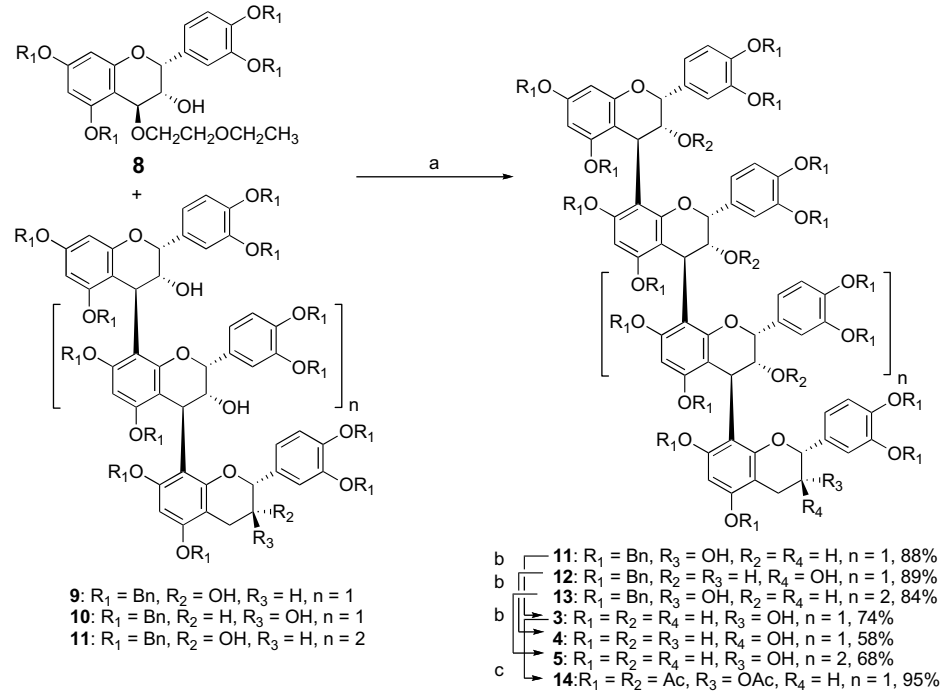
Figure 2. The structure of epicatechin series procyanidin oligomers.

2. Result and discussion

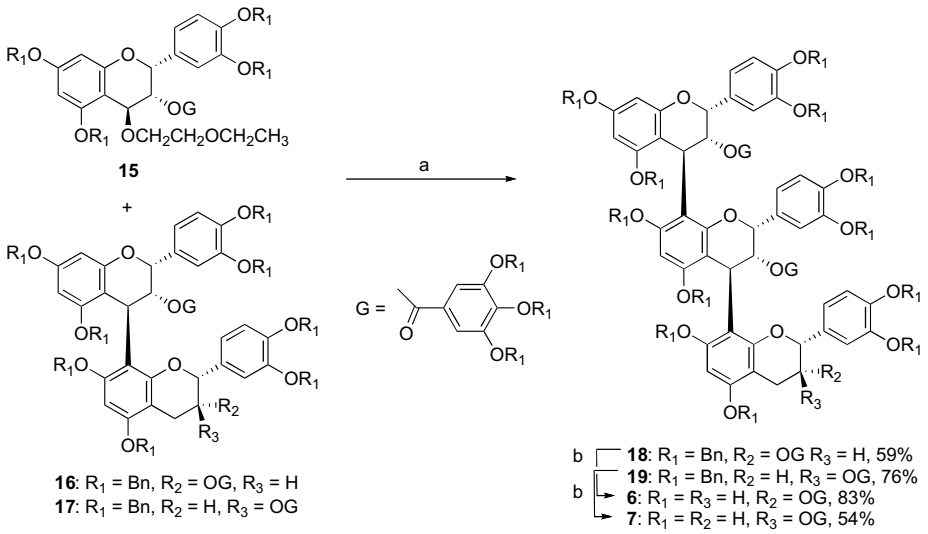
2.1. Synthesis

There have been numerous studies concerning isolation, semisynthesis, and bioactivity.[18] Many condensation methods for procyanidin oligomers using Lewis acids were studied after Kawamoto's report,[19] however, systematic study of proanthocyanidins is still difficult even now. As previously mentioned separating purely individual structural analogues from the plant is very difficult because these compounds are presented as mixtures of a number of structurally related compounds. Furthermore, the structural determination of these compounds is not easy. Therefore, a technology for synthesizing these compounds purely and systematically is very useful and important. We already developed and reported on a synthesis methodology applicable to various (4–8) linked procyanidin dimers, trimers, and their gallate derivatives. We report here further study of the synthesis of epicatechin series tetramers (**3**, **4**), pentamers (**5**), and gallate trimers (**6**, **7**).

The key step is the coupling reaction between the oligomer nucleophile and monomer electrophile using Lewis acid as an activator. We created 2-ethoxyethoxy derivatives on the C-4 position as building blocks for procyanidin synthesis. Treatment of 5,7,3′,4′-tetrabenzylepicatechin with DDQ in the presence of 2-ethoxyethanol provided the 2-ethoxyethoxy derivative **8**.[5] As shown in Scheme 1, condensation of monomer electrophile **8** with trimer nucleophiles **9**[14] and **10**[14] in the presence of TMSOTf in CH_2Cl_2 at −40 °C gave corresponding tetramers **11** and **12** in 88% and 89% yields, respectively. Pentamer **13** was also obtained from the condensation of **8** and tetramer **11** in 84% using same procedure. In the condensation reaction, nucleophiles **9**–**11** were used in fourfold excess to avoid higher oligomer formation. The **8** reacted with **9**–**11**



Scheme 1. Synthesis of epicatechin tetramers and pentamer. Reagents: (a) TMSOTf, CH_2Cl_2, −40 °C; (b) $Pd(OH)_2/C$, H_2, THF/MeOH/H_2O; (c) Ac_2O, DMAP, py.



Scheme 2. Synthesis of galloyl epicatechin trimers. Reagents: (a) TMSOTf, CH_2Cl_2, −40 °C; (b) $Pd(OH)_2/C$, H_2, THF/MeOH/H_2O.

at C-4 position stereoselectively to give 3,4-trans oligomers preferentially. These protected oligomers were hydrogenated in the presence of $Pd(OH)_2/C$ and purified with LH-20 short column and HPLC to give free tetramers **3**, **4**, and pentamer **5** in 74%, 58%, and 68% yields, respectively. The all spectral data of synthesized **3**, **5**, and peracetate of **3** (**14**) agreed with the those of the reported data.[3a]

The synthesis of two 3,3″,3‴″-*O*-trigallates substituted trimers is shown in Scheme 2. Electrophile **15**[14] was condensed with nucleophiles **16** and **17**[14] in the presence of TMSOTf at −20 °C to afford trimers **18** and **19** with yields of 59% and 76%, respectively. And the deprotection of all benzyl groups under hydrogenation conditions and purification yielded tetramers **6** and **7** in yields of 83% and 54%, respectively.[20]

2.2. Biological activity of synthetic procyanidin oligomers

2.2.1. DPPH radical scavenging activity[21]

Proanthocyanidins are known as strong antioxidants and radical scavengers.[22] In previous papers,[12–14] we investigated the DPPH radical scavenging activity of synthesized procyanidin oligomers, and 3-*O*-gallate dimers.

