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ARTICLE

# Asymmetric total synthesis of talienbisflavan A

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The first asymmetric total syntheses of talienbisflavan A and bis-8,8′-epicatechinylmethane as well as a facile synthesis of bis-8,8′-catechinylmethane has been accomplished from readily available starting materials by using a newly developed direct regioselective methylenation of catechin derivatives as one of the key steps.

## Introduction

Flavan-3-ols and the oligomeric procyanidins constitute one of the major families of polyphenols. These catechin-class polyphenols possess potential health benefits as a result of their antibacterial,[1] anticancer,[2] antioxidant[3] and antiviral[4] actions. Among them, dimeric flavanols are a class of compounds that flavan-3-ol derivatives linked through a methylene bridge. The typical natural products are talienbisflavan A (**1**), bis-8,8′-catechinylmethane (**2**) and bis-8,8′-epicatechinylmethane (**3**), which were isolated from *Camellia taliensis*,[5] cacao liquor[6] and *Litchi chinensis*,[7] respectively. The preliminary studies showed that these talienbisflavan A-type flavan-3-ol dimers with more catechol and/or pyrogallol groups attached to the molecules led to stronger radical scavenging activities.[5,8] Unfortunately, these talienbisflavan A-type natural products are difficult to obtain in large quantities on account of the limited quantities components from the natural sources, and thereby prevent their clinical pharmacological research or development into commercial products. To overcome this problem, development of regioselective strategies for the efficient synthesis of these bioactive natural products becomes a high priority. The condensation of catechin with formaldehyde has been widely studied as a model reaction to investigate the utilization of condensed tannins as wood adhesive[9] and HCHO scavenger[10] to solve the problem of indoor air pollution caused by volatile organic compounds. This strategy seems to be one of the simplest and most straightforward methods for the synthesis of methylene linked flavanol dimers. However, the goal is difficult to achieve as the condensation of catechin with formaldehyde is easy to form the complex higher oligomers

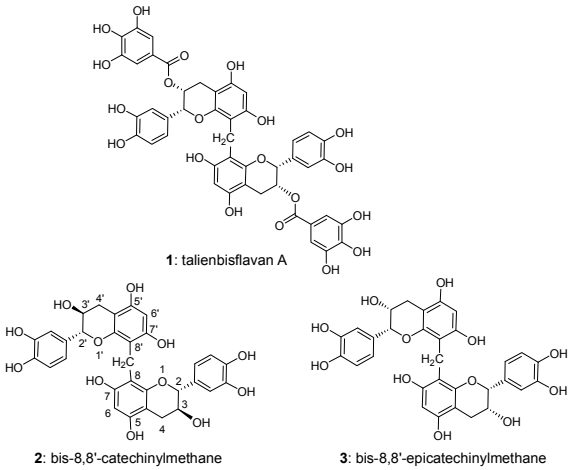


**Fig. 1** Representatives of talienbisflavan A-type natural products.

mixtures.[10] The poor C8-C8′/C8-C6′ regioselectivity makes this endeavour even more demanding.[10] Accordingly, regioselective and concise synthesis of talienbisflavan A-type flavan-3-ol dimers from catechin is still a challenge to date. Ducrot reported an elegant synthesis of bis-8,8′-catechinylmethane (**2**) via the transformation of tetra-*O*-benzyl catechin (**4**) to the corresponding penta-*O*-benzyl 8-formyl-catechin (**5**)[11,12] and subsequent reaction with catechin under hydrogenolysis conditions.[11] Bis-8,8′-catechinylmethane (**2**) and bis-8,6′-catechinylmethane (**7**) were obtained in 28% and 19% yields, respectively (Scheme 1). The result reflected that the C8-C8′regioselectivity is poor when using catechin as the nucleophile. Recently, Selenski developed a regioselective synthesis of deca-O-benzyl bis-8,8′-catechinylmethane (**9**) from tetra-*O*-benzyl catechin (**4**) in 5 steps via the key acid intermediate **8** (Scheme 1).[12] With the use of penta-benzylated catechin instead of catechin as the nucleophile, **9** was obtained as a single diastereomer (Scheme 1).[12] In contrast to the C8 position of penta-benzylated catechin, the C6 position suffers from severe steric congestion due to freely rotating substituents,[13] and thereby leads to a high C8-C8′