The SC_{50} values (the concentration of 50% scavenging activity) of monomeric (−)-epicatechin (**1**), (+)-catechin (**2**), and synthesized trimers to pentamer (**3**–**7**) were 2.2, 2.6, 0.4, 0.4, 0.4, 0.4, and 0.6 μM, respectively. It appears that these oligomers have significant radical scavenging activity, compared to monomeric compounds and DL-α-Tocopherol. It was shown that elongation of oligomer length and modification of 3-*O*-positions with galloyl groups are effective for DPPH radical scavenging activity, compared to trimers epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin (**20**)[10] and epicatechin-(4β-8)-epicatechin-(4β-8)-catechin (**21**)[10] (Table 1, Fig. 3).

Table 1
DPPH radical scavenging activity

Entry	Compound	SC_{50} values (μM)
1	**1**	2.2
2	**2**	2.6
3	**3**	0.4
4	**4**	0.4
5	**5**	0.4
6	**6**	0.4
7	**7**	0.6
8	**20**	0.7
9	**21**	0.7
10	DL-α-Tocopherol	17

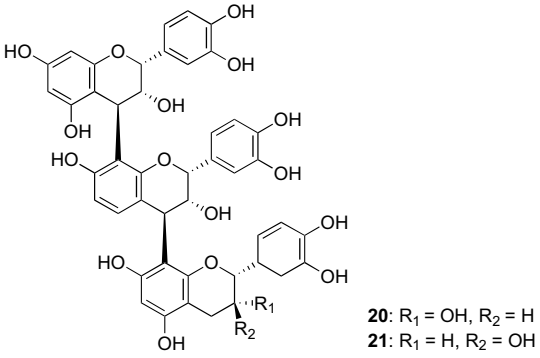


Figure 3. Structure of procyanidin trimers.

2.3. Mammalian DNA polymerase inhibitory activities

Monomeric flavan-3-*O*-gallates, (−)-epicatechin-3-*O*-gallate, (−)-epigallocatechin-3-*O*-gallate, etc., are known as inhibitors of DNA and RNA polymerases,[23] and it was apparent that the galloyl group appears essential for the inhibitory effect. As we described in a previous paper, 3-*O*-galloyl-substituted flavan-3-ols actively inhibit against DNA polymerase α.[13–15,24] DNA polymerase α, which is a DNA replicative polymerase, is regarded as the target of some anticancer drugs, because DNA polymerase plays a central roles in the DNA replication indispensable for the prolification of cancer cells. Thus, we expect galloyl-substituted procyanidin oligomers to be effective inhibitors of DNA polymerase. As our previous report demonstrated that procyanidin dimers have moderate DNA polymerase inhibitory activity, whereas monomeric (−)-epicatechin and (+)-catechin have none.[13]

We also interested in the relationships between activity and oligomer length. Table 2 shows the IC_{50} values of synthesized procyanidin oligomers against calf DNA polymerase α and rat DNA polymerase β. All oligomeric procyanidins inhibit DNA polymerase α, and the activity tends to be stronger with the oligomer length.(−)-Epicatechin pentamer **5**, in particular, potently inhibited

Table 2
IC_{50} values of compounds on the activities of mammalian DNA polymerases α and β[25]

Entry	Compound	IC_{50} values (μM)	
		Calf DNA polymerase α	Rat DNA polymerase β
1	**1**	>100	>100
2	**2**	>100	>100
3	**3**	0.178±0.009	31.2± 1.6
4	**5**	0.075±0.004	26.0±1.3
5	**6**	0.230±0.011	38.5±1.9
6	**7**	0.243±0.012	40.7±2.1
7	**20**	0.575±0.028	57.9±3.0

Calf DNA polymerase α, and the substitution of 3-*O*-position with galloyl groups was highly efficacious in inhibition of DNA polymerase α.

3. Conclusion

We have developed a simple and versatile method of synthesizing procyanidin oligomers. We showed here the synthesis of (−)-epicatechin series tetramers, pentamer, and 3-*O*-galloyl trimers. DPPH radical scavenging activity, and DNA polymerase inhibitory activity of synthesized oligomers were also investigated. All of the oligomers showed strong DPPH radical scavenging activity. Furthermore, synthesized oligomers had potent inhibitory activity against DNA polymerase α. The elongation of oligomers and the substitution of 3-*O*-position with the galloyl group were shown to be highly effective for DNA polymerase inhibition.

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. [4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-3‴,4‴-trans-2⁗,3⁗-cis-Hexadeca-O-benzyl-tetra-(−)-epicatechin (**11**)*