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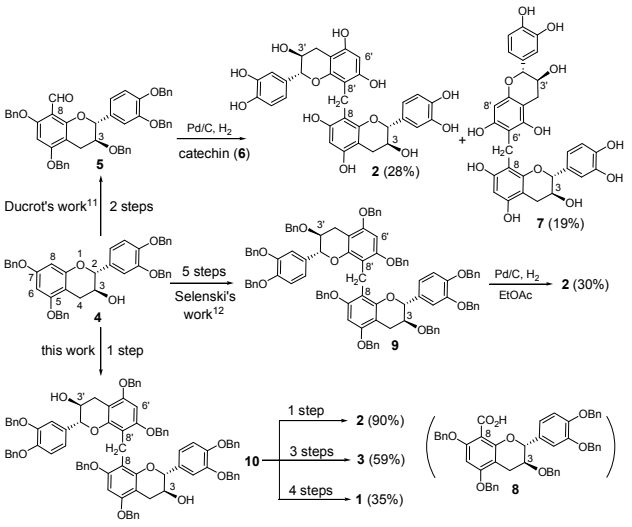
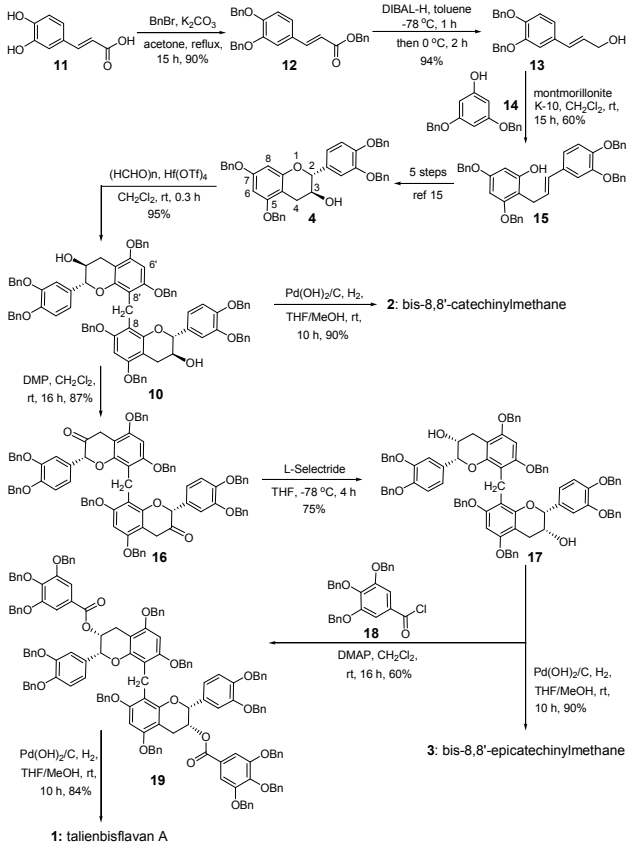



**Scheme 1** Synthesis of methylene linked flavanol dimers.

regioselectivity (Scheme 1). Removal of the ten *O*-Bn functions in deca-*O*-benzyl bis-8,8´-catechinylmethane (**9**) under the hydrogenolysis conditions afforded bis-8,8´-catechinylmethane (**2**) in a quite low yield (30%, Scheme 1).[12] Considering removal of an aromatic *O*-Bn function is usually easier than that of an aliphatic *O*-Bn function, we envisioned that **2** might be obtained in a higher yield with the use of octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) instead of **9** as the intermediate (Scheme 1). In connection with our consistent interest towards the development of concise strategies for the synthesis of bioactive compounds,[14] herein we would like to report the first direct methylenation of tetra-*O*-benzyl catechin (**4**) with paraformaldehyde to afford the desired octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) as a single diastereomer. The newly developed strategy was then used for the efficient synthesis of bis-8,8´-catechinylmethane (**2**), as well as the first total synthesis of bis-8,8´-epicatechinylmethane (**3**) and talienbisflavan A (**1**, Scheme 1). The concise synthesis could be used for the preparation of sufficient quantities of these bioactive molecules for biological and medical studies.

## Results and discussion

As shown in Scheme 2, the synthesis of talienbisflavan A commenced with commercially available and inexpensive caffic acid (**11**). Treatment of caffic acid (**11**) with BnBr in acetone in the presence of $K_2CO_3$ under reflux for 15 hours afforded ester **12** in 90% yield. Reduction of ester **12** with DIBAL-H occurred smoothly to provide alcohol **13** in 94% yield. Friedel–Craft alkylation of 3,5-bis(benzyloxy)phenol (**14**) with alcohol **13** in the presence of montmorillonite K-10 generated phenol **15** in 60 % yield. Following Chan's procedure,[15] phenol **15** was converted to tetra-*O*-benzyl catechin (**4**) in five steps with 39% overall yield. The physical, spectroscopic, and spectrometric data ($^1$H NMR, $^{13}$C NMR, $[\alpha]_D$ and HRMS) of the synthetic material are identical to those reported in the literature.[15]




**Scheme 2** Total synthesis of talienbisflavan A (**1**), bis-8,8´-catechinylmethane (**2**) and bis-8,8´-epicatechinylmethane (**3**).

The direct methylenation of **4** with paraformaldehyde was extensively investigated, and the representative results are shown in Table 1. This methylenation reaction should be performed as mild as possible to improve its C8-C8´/C8-C6´ regioselectivity (Schemes 1 and 2). By treating tetra-*O*-benzyl catechin (**4**) with paraformaldehyde in the presence of a catalytic amount of montmorillonite K-10 (1 mol %) or acitic acid ($CH_3CO_2H$, 1 mol %) in dichloromethane ($CH_2Cl_2$) at room temperature for 12 hours, no reaction took place and the starting material of **4** was recovered (Table 1, entries 1 and 2). Gratifyingly, trifluoroacetic acid ($CF_3CO_2H$, 1 mol %), *p*-toluenesulfonic acid (*p*-TsOH, 1 mol %), aqueous hydrochloric acid (HCl, 1 mol %) and concentrated sulfuric acid ($H_2SO_4$, 1 mol %) displayed some efficiency for this reaction. Treatment of **4** with paraformaldehyde in the presence of these Brønsted acids afforded octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**), in 30–32% yields, as a single diastereomer at room temperature within 12 hours (entries 3–6). When 1 mol % of $TiCl_4$, $SnCl_4$ or $CuCl_2$ was used, treatment of **4** with paraformaldehyde afforded **10** in 20–23% yields under the same conditions, albeit within a shorter reaction time (i.e., 5 h *versus* 12 h, entries 3–9). The direct methylenation of **4** with paraformaldehyde could be accomplished in 55–70% yields with the use of $BiCl_3$ (1 mol %), $InCl_3$ (1 mol %), $FeCl_3$ (1 mol %) or $BF_3{\cdot}Et_2O$ (1 mol %) as the promoter (entries 10–13). Other

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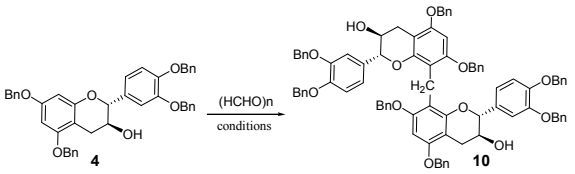
**T**able 1 Survey of conditions for the direct methylenation of tetra-*O*-benzyl catechin (**4**) with paraformaldehyde [a]