To a solution of **9** (779 mg, 0.40 mmol) and **8** (73.9 mg, 0.10 mmol) in CH_2Cl_2 (80 mL) was added dropwise TMSOTf (0.20 mL, 0.10 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 a 228 mg of **11** (0.088 mmol, 88%) of as a colorless oil: $[\alpha]_D^{24}$ +104.8 (*c* 0.94, $CHCl_3$), $[\alpha]_D^{24}$ +80.5 (*c* 1.00, EtOAc), {lit.[3a] $[\alpha]_D$ +85.9 (*c* 12.0 g L^{-1}, EtOAc)}; ^{1}H NMR (400 MHz, $CDCl_3$, 0.5:0.5 mixture of rotational isomers) 7.50–6.39 (89H, m), 6.39 (0.5H, s), 6.37 (0.5H, d, *J*=8.3 Hz), 6.33 (0.5H, d, *J*=8.3 Hz), 6.27 (0.5H, d, *J*=2.2 Hz), 6.23 (0.5H, s), 6.14 (0.5H, dd, *J*=1.7, 8.3 Hz), 6.07 (0.5H, d, *J*=2.2 Hz), 6.05 (0.5H, d, *J*=8.3 Hz), 6.03 (0.5H, dd, *J*=1.7, 8.3 Hz), 5.91 (0.5H, s), 5.90 (0.5H, s), 5.88 (0.5H, s), 5.86 (0.5H, d, *J*=2.2 Hz), 5.75 (0.5H, s), 5.75 (0.5H, br s), 5.63 (0.5H, d, *J*=2.2 Hz), 5.23 (0.5H, br s), 5.43 (0.5H, dd, *J*=1.7, 8.3 Hz), 5.39 (0.5H, br s), 5.37 (0.5H, br s), 5.23–3.92 (37H, m), 4.30–4.22 (0.5H, m), 4.25–4.20 (0.5H, m), 4.11–4.05 (1H, m), 4.01–3.93 (1.5H, m), 3.68–3.64 (0.5H, m), 2.93–2.83 (2H, m), 1.80 (0.5H, d, *J*=5.8 Hz, OH), 1.60 (0.5H, d, *J*=6.4 Hz, OH), 1.53–1.52 (0.5H, m, OH), 1.43 (0.5H, d, *J*=7.3 Hz, OH), 1.37 (0.5H, d, *J*=7.5 Hz, OH), 1.35 (0.5H, d, *J*=7.0 Hz, OH), 1.15 (0.5H, d, *J*=7.3 Hz, OH), 1.06 (0.5H, d, *J*=8.0 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) 158.3, 158.05, 158.03, 157.3, 156.7, 156.6, 156.4, 156.3, 156.2, 156.14 (×3), 156.06, 156.00, 155.70, 155.67, 155.4, 155.2, 154.8, 153.2, 153.1, 152.80 (×2), 152.76, 149.3, 149.1, 149.0, 148.91, 148.87, 148.86, 148.83, 148.77, 148.6, 148.4 (×2), 148.3, 148.14, 148.08, 147.8, 147.7, 138.8, 138.1, 137.6–136.9 (C×32), 133.0, 132.57, 132.54, 132.52 (×2), 132.3, 131.3 (×2), 128.6–125.9 (C×94), 119.9, 119.7, 119.2, 119.0 (×2), 118.72, 118.67, 118.5, 115.1 (×2), 115.00, 114.95, 114.82, 114.77, 114.1, 113.6 (×3), 113.4, 113.21, 113.15 (×2), 112.8, 111.2, 110.99, 110.96, 110.6, 110.2, 110.0, 106.3, 105.6, 105.1, 104.8, 104.5, 104.2, 101.2, 101.0, 94.4, 93.9 (×2), 93.4, 92.5, 92.4, 92.3, 92.2, 91.3, 90.4, 78.1, 78.0, 76.2, 75.85 (×2), 75.74, 75.66 (×2), 72.8, 72.6, 72.5, 71.7, 71.4–69.1 (C×34), 64.9, 60.4, 36.9, 36.3, 35.6, 35.5, 35.1 (×2), 28.5 (×2); IR (neat, cm^{-1}) 3569 (m), 3400 (br), 3065 (m), 3030 (m), 2930 (m), 2361 (m), 2342 (m), 1952 (w), 1850 (w), 1813 (w), 1599 (s), 1512 (s), 1454 (s), 1423 (m), 1383 (m), 1265 (m), 1217 (m), 1121 (s), 1076 (m), 1026 (m), 910 (w), 852 (w), 752 (m); FABMS (*m*/*z*) 2620 (60), 2619 (95), 2618 ($[M+Na]^+$, 21), 2598 (27), 2597 (51), 2596 ($[M+H]^+$, 19), 2438 (60), 2355 (72), 2156 (88), 2068 (100), 1770 (63), 1640 (62), 1322 (62), 1112 (79); FAB-HRMS calcd for $C_{172}H_{147}O_{24}$ $[M+H]^+$, 2596.0282; found: 2596.0212.

*4.1.2. [4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-3‴,4‴-trans-2⁗,3⁗-trans-Hexadeca-O-benzyl-(−)-epicatechin-(−)-epicatechin-(−)-epicatechin-(+)-catechin (**12**)*

To a solution of **10** (277 mg, 0.14 mmol) and **8** (26.2 mg, 0.036 mmol) in CH_2Cl_2 (50 mL) was added dropwise TMSOTf (0.072 mL, 0.036 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 a 83 mg of **12** (0.032 mmol, 89%) of as a colorless oil: $[\alpha]_D^{24}$ +102.4 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 0.5:0.5 mixture of rotational isomers) 7.53–5.89 (89.5H, m), 6.39 (0.5H, s), 6.33 (0.5H, d, *J*=8.3 Hz), 6.26 (0.5H, d, *J*=2.2 Hz), 6.22 (0.5H, s), 6.17 (0.5H, dd, *J*=1.7, 8.3 Hz), 6.07 (0.5H, d, *J*=2.2 Hz), 6.04 (0.5H, d, *J*=8.3 Hz), 6.01 (0.5H, dd, *J*=1.7, 8.3 Hz), 5.92 (0.5H, s), 5.91 (0.5H, s), 5.89 (0.5H, s), 5.85 (0.5H, d, *J*=2.2 Hz), 5.74 (0.5H, s), 5.74 (0.5H, br s), 5.63 (0.5H, d, *J*=2.2 Hz), 5.52 (0.5H, br s), 5.41–5.36 (0.5H, m), 5.39 (0.5H, br s), 5.37 (0.5H, br s), 5.22 (0.5H, br s), 5.20–4.32 (34.5H, m), 5.17 (0.5H, d, *J*=1.9 Hz), 5.14–5.13 (0.5H, m), 4.22 (0.5H, d, *J*=14.1 Hz), 4.14 (0.5H, d, *J*=12.2 Hz), 4.09–4.07 (0.5H, m), 4.00–3.97 (1H, m), 3.97–3.93 (0.5H, m), 3.91–3.88 (0.5H, m), 3.65 (0.5H, br s), 3.47–3.38 (0.5H, m), 3.30–3.25 (0.5H, m), 2.99 (0.5H, dd, *J*=5.6, 16.3 Hz), 2.92 (0.5H, dd, *J*=5.4, 16.1 Hz), 2.60 (0.5H, dd, *J*=9.3, 16.1 Hz), 2.54 (0.5H, dd, *J*=9.3, 16.3 Hz), 1.79 (0.5H, d, *J*=5.6 Hz, OH), 1.58 (0.5H, d, *J*=6.3 Hz, OH), 1.55–1.50 (1H, m, OH), 1.48 (0.5H, d, *J*=3.1 Hz, OH), 1.41 (0.5H, d, *J*=7.1 Hz, OH), 1.22 (0.5H, d, *J*=6.1 Hz, OH), 1.18 (0.5H, d, *J*=7.1 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) 158.3, 158.0 (×2), 157.3, 156.7, 156.6, 156.3, 156.2 (×2), 156.0 (×3), 155.68, 155.65, 155.45, 155.40, 155.35, 155.2, 154.7, 153.22, 153.18, 152.85 (×2), 152.81, 149.2 (×2), 149.00, 148.95 (×2), 148.91, 148.83 (×2), 148.77, 148.76, 148.5, 148.2, 148.03, 147.96, 147.8, 147.6, 138.8, 138.1, 137.6–136.8 (C×32), 132.9, 132.57 (×2), 132.55 (×2), 132.3, 131.4, 131.3, 128.6–125.9 (C×94), 120.1 (×2), 119.9, 119.7, 119.2, 119.0 (×2), 118.5, 115.1–112.8 (C×16), 111.1, 110.8, 110.7, 110.4, 110.1, 109.9, 106.3, 105.6, 105.3, 104.8, 104.5, 104.4, 102.2, 101.9, 94.4, 93.9, 93.8, 93.4, 92.5, 92.1, 91.9, 91.8, 90.9, 90.4, 81.2 (×2), 76.1, 75.8, 75.6 (×2), 75.5 (×2), 72.74, 72.72, 72.55, 72.50, 71.9–69.0 (C×34), 68.10, 68.08, 36.8, 36.3, 35.7,

35.4, 35.1, 35.0, 27.4 (×2); IR (neat, cm^{-1}) 3569 (m), 3450 (br), 3088 (w), 3065 (m), 3080 (m), 2930 (m), 2872 (m), 1954 (w), 1869 (w), 1811 (w), 1601 (s), 1510 (s), 1423 (s), 1327 (m), 1265 (s), 1217 (s), 1122 (s), 1026 (s), 910 (w), 854 (w), 754 (s); FABMS (*m*/*z*) 2618 ($[M+Na]^+$, 46), 2598 (30), 2596 ($[M+H]^+$, 38), 2524 (45), 2440 (43), 2163 (72), 2134 (49), 1824 (100).

4.1.3. *[4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴, 3‴-cis-3‴,4‴-trans-2⁗,3⁗-cis-3⁗,4⁗-trans:2⁗ ⁗, 3⁗ ⁗-cis-Eicosa-O-benzyl-(−)-epicatechin-(−)-epicatechin-(−)-epicatechin-(−)-epicatechin-(−)-epicatechin* (**13**)

To a solution of **11** (260 mg, 0.10 mmol) and **8** (19.5 mg, 0.025 mmol) in CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.050 mL, 0.025 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, twice development) afforded a 67 mg of **13** (0.021 mmol, 84%) of as a colorless oil: $[\alpha]_D^{23}$ +107.2 (*c* 0.43, $CHCl_3$), $[\alpha]_D^{25}$ +102.1 (*c* 1.26, EtOAc) {lit.[3a] $[\alpha]_D$ +100 (*c* 13.0 g L^{-1}, EtOAc)}; ^1H NMR (400 MHz, $CDCl_3$, 0.5:0.5 mixture of rotational isomers) 7.53–5.39 (115.5H, m), 6.39 (0.5H, s), 6.23 (0.5H, s), 6.04 (0.5H, d, *J*=2.2 Hz), 5.95 (0.5H, s), 5.93 (0.5H, s), 5.88–5.87 (1H, s), 5.86 (0.5H, d, *J*=2.2 Hz), 5.75 (0.5H, br s), 5.71 (0.5H, s), 5.62 (0.5H, d, *J*=2.2 Hz), 5.50 (0.5H, br s), 5.47 (0.5H, d, *J*=2.2 Hz), 5.43 (0.5H, br s), 5.39 (0.5H, br s), 5.26 (0.5H, br s), 5.25–4.15 (47.5H, m), 4.27 (1H, br s), 4.10 (0.5H, br), 4.04 (0.5H, br), 4.01–3.93 (2.0H, m), 3.88 (0.5H, d, *J*=7.1 Hz), 3.66 (0.5H, br), 3.00–2.85 (2H, m), 1.80 (0.5H, d, *J*=6.1 Hz, OH), 1.60 (0.5H, d, *J*=5.9 Hz, OH), 1.42 (0.5H, br, OH), 1.42–1.40 (0.5H, m, OH), 1.38 (0.5H, d, *J*=7.3 Hz, OH), 1.32 (0.5H, d, *J*=7.4 Hz, OH), 1.31 (0.5H, d, *J*=7.0 Hz, OH), 1.26–1.21 (0.5H, m, OH), 1.14 (0.5H, d, *J*=7.8 Hz, OH), 1.10 (0.5H, d, *J*=7.6 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) 158.3, 158.05 (×2), 158.02, 157.3, 156.7, 156.6, 156.41, 156.37, 156.29 (×3), 156.17 (×2), 156.0 (×3), 156.9 (×2), 155.5, 155.4, 155.2, 154.8, 153.2 (×2), 153.1, 153.94, 152.95, 152.8, 152.7, 149.2–147.6 (C×20), 138.8, 138.1, 138.0, 137.9, 137.7–136.8 (C×40), 133.0, 132.62 (×2), 132.57 (×2), 132.50 (×2), 132.3, 131.2 (×2), 128.8–126.0 (C×136), 119.9, 119.8, 119.3, 118.99, 118.95, 118.8, 118.7, 118.6, 118.5 (×2), 115.1–112.8 (C×20), 111.19, 111.16, 111.0, 110.6 (×2), 110.2, 110.1, 110.0, 106.4, 105.7, 105.4, 105.0, 104.8, 104.6, 104.5 (×2), 101.2, 101.1, 94.3, 93.8 (×3), 93.4, 92.5, 92.2 (×2), 97.8 (×2), 91.4, 90.4, 78.0, 77.9, 76.1, 75.94, 75.86 (×2), 75.80 (×2), 75.66 (×2), 72.7, 72.6 (×2), 71.7 (×2), 71.4–69.1 (C×27), 64.9, 64.8, 37.0 (×2), 36.3, 35.7, 35.4, 35.3, 35.1, 34.0, 28.5 (×2); IR (neat, cm^{-1}) 3569 (m), 3065 (m), 3030 (m), 2932 (m), 2874 (m), 1954 (w), 1869 (w), 1811 (w), 1734 (w), 1597 (s), 1514 (s), 1423 (s), 1375 (s), 1266 (s), 1217 (s), 1120 (s), 1026 (s), 910 (w), 852 (w), 750 (m); FABMS (*m*/*z*) 3271 (25), 3270 (34), 3269 (39), 3268 (81), 3267 (40), 3266 ($[M+Na]^+$, 39), 3246 (70), 3246 (91), 3245 (87), 3244 ($[M+H]^+$, 20), 2821 (56), 2806 (41), 2805 (46), 2694 (46), 2518 (48), 2486 (58), 1043 (100).