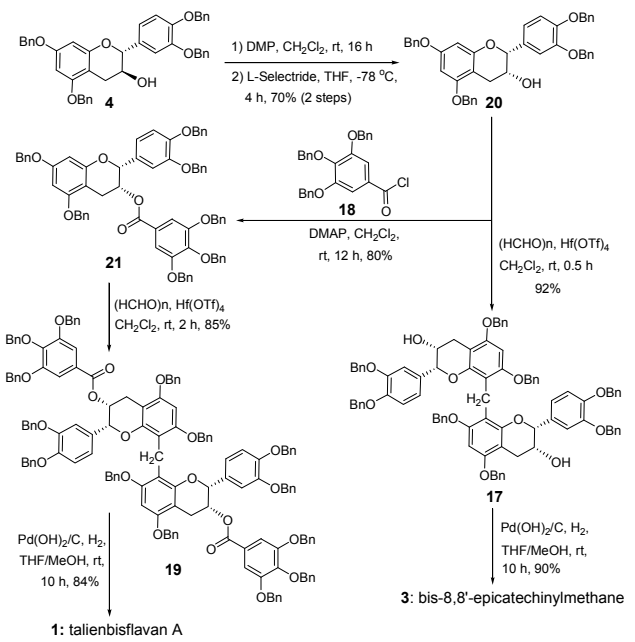

| Entry | Promoter | Equiv. | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | montmorillonite K-10 | 0.01 | 12 | 0 |
| 2 | $CH_3CO_2H$ | 0.01 | 12 | 0 |
| 3 | $CF_3CO_2H$ | 0.01 | 12 | 30 |
| 4 | *p*-TsOH | 0.01 | 12 | 32 |
| 5 | HCl (37%, $H_2O$) | 0.01 | 12 | 30 |
| 6 | $H_2SO_4$ | 0.01 | 12 | 31 |
| 7 | $TiCl_4$ | 0.01 | 5 | 20 |
| 8 | $SnCl_4$ | 0.01 | 5 | 20 |
| 9 | $CuCl_2$ | 0.01 | 5 | 23 |
| 10 | $BiCl_3$ | 0.01 | 5 | 55 |
| 11 | $InCl_3$ | 0.01 | 5 | 60 |
| 12 | $FeCl_3$ | 0.01 | 5 | 70 |
| 13 | $BF_3$•$Et_2O$ | 0.01 | 5 | 55 |
| 14 | $Yb(OTf)_3$ | 0.01 | 2 | 28 |
| 15 | $La(OTf)_3$ | 0.01 | 2 | 20 |
| 16 | $Al(OTf)_3$ | 0.01 | 1 | 80 |
| 17 | $Sc(OTf)_3$ | 0.01 | 1 | 85 |
| 18 | $Hf(OTf)_4$ | 0.01 | 0.3 | 95 |
| 19 | $Hf(OTf)_4$ | 0.003 | 5 | 90 |

[a] General conditions: **4** (0.03 mmol, 1.0 equiv.), paraformaldehyde (0.03 mmol, 1.0 equiv.) and promoter ($9\times10^{-5}$–$3\times10^{-4}$ mmol, 0.003–0.01 equiv.) in $CH_2Cl_2$ (c = 1 M) at room temperature for 0.3–12 h.

Lewis acids were also investigated, reaction of **4** with paraformaldehyde in the presence of various triflate salts (1 mol %) could be finished within 0.3–2 hours (entries 14–18). The reaction was a little complex in the presence of $Yb(OTf)_3$ (1 mol %) or $La(OTf)_3$ (1 mol %) in $CH_2Cl_2$ at room temperature, and the desirable octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) was obtained in only 28% and 20% yields, respectively (entries 14 and 15). Instead, $Al(OTf)_3$ (1 mol %) or $Sc(OTf)_3$ (1 mol %) was quite effective for this reaction, which afforded **10** in 80% and 85% yields, respectively (entries 16 and 17). Fortuitously, **10** was obtained in 95% yield within only 0.3 h when the reaction was performed in the presence of $Hf(OTf)_4$ (1 mol %, entry 18). The reaction was still quite effective when the loading of $Hf(OTf)_4$ was decreased down to 0.3 mol % (entry 19). These results are in good agreement with the related reports in the literature that oxophilic $Hf(OTf)_4$, superior to the other selected Lewis acids and Brønsted acids,[16] is a mild and efficient catalyst for the promotion of hydroxyl- or/and carbonyl-involved reactions.[17]

With the desired octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) in hand, we turned our efforts towards the total synthesis of talienbisflavan A (**1**), bis-8,8´-catechinylmethane (**2**) and bis-8,8´-epicatechinylmethane (**3**, Scheme 2). Removal of the eight *O*-Bn functions in **10** under the hydrogenolysis conditions afforded bis-8,8´-catechinylmethane (**2**) in 90% yield (Scheme 2). This is an obviously higher yield in comparison to the hydrogenolysis of **9** (i.e., 30% *versus* 90%),[12] supporting our previous anticipation (Schemes 1 and 2). On the other hand, Dess–Martin oxidation of **10** gave ketone **16** in 87% yield, which, in turn, was reduced by L-selectride to provide exclusively the *cis*-substituted octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**) in 75% yield. As in the case of **10**, removal of the eight *O*-Bn functions in **17** under the hydrogenolysis conditions did afford the desirable bis-8,8´-epicatechinylmethane (**3**) in an excellent yield (Scheme 2). Esterification of **17** with 3,4,5-tri-*O*-benzylgalloyl chloride (**18**), prepared from 3,4,5-tri-*O*-benzylgalloyl acid and oxalyl chloride in $CH_2Cl_2$, gave ester **19** in 85% yield. Finally, removal of the fourteen *O*-Bn functions in **19** under the hydrogenolysis conditions afforded talienbisflavan A (**1**) in 84% yield (Scheme 2). The physical, spectroscopic, and spectrometric data ($^1$H NMR, $^{13}$C NMR, $[\alpha]_D$ and HRMS) of the synthetic materials **1**–**3** are identical to those of natural products.[5–7]