4.1.4. *[4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-3‴,4‴-trans-2⁗,3⁗-cis-Tetra-(−)-epicatechin* (**3**)

A solution of **11** (83 mg, 0.032 mmol) in 22 mL of THF/MeOH/H_2O, 20:1:1 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 short column chromatography (MeOH) and HPLC purification to give 27.4 mg of pure **3** (0.025 mmol, 74%) as an amorphous solid: $[\alpha]_D^{25}$ +102.9 (*c* 0.11, MeOH) {lit.[3a] $[\alpha]_D$ +93.3 (*c* 9.3 g L^{-1}, MeOH)}; ^1H NMR (400 MHz, CD_3OD, −20 °C) 7.13 (1H, d, *J*=1.7 Hz), 7.10 (1H, d, *J*=1.7 Hz), 7.03 (1H, d, *J*=1.7 Hz), 6.91 (1H, dd, *J*=1.7, 8.3 Hz), 6.90 (1H, d, *J*=1.7 Hz), 6.79–6.68 (7H, m), 6.01 (1H, d, *J*=2.2 Hz), 5.98 (1H, d, *J*=2.2 Hz), 5.95 (1H, s), 5.94 (1H, s), 5.93 (1H, s), 5.31 (1H, d, *J*=2.2 Hz), 5.30–5.20 (1H, m), 5.09 (1H, br s), 5.10–4.95 (1H, m), 4.75 (1H, br s), 4.73–4.71 (2H, br s), 4.35–4.31 (1H, m), 4.07 (1H, d, *J*=1.7 Hz), 3.99 (1H, d, *J*=2.6 Hz), 3.97 (1H, d, *J*=2.0 Hz), 2.95 (1H, dd, *J*=2.7, 16.4 Hz), 2.81 (1H, d, *J*=16.4 Hz); ^{13}C NMR (100 MHz, CD_3OD, −20 °C) 158.1, 157.9, 157.8, 157.0, 156.9, 156.7, 156.6, 156.3 (×2), 155.0, 154.8, 154.6, 146.0, 145.9, 145.7, 145.7, 145.6, 145.40, 145.38, 145.2, 132.64, 132.56, 132.51, 132.0, 119.1, 118.8, 118.6 (×2), 116.0, 115.8 (×2), 115.8, 115.1, 115.0 (×2), 114.8, 107.6, 107.3, 107.1, 102.4, 102.2, 101.8, 100.0, 97.3, 97.0, 96.8, 95.8, 95.7, 79.5, 76.9, 76.8, 76.7, 73.5, 73.1, 72.9, 66.7, 37.4, 37.3, 37.1, 30.0; FABMS (*m*/*z*) 1179 (11), 1178 (12), 1177 ($[M+Na]^+$, 30), 1176 (17), 1156 (14), 1155 ($[M+H]^+$, 24), 1154 (21), 1153 (24), 999 (20), 867 (27), 866 (29), 578 (100); FAB-HRMS calcd for $C_{60}H_{51}O_{24}$ $[M+H]^+$, 1155.2770; found: 1155.2822.

4.1.5. *[4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-3‴,4‴-trans-2⁗,3⁗-trans-(−)-Epicatechin-(−)-epicatechin-(−)-epicatechin-(+)-catechin (arecatannin A1)* (**4**)

A solution of **12** (66 mg, 0.025 mmol) in 22 mL of THF/MeOH/H_2O, 20:1:1 was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 12 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (MeOH) and HPLC purification to give 16.8 mg of pure **4** (0.015 mmol, 58%) as an amorphous solid. $[\alpha]_D^{25}$ +73.3 (*c* 0.10, MeOH), lit.[28] {$[\alpha]_{589}$ +100}; ^1H NMR (400 MHz, CD_3OD, −20 °C, a small mount of rotational isomer was observed) 7.10 (1H, d, *J*=1.7 Hz), 7.05 (1H, d, *J*=1.7 Hz), 7.13–6.68 (10H, m), 6.02–5.88 (5H, m), 5.33 (1H, br s), 5.26–5.19 (1H, m), 5.08 (1H, br s), 5.12 (1H, d, *J*=4.9 Hz), 4.78 (1H, br s), 4.75 (1H, br s), 4.72 (1H, br s), 4.19 (1H, ddd, *J*=4.6, 4.8, 4.9 Hz), 4.11 (1H, br s), 4.10 (1H, br s), 3.97 (1H, br s), 2.62 (1H, dd, *J*=4.6, 16.8 Hz), 2.55 (1H, dd, *J*=4.8, 16.8 Hz); ^{13}C NMR (100 MHz, CD_3OD, −20 °C) 157.9, 157.8, 157.11, 157.06, 156.8, 156.4 (×2), 155.8, 154.9, 154.83, 154.80, 153.7, 146.1, 145.84, 145.78, 145.74, 145.68, 145.4, 145.3, 145.2, 132.7, 132.62, 132.57, 132.4, 119.2, 119.1, 118.7, 118.6, 116.01 (×2), 115.98, 115.95, 115.8, 115.0 (×3), 114.9, 114.8, 113.9, 108.2, 107.2, 106.8, 102.7, 102.1, 101.8, 100.2, 97.04, 97.02, 81.6, 76.94, 76.85, 76.7, 73.5, 73.0, 72.1, 68.2, 37.4, 37.2, 37.1, 26.3; FABMS (*m*/*z*) 1178 (19), 1177 ($[M+Na]^+$, 31), 1176 (15), 1175 (11), 1156 (13), 1155 ($[M+H]^+$, 83), 1031 (43), 973 (39), 957 (38), 937 (43), 846 (43), 666 (100); FAB-HRMS calcd for $C_{60}H_{50}O_{24}$ $[M+Na]^+$, 1177.2590; found: 1177.2629.