Scheme 3 illustrates an alternative synthesis of talienbisflavan A (**1**) and bis-8,8´-epicatechinylmethane (**3**) via the newly developed regioselective methylenation strategy mentioned above. The treatment of tetra-*O*-benzyl catechin (**4**) with Dess–Martin periodinane followed by reduction with L-selectride afforded exclusively the *cis*-substituted tetra-*O*-benzyl epicatechin (**20**) in 75% overall yield (Scheme 3). The direct methylenation of **20** with paraformaldehyde went smoothly in the presence of $Hf(OTf)_4$ (1 mol %) under mild conditions to afford octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**) as a single diastereomer in 92% yield. **17** underwent *O*-Bn deprotection to generate bis-8,8´-epicatechinylmethane (**3**) in 90% yield (Scheme 3). On the other hand, Acylation of **20** with 3,4,5-tris(benzyloxy)galloyl chloride (**18**) gave ester **21** in 80% yield (Scheme 3). Treatment




**Scheme 3** An alternative synthesis of talienbisflavan A (**1**) and bis-8,8´-epicatechinylmethane (**3**).

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of **21** with paraformaldehyde in the presence of $Hf(OTf)_4$ (5 mol %) and subsequent *O*-Bn deprotection afforded talienbisflavan A (**1**) in 71% overall yield (Scheme 3).

## Experimental

### General methods

Common reagents and materials were purchased from commercial sources and were used without further purification. TLC plates were visualized by exposure to ultra violet light (UV). Chemical shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents [$CHCl_3$: δ 7.26, $(CD_3)_2CO$: δ 2.05, $CD_3OD$: δ 3.31]. Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, $CD_3OD$: δ 49.05). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant in Hertz (Hz).

### Total synthesis of talienbisflavan A (1), bis-8,8´-catechinylmethane (2) and bis-8,8´-epicatechinylmethane (3, Scheme 2)

**Synthesis of ester 12.** To a solution of caffeic acid (**11**, 1.5 g, 8.3 mmol) in acetone (20 mL) were added potassium carbonate (3.45 g, 25 mmol) and benzyl bromide (3.95 mL, 33.3 mmol). The resulting mixture was stirred under reflux for 15 h, and was added with water (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The syrupy residue was purified by crystallization in ethanol to afford ester **12** as a white solid (3.38 g). Yield: 90%; m.p. = 80–81 °C (lit.,[18] 80-82 °C); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.64 (d, 1H, *J* = 15.9 Hz), 7.48–7.34 (m, 15H), 7.15 (s, 1H), 7.09 (d, 1H, *J* = 8.3 Hz), 6.94 (d, 1H, *J* = 8.3 Hz), 6.32 (d, 1H, *J* = 15.9 Hz), 5.26 (s, 2H), 5.22 (s, 2H), 5.19 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 166.9, 151.1, 149.0, 144.9, 136.8, 136.7, 136.2, 128.5, 128.2, 128.2, 127.9, 127.8, 127.3, 127.1, 122.9, 115.8, 114.3, 113.8, 71.3, 71.0, 66.2; IR (film): $\nu_{max}$ = 3068, 3025, 2907, 2857, 1683, 1595, 1516, 1445, 1390, 1272, 1130, 1021, 946, 871, 840, 816 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{30}H_{27}O_4$ $[M+H]^+$: 451.1909, found: 451.1913.

**Synthesis of alcohol 13.** To a solution of ester **12** (1.0 g, 2.22 mmol) in toluene (10 mL) was added DIBAL-H (1.5 M in toluene, 3.7 mL, 5.55 mmol) at –78 °C. The mixture was stirred at –78 °C for 1 h, warmed to 0 °C and stirred at this temperature for 2 h, then water (5 mL) was added dropwise, and the resulting reaction mixture was diluted with water (10 mL) and diethyl ether (10 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Recrystallization of the crude product from hexanes and dichloromethane provided alcohol **13** as a white solid (0.72 g). Yield: 94%; m.p. = 77–78 °C (lit.,[15] 75-76 °C); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.49–7.33 (m, 10H), 7.05 (s, 1H), 6.92 (s, 2H), 6.52 (d, 1H, *J* = 15.9 Hz), 6.21 (td, 1H, *J* = 15.9, 5.9 Hz), 5.19 (s, 2H), 5.18 (s, 2H), 4.69 (s, 1 H, OH), 4.30 (dd, 2H, *J* = 5.8 Hz, 1.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 149.1, 148.9, 137.2, 130.5, 128.5, 127.8, 127.3, 127.2, 126.9, 120.3, 115.0, 113.1, 71.4, 71.3, 63.7; IR (film): $\nu_{max}$ = 3294, 3063, 3033, 2924, 2861, 1653, 1599, 1581, 1510, 1454, 1425, 1380, 1342, 1318, 1260, 1235, 1221, 1163, 1134, 1197, 1080, 1043, 1007, 963 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{23}H_{23}O_3$ $[M + H]^+$: 347.1647, found: 347.1650.

**Synthesis of phenol 15.** To a well stirred mixture of 3,5-bis(benzyloxy)phenol (**14**, 480 mg, 1.57 mmol) in anhydrous dichloromethane (20 mL) under nitrogen was added montmorillonite K-10 (480 mg) at room temperature. Then, a solution of alcohol **13** (181 mg, 0.52 mmol) in anhydrous dichloromethane (10 mL) was added dropwise over 30 min. The resulting purple mixture was stirred at room temperature for 15 h and then filtered through a pad of Celite, which was rinsed with ethyl acetate (200 mL). After evaporation, the residue was purified by column chromatography over silica gel to afford phenol **15** as a white amorphous foam (198 mg). Yield: 60%; $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.43–7.32 (m, 20H), 6.95 (d, 1H, *J* = 1.2 Hz), 6.84–6.81 (m, 2H), 6.37 (d, 1H, *J* = 15.5 Hz), 6.27 (d, 1H, *J* = 1.7 Hz), 6.16 (d, 1H, *J* = 1.7 Hz), 6.14–6.10 (dd, 1H, *J* = 15.5, 5.8 Hz), 5.12 (s, 2H), 5.11 (s, 2H), 5.01 (s, 2H), 4.98 (s, 2H), 3.55 (d, 2H, *J* = 5.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 158.5, 157.6, 155.5, 148.7, 148.1, 137.0, 136.8, 136.6, 130.9, 129.8, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 127.1, 127.0, 126.4, 119.6, 114.8, 112.3, 106.7, 94.8, 93.4, 76.9, 71.1, 70.1, 69.8, 26.1; IR (film): $\nu_{max}$ = 3492, 3029, 1621, 1506, 1374, 1116, 997 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{43}H_{38}O_5Na$ $[M+Na]^+$: 657.2617, found: 657.2631.

**Synthesis of tetra-*O*-benzyl catechin (4).** Tetra-*O*-benzyl catechin (**4**) was synthesized from phenol **15** according to the literature[15]. M.p. = 115–116°C (lit.,[19] 115–116 °C); $[\alpha]_D^{25}$ +3 (c = 1.0, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.54–7.38 (m, 20H), 7.14 (s, 1H), 7.02 (s, 2H), 6.38 (s, 1H), 6.34 (s, 1H), 5.23 (s, 4H), 5.18–5.02 (m, 4H), 4.70 (d, 1H, *J* = 8.1 Hz), 4.05 (dd, 1H, *J* = 14.0, 7.9 Hz), 3.19 (dd, 1H, *J* =16.4, 5.5 Hz), 2.74 (dd, 1H, *J* = 16.4, 8.7 Hz,); $^{13}$C NMR (100 MHz,$CDCl_3$): δ/ppm = 158.7, 157.6, 155.2, 149.1, 148.9, 137.0, 136.9, 136.8, 136.8, 131.0, 128.7, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 127.1, 127.0, 120.4, 114.8, 113.8, 102.2, 94.3, 93.7, 81.4, 71.1, 71.0, 69.9, 69.7, 67.9, 27.5. IR (film): $\nu_{max}$ = 3030, 1613, 1593, 1512, 1497, 1453, 1377, 1263, 1215, 1139, 1116, 744, 690 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{43}H_{39}O_6$ $[M + H]^+$: 651.2747, found: 651.2744.