4.1.6. *[4,8:4″,8″:4‴,8‴]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-3‴,4‴-trans:2⁗ ⁗,3⁗ ⁗-cis-Penta-(−)-epicatechin* (**5**)

A solution of **13** (30 mg, 0.0092 mmol) in 22 mL of THF/MeOH/H_2O, 20:1:1 was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 4 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (MeOH) and HPLC purification to give 9.0 mg of pure **5** (0.0062 mmol, 68%) as an amorphous solid. $[\alpha]_D^{24}$ +96.0 (*c* 0.17, MeOH) {lit.[3a] $[\alpha]_D$ +116 (*c* 8.3 g L^{-1}, MeOH)}; ^1H NMR (400 MHz, CD_3OD, −20 °C) 7.13 (1H, d, *J*=1.7 Hz), 7.11 (1H, d, *J*=1.7 Hz), 7.10 (1H, d, *J*=1.7 Hz), 7.04 (1H, d, *J*=1.7 Hz), 6.92 (1H, d, *J*=1.7 Hz), 6.91 (1H, dd, *J*=1.7, 8.3 Hz), 6.80 (1H, dd, *J*=1.7, 8.3 Hz), 6.80–6.69 (8H, m), 6.02 (1H, d, *J*=2.2 Hz), 5.98 (1H, d, *J*=2.2 Hz), 5.98 (1H, s), 5.95 (1H, s), 5.93 (2H, s), 5.31 (1H, br s), 5.30 (1H, br s), 5.27 (1H, br s), 5.09 (1H, br s), 5.00 (1H, br s), 4.78 (1H, br s), 4.77 (1H, br s), 4.73 (1H, br s), 4.71 (1H, br s), 4.35–4.30 (1H, m), 4.11 (1H, d, *J*=2.2 Hz), 4.10 (1H, d, *J*=2.0 Hz), 4.00 (1H, d, *J*=1.7 Hz), 3.98 (1H, d, *J*=2.2 Hz), 2.96 (1H, dd, *J*=3.4, 16.1 Hz), 2.81 (1H, d, *J*=16.1 Hz); ^{13}C NMR (100 MHz, CD_3OD, −20 °C) 158.2, 158.0, 157.9, 157.1, 157.0, 156.9, 156.7, 156.6, 156.4, 156.3, 156.2, 155.1, 155.0, 154.9, 154.7, 146.0, 145.9, 145.8, 145.74, 145.69, 145.66, 145.41, 145.40, 145.3, 145.2, 132.63 (×2), 132.58, 132.54, 132.0, 119.0, 118.9, 118.73, 118.65 (×2),

116.03, 115.97, 115.86 (×2), 115.78 (×2), 115.1, 115.0 (×2), 114.9, 107.6, 107.5, 107.4, 107.2, 102.5, 102.4, 102.3, 101.8, 100.0, 97.3 (×2), 97.2, 97.0, 96.2, 96.0, 79.5, 76.9, 76.80, 76.76, 76.6, 73.5, 73.1, 72.9 (×2), 66.7, 37.5 (×2), 37.3, 37.1, 30.0; FABMS (*m*/*z*) 1446 (25), 1465 ([M+Na]$^+$, 33), 1464 (21), 1444 (9.6), 1443 ([M+H]$^+$, 34), 1442 (20), 1177 (28), 1162 (31), 1100 (37), 1024 (29), 981 (33), 944 (31), 886 (32), 746 (50), 694 (69), 693 (100); FAB-HRMS calcd for $C_{75}H_{63}O_{30}$ [M+H]$^+$, 1443.3404; found: 1443.3331.

4.1.7. *Peracetate of **3** (**14**)*

Acetylation of **3** (5.9 mg, 5.0 μmol) with general procedure gave **14** (9.5 mg, 4.8 μmol, 95%) as colorless amorphous. $[\alpha]_D^{25}$ +68.1 (*c* 0.45, $CHCl_3$), $[\alpha]_D^{24}$ +79.9 (*c* 0.48, EtOAc) {lit.[3a] $[\alpha]_D$ +82.2 (*c* 18.7 g L^{-1}, EtOAc)}; ^{1}H NMR (400 MHz, $CDCl_3$, 0.5:0.5 mixture of rotational isomers) 7.36–6.69 (12H, m), 6.89 (0.5H, s, 6), 6.77 (0.5H, d, *J*=2.2 Hz, A8), 6.75 (0.5H, s, 6), 6.71 (0.5H, s, 6), 6.65 (0.5H, d, *J*=2.2 Hz, A6), 6.64 (0.5H, s, 6), 6.62 (0.5H, s, 6), 6.58 (0.5H, s, 6), 6.25 (0.5H, d, *J*=2.2 Hz, A8), 5.88 (0.5H, d, *J*=2.2 Hz, A6), 5.74 (0.5H, br s), 5.50–5.46 (1H, m, L3×2), 5.45 (1H, br s), 5.36 (1H, br s), 5.34 (0.5H, br s), 5.31 (0.5H, br s), 5.29 (1H, br s), 5.22–5.18 (1H, br s, L2×2), 5.15 (0.5H, br s), 4.97–4.94 (0.5H, m), 4.84 (0.5H, br s), 4.80 (0.5H, br s), 4.76 (0.5H, br s), 4.66 (0.5H, br s), 4.61 (0.5H, br s), 4.56 (0.5H, br s), 4.51 (0.5H, d, *J*=2.2 Hz), 3.10–3.05 (1H, m, L4), 2.99–2.93 (1H, m, L4), 2.38 (1.5H, s, Ac), 2.32 (1.5H, s, Ac), 2.30 (1.5H, s, Ac), 2.290 (1.5H, s, Ac), 2.286 (1.5H, s, Ac), 2.281 (1.5H, s, Ac), 2.27 (6H, s, Ac), 2.26 (3H, s, Ac), 2.25 (1.5H, s, Ac), 2.245 (1.5H, s, Ac), 2.239 (1.5H, s, Ac), 2.22 (4.5H, s, Ac), 2.18 (1.5H, s, Ac), 2.17 (1.5H, s, Ac), 2.05 (1.5H, s, Ac), 1.99 (3H, s, Ac), 1.97 (1.5H, s, Ac), 1.94 (1.5H, s, Ac), 1.91 (1.5H, s, Ac), 1.89 (1.5H, s, Ac), 1.88 (3H, s, Ac), 1.86 (1.5H, s, Ac), 1.85 (1.5H, s, Ac), 1.79 (1.5H, s, Ac), 1.77 (1.5H, s, Ac), 1.64 (1.5H, s, Ac), 1.52 (1.5H, s, Ac), 1.45 (1.5H, s, Ac), 1.44 (1.5H, s, Ac), 1.43 (1.5H, s, Ac), 1.35 (1.5H, s, Ac), 1.25 (1.5H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1 (×2), 170.0 (×2), 169.2, 169.1, 169.0, 168.9 (×2), 168.8, 168.7 (×3), 168.5, 168.39, 168.36, 168.32, 168.29, 168.18, 168.11, 168.1–167.7 (C×19), 167.6, 155.9, 154.9, 154.1, 151.91, 151.88, 151.84, 151.7, 151.6, 149.92, 149.88, 149.85, 149.0, 148.7, 148.6, 148.53, 148.48, 148.0, 147.9, 147.5 (×2), 147.4, 147.3 (×2), 147.2, 142.24, 142.18, 142.16, 142.09, 142.07 (×3), 142.0, 141.94, 141.89, 141.84, 141.81 (×3), 141.73, 141.69, 136.5, 135.8 (×2), 135.5, 135.38, 135.35, 135.1, 133.1, 124.9–121.4 (C×26), 118.5, 118.2, 117.8 (×2), 117.41, 117.39, 112.7, 112.6, 112.3, 111.7, 111.3, 110.8 (×2), 110.7, 110.6, 109.9, 109.8, 109.4, 108.2, 107.6, 107.3, 77.6, 77.2–76.6 (C×3), 76.4, 75.4, 75.1 (×2), 74.7, 73.9, 71.5, 71.3, 71.0, 70.7, 66.6 (×2), 35.7, 35.3, 35.2 (×2), 34.3, 32.9, 26.4 (×2), 21.1, 21.0, 20.78, 20.76, 20.7–20.6 (C×18), 20.54, 20.46, 20.44, 20.32, 20.31 (×2), 20.20, 20.17, 20.12, 20.11, 29.05 (×2), 19.99, 19.7, 19.6, 19.5 (×2), 19.3; IR (neat, cm^{-1}) 3063 (m), 2988 (m), 2936 (m), 2853 (w), 2413 (w), 2309 (w), 2091 (w), 1748 (s), 1600 (s), 1507 (s), 1429 (s), 1372 (s), 1262 (s), 1206 (s), 1109 (s), 1043 (s), 976 (m), 949 (m), 902 (s), 841 (m); FABMS (*m*/*z*) 2021 (28), 2020 (59), 2018 (100), 2017 ([M+Na]$^+$, 100), 1977 (24), 1975 (47), 1894 (29), 1893 (39), 1892 (36), 1791 (28), 1790 (30), 1789 (28), 1382 (26), 1172 (29), 972 (30), 971 (32); FAB-HRMS calcd for $C_{100}H_{90}O_{44}Na$ [M+Na]$^+$, 2017.4703; found: 2017.4696.