**Synthesis of octa-*O*-benzyl bis-8,8´-catechinylmethane (10).** To a solution of tetra-*O*-benzyl catechin (**4**, 100 mg, 0.15 mmol) in anhydrous dichloromethane (0.15 mL) were added paraformaldehyde (4.5 mg, 0.15 mmol) and $Hf(OTf)_4$ (1.16 mg, 0.0015 mmol). The mixture was stirred at room temperature for 0.3 h. Water was poured into the solution, and the mixture was extracted with ethyl acetate (3 × 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) as a yellow oil (95.9 mg). Yield: 95%; $[\alpha]_D^{25}$ -5.0 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.47–7.17 (m, 40H), 6.79 (dd, 4H, *J* = 9.1, 4.9 Hz), 6.59 (dd, 2H, *J* = 8.2, 1.5 Hz), 6.13 (s, 2H), 5.16–4.98 (m, 14H), 4.73 (d, 2H, *J* = 11.8 Hz), 4.57 (d, 2H, *J* = 11.8 Hz), 4.14 (d, 2H, *J* = 8.5 Hz), 4.05 (s, 2H), 3.14 (dd, 2H, *J* = 16.2, 5.7 Hz), 2.60 (dd, 2H, *J* = 16.2, 9.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 156.1, 154.6, 153.5, 148.9, 148.8, 137.8, 137.3, 137.3, 137.0, 131.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7,

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127.7, 127.6, 127.4, 127.3, 127.2, 127.1, 127.1, 120.6, 114.6, 113.8, 111.2, 102.2, 91.1, 80.9, 71.3, 71.0, 70.0, 69.9, 68.5, 26.9, 17.4; IR (film): $\nu_{max}$ = 3035, 1624, 1593, 1510, 1495, 1444, 1376, 1254, 1218, 1128, 1113, 742, 695 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ $[M + H]^+$: 1313.5415, found: 1313.5418.

**Synthesis of ketone 16.** To a solution of octa-*O*-benzyl bis-8,8′-catechinylmethane (**10**, 90 mg, 0.068 mmol) in anhydrous dichloromethane (0.5 mL) were added Dess–Martin periodinane (87.18 mg, 0.21 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for about 16 h until TLC showed the absence of starting material. Subsequently, saturated aqueous $NaHCO_3$ solution (1 mL) and 10% aqueous $Na_2S_2O_3$ solution (1 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford ketone **16** as a yellow oil (78.06 mg). Yield: 87%; $[\alpha]_D^{25}$ -5.8 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.44–7.20 (m, 40H), 6.85 (s, 2H), 6.78 (d, 2H, *J* = 8.3 Hz), 6.67 (d, 2H, *J* = 8.2 Hz), 6.19 (s, 2H), 5.11 (s, 4H), 4.98 (s, 8H), 4.71 (d, 2H, *J* = 11.5 Hz), 4.60 (d, 2H, *J* = 11.4 Hz), 4.52 (s, 2H), 4.19 (s, 2H), 3.68 (d, 2H, *J* = 20.3 Hz), 3.33 (d, 2H, *J* = 20.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 206.5, 156.7, 154.1, 153.4, 149.0, 148.7, 137.2, 137.1, 137.0, 136.8, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7, 127.6, 127.4, 127.2, 127.2, 120.3, 114.5, 113.6, 112.8, 102.9, 92.7, 83.0, 71.1, 70.3, 70.1, 67.9, 26.9, 17.6; IR (film): $\nu_{max}$ = 3035, 1723, 1620, 1594, 1515, 1503, 1380, 1160, 736, 696 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{87}H_{73}O_{12}$ $[M + H]^+$: 1309.5102, found: 1309.5107.

**Synthesis of octa-*O*-benzyl bis-8,8′-epicatechinylmethane (17).** To a solution of ketone **16** (65 mg, 0.05 mmol) in dry THF (0.5 mL) was added dropwise L-selectride (0.1 mL, 1.0 M solution in THF, 0.1 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 4 h, and TLC showed the reaction was complete. Saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8′-epicatechinylmethane (**17**) as a colourless oil (48.9 mg). Yield: 75%; $[\alpha]_D^{25}$ -28.4 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.46–7.11 (m, 40H), 6.93 (s, 2H), 6.84 (d, 2H, *J* = 8.2 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.21 (s, 2H), 5.22–5.11 (m, 14H), 4.75 (d, 2H, *J* = 13.1 Hz), 4.33 (s, 2H), 4.17 (s, 2H), 4.00 (s, 2H), 3.01 (d, 2H, *J* = 17.0 Hz), 2.82 (dd, 2H, *J* = 17.3, 3.9 Hz); $^{13}$C NMR (100 MHz,$CDCl_3$): δ/ppm = 156.2, 155.3, 153.4, 148.6, 148.4, 137.7, 137.4, 137.4, 137.2, 132.1, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 127.3, 127.2, 119.6, 114.7, 113.6, 111.5, 101.0, 91.8, 77.8, 71.2, 71.1, 70.5, 70.0, 66.1, 26.9, 17.6; IR (film): $\nu_{max}$ = 3547, 1619, 1592, 1516, 1494, 1460, 1441, 1379, 1261, 1219, 1146, 1110, 753, 699 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ $[M + H]^+$: 1313.5415, found: 1313.5418.