4.1.8. *[4,8:4″,8″]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-Dodeca-O-benzyl-tri-(−)-epicatechin-3,3″,3‴-O-(tri-O-benzyl)gallate (**18**)*

To a solution of **16** (284 mg, 0.13 mmol) and **15** (35.0 mg, 0.030 mmol) in CH_2Cl_2 (60 mL) was added dropwise TMSOTf (0.036 mL, 0.018 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/AcOEt/$CHCl_3$, 9:1 to 2:1) afforded a 57 mg of **18** (0.018 mmol, 57%) as a colorless amorphous: $[\alpha]_D^{24}$ −5.0 (*c* 0.34, $CHCl_3$), $[\alpha]_D^{24}$ 0.0 (*c* 0.32, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, 0.80:0.20 mixture of rotational isomers) major isomer: 7.48–6.09 (96H, m), 6.32 (0.8H, s), 6.04 (0.8H, d, *J*=2.2 Hz), 6.01 (0.8H, br s), 5.94 (0.8H, s), 5.84 (0.8H, br s), 5.66 (0.8H, d, *J*=2.2 Hz), 5.59 (0.8H, br s), 5.58–5.53 (0.8H, m), 5.38–3.96 (34.4H, m), 5.16 (0.8H, br s), 3.92 (0.8H, d, *J*=11.7 Hz), 3.81 (0.8H, d, *J*=11.7 Hz), 3.27–3.14 (1.6H, m); minor isomer: 7.48–6.09 (24.6H, m), 6.25 (0.2H, s), 6.04–3.83 (10H, m), 3.27–3.14 (0.4H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 0.80:0.20 mixture of rotational isomers) major isomer: 165.3, 164.2, 163.8, 158.1, 156.6, 156.5, 156.2, 156.1, 155.9, 155.5, 154.7, 153.5, 152.6, 152.1, 152.0, 149.3, 149.1, 148.9, 148.7, 148.1, 148.0, 143.2, 142.23, 142.17, 138.0–136.4 (C×24), 131.6, 131.2, 130.6, 128.6–125.9 (C×50), 125.3, 124.9, 120.2 (×2), 119.3, 113.9, 113.8, 113.5, 113.4, 113.0, 111.4, 109.84, 109.76, 109.0, 108.8, 106.2, 105.0, 101.7, 93.8, 93.4, 91.9, 90.6, 77.6, 77.5, 76.1, 75.6, 75.0, 74.9, 74.8, 74.7, 72.9, 71.8–68.9 (C×15), 35.1, 33.8, 26.5; minor isomer was not identified. IR (neat, cm^{-1}) 3090 (w), 3065 (m), 3031 (m), 2936 (m), 2870 (m), 1952 (w), 1860 (w), 1811 (w), 1721 (s), 1593 (s), 1514 (s), 1429 (s), 1373 (s), 1329 (s), 1267 (s), 1217 (s), 1169 (s), 1028 (s), 911 (w), 856 (w); FABMS (*m*/*z*) 3236 ([M+Na]$^+$, 23), 3229 (46), 3218 (56), 3214 ([M+H]$^+$, 38), 3196 (39), 3042 (51), 3008 (71), 2958 (77), 2900 (100), 2684 (80), 2598 (64), 2586 (62), 2585 (87), 2425 (77), 2411 (76), 2330 (95), 2293 (83), 2244 (88), 2148 (75), 2108 (73), 2061 (94), 1749 (95), 1611 (100).

4.1.9. *[4,8:4″,8″]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-trans-Dodeca-O-benzyl-(−)-epicatechin-(−)-epicatechin-(+)-catechin-3,3″,3‴-O-(tri-O-benzyl)gallate (**20**)*

To a solution of **17** (155 mg, 0.072 mmol) and **15** (20.9 mg, 0.018 mmol) in CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.036 mL, 0.018 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 (hex–AcOEt–$CHCl_3$, 9:1–2:1) afforded a 44 mg of **19** (0.014 mmol, 76%) as a colorless amorphous: $[\alpha]_D^{26}$ +50.9 (*c* 0.60, $CHCl_3$), $[\alpha]_D^{25}$ +46.5 (*c* 0.62, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, 0.70:0.30 mixture of rotational isomers) major isomer: 7.48–6.25 (84H, m), 6.41 (0.7H, s), 6.01 (0.7H, d, *J*=2.2 Hz), 5.95 (0.7H, s), 5.92 (0.7H, br s), 5.75 (0.7H, br s), 5.66 (0.7H, d, *J*=2.2 Hz), 5.51 (0.7H, br s), 5.26–5.20 (0.7H, m), 5.20 (0.7H, br s), 5.14–5.13 (0.7H, m), 5.13 (0.7H, br s), 5.10–4.46 (25.2H, m), 4.44 (0.7H, d, *J*=13.9 Hz), 4.36 (0.7H, d, *J*=12.2 Hz), 4.29 (0.7H, d, *J*=13.9 Hz), 4.01 (0.7H, d, *J*=11.5 Hz), 3.94 (0.7H, d, *J*=11.5 Hz), 3.81 (0.7H, d, *J*=11.5 Hz), 3.11 (0.7H, dd, *J*=5.6, 16.9 Hz), 2.87 (0.7H, dd, *J*=7.5, 17.3 Hz); minor isomer: 7.48–5.58 (36.6H, m), 6.23 (0.3H, s), 6.07 (0.3H, s), 5.26–3.80 (15H, m), 3.14–3.09 (0.3H, m), 2.97–2.90 (0.3H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 0.70:0.30 mixture of rotational isomers) major isomer: 165.3, 164.7, 163.8, 158.1, 156.6, 156.2, 156.09, 156.07, 155.7, 155.5, 154.9, 152.6, 152.5, 152.1, 149.3, 149.1, 148.8 (×2), 148.4, 148.2, 143.0, 142.4, 142.1, 138.2–136.4 (C×24), 131.7, 131.4, 131.0, 128.7–126.8 (C×54), 120.4, 120.1, 119.6, 113.9, 113.7, 113.6, 113.4, 113.0, 111.0, 109.7, 108.9, 108.8, 106.4, 105.1, 101.7, 93.8, 93.6, 92.0, 90.6, 78.3 (2), 76.0 (2), 75.5 (2), 75.1, 74.9 (×2), 74.0, 723.9, 71.7–69.1 (C×16), 34.4 (4), 33.8 (4), 24.9 (4); minor isomer was not identified. IR (neat, cm^{-1}) 3065 (m), 3032 (m), 2934 (m), 2870 (m), 1952 (w), 1871 (w), 1811 (w), 1720 (s), 1598 (s), 1498 (s), 1429 (s), 1329 (s), 1215 (s), 1119 (s), 1028 (s), 910 (w), 858 (w), 810 (w), 754 (s); FABMS (*m*/*z*) 3236 ([M+Na]$^+$, 48), 3214 ([M+H]$^+$, 19), 3149 (37), 3117 (46), 3073 (55), 3019 (44), 2788 (77), 2713 (79), 2666 (87), 2340 (100), 2244 (75), 1987 (85), 1763 (69), 1725 (78).

*4.1.10. [4,8:4″,8″]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-cis-Tri-(−)-epicatechin-3,3″,3‴-O-gallate (**6**)*

A solution of **18** (30 mg, 0.0093 mmol) in 22 mL of THF/MeOH/H_2O, 20:1:1 was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 4 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (MeOH) and HPLC purification to give 10.2 mg of pure **6** (0.0077 mmol, 83%) as an amorphous solid. $[\alpha]_D^{25}$ +11.3 (*c* 0.28, acetone) {lit.[29] $[\alpha]_D^{28}$ +13.4 (*c* 0.93, acetone)}; ^{1}H NMR (400 MHz, CD_3OD, 0.6:0.4 mixture of rotational isomers, −40 °C) 7.05–5.03 (17.8H, m), 6.18 (0.6H, s), 6.59 (0.4H, dd, *J*=3.2, 8.3 Hz), 6.50 (0.4H, d, *J*=8.3 Hz), 6.18 (0.4H, s), 6.01 (0.6H, s), 6.00 (0.6H, d, *J*=2.2 Hz), 5.95 (0.6H, d, *J*=2.2 Hz), 5.92 (0.6H, s), 5.87 (0.4H, s), 5.75 (0.4H, d, *J*=2.2 Hz), 5.72 (0.4H, br s), 5.68 (0.6H, br s), 5.57 (0.4H, br s), 5.27 (0.4H, m), 5.05–5.01 (1H, m), 4.96 (0.6H, d, *J*=1.7 Hz), 4.81 (0.4H, br s), 4.65 (0.4H, br s), 3.10–2.95 (1H, m), 2.94–2.88 (1H, m); FABMS (*m*/*z*) 1346 (21), 1345 ($[M+Na]^+$, 93), 1344 (41), 1310 (43), 1265 (51), 1229 (60), 1227 (46), 1170 (53), 1067 (50), 1022 (69), 975 (65), 894 (53), 874 (48), 863 (51), 823 (54), 787 (63), 749 (72), 736 (73); FAB-HRMS calcd for $C_{66}H_{50}O_{30}Na$ $[M+H]^+$, 1345.2285; found: 1345.2264.

*4.1.11. [4,8:4″,8″]-2,3-cis-3,4-trans:2″,3″-cis-3″,4″-trans:2‴,3‴-trans-(−)-Epicatechin-(−)-epicatechin-(+)-catechin-3,3″,3‴-O-gallate (**7**)*

A solution of **19** (29 mg, 0.0090 mmol) in 22 mL of THF/MeOH/H_2O, 20:1:1 was hydrogenated over 20% $Pd(OH)_2$/C (5 mg) for 7 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (MeOH) and HPLC purification to give 6.4 mg of pure **7** (0.0048 mmol, 54%) as an amorphous solid: $[\alpha]_D^{25}$ +34.0 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, CD_3OD, 0.55:0.45 mixture of rotational isomers, −40 °C) 7.05–5.25 (19.8H, m), 6.20 (0.55H, s), 5.87 (0.55H, s), 5.73 (0.55H, *J*=2.2 Hz), 5.70 (0.55H, br s), 5.68 (0.45H, br s), 5.62 (0.55H, br s), 5.56 (0.55H, br s), 5.53 (0.45H, br s), 5.48 (0.55H, br s), 5.50 (0.55H, br s), 4.97 (0.45H, br s), 4.86 (0.55H, br s), 4.74 (0.45H, br s), 4.61 (0.45H, br s), 2.90–2.78 (2H, m); FABMS (*m*/*z*) 1346 (20), 1345 ($[M+Na]^+$, 32), 1323 ($[M+H]^+$, 4.5), 1203 (70), 1202 (40), 1166 (55), 1128 (66), 1064 (29), 985 (55), 970 (50), 955 (49), 899 (44), 845 (43), 840 (53), 757 (100); FAB-HRMS calcd for $C_{66}H_{50}O_{30}Na$ $[M+H]^+$, 1345.2285; found: 1345.2253.

Acknowledgements

Partial financial support of this research under the NOVARTIS Foundation (Japan) for the Promotion of Science is gratefully acknowledged. We also thank the Japan Society for the Promotion of Science (JSPS) for the Young Science Research Fellowship (to A.S.).

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