**Synthesis of ester 19.** To a suspension of tri-*O*-benzyl gallic acid (53.66 mg, 0.12 mmol) and one drop of DMF in anhydrous dichloromethane (1 mL) was slowly added oxalyl chloride (0.1 mL) in a nitrogen atmosphere. The resulting mixture was stirred under reflux for 3 h. The excess oxally chloride and solvent were removed by distillation and the residue was dried under vacuum for 3 h. To this mixture (3,4,5-tri-*O*-benzylgalloyl chloride, **18**) was added octa-*O*-benzyl bis-8,8′-epicatechinylmethane (**17**, 40 mg, 0.03 mmol) and DMAP (7.44 mg, 0.06 mmol) in dichloromethane (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 16 h, and was then added with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford ester **19** as a colourless oil (39.4 mg). Yield: 60%; $[\alpha]_D^{25}$ -105.0 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35–7.17 (m, 70H), 7.05 (d, 4H, *J* = 7.1 Hz), 6.84 (s, 2H), 6.69 (d, 2H, *J* = 8.1 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.19 (s, 2H), 5.38 (s, 2H), 5.08–4.94 (m, 26H), 4.73–4.65 (m, 4H), 4.24–4.21 (m, 2H), 3.04–2.93 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 165.2, 156.3, 154.9, 153.7, 152.3, 148.7, 148.5, 142.8, 137.4, 137.3, 137.1, 136.5, 131.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.3, 127.1, 119.9, 114.5, 113.7, 111.7, 109.5, 101.1, 91.6, 75.0, 71.2, 71.2, 70.6, 70.0, 68.6, 29.7, 17.4; IR (film): $\nu_{max}$ = 3065, 3028, 2934, 2870, 1718, 1614, 1590, 1499, 1446, 1428, 1371, 1322, 1269, 1119, 868, 813, 735, 694 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{143}H_{120}O_{20}Na$ $[M + Na]^+$: 2179.8271, found: 2179.8268.

**Synthesis of talienbisflavan A (1).** To a solution of ester **19** (21.6 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2$/C (5%, 40 mg) in a hydrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography (AcOH/MeOH/$CH_2Cl_2$ = 1:5:50) over silica gel to afford talienbisflavan A (**1**) as a yellow amorphous powder (7.5 mg). Yield: 84%; $[\alpha]_D^{14}$ -105.4 (c = 0.1, methanol); $^1$H NMR (400 MHz, $CD_3OD$): δ/ppm = 6.92 (s, 4H), 6.84 (s, 2H), 6.69–6.65 (m, 4H), 6.01 (s, 2H), 5.40 (s, br, 2H), 4.81 (s, br, 2H), 3.92 (s, 2H), 2.93 (dd, 2H, *J* = 17.9, 3.4 Hz), 2.77 (dd, 2H, *J* = 17.9, 3.4 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$): δ/ppm = 167.6, 155.6, 155.3, 153.8, 146.2, 146.1, 145.8, 140.0, 130.3, 121.6, 120.0, 116.1, 115.0, 110.3, 106.7, 99.9, 96.8, 79.0, 69.4, 26.4, 16.6; IR (film): $\nu_{max}$ = 3407, 1695, 1615, 1451, 1229, 1038, 766 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{45}H_{35}O_{20}$ $[M - H]^-$: 895.1722, found: 895.1725.

**Synthesis of bis-8,8′-catechinylmethane (2).** To a solution of octa-*O*-benzyl bis-8,8′-catechinylmethane (**10**, 13.1 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2$/C (5%, 40 mg) under hydrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was purified by flash chromatography (AcOH/MeOH/$CH_2Cl_2$ = 1:5:50) over silica gel to afford bis-8,8′-catechinylmethane (**2**) as a yellow amorphous powder (5.3 mg). Yield: 90%; $[\alpha]_D^{25}$ -104.7 (c = 1.5, MeOH); $^1$H NMR [400 MHz, $(CD_3)_2CO$]: δ/ppm = 6.94 (s, 2H), 6.80 (s, 4H), 5.98 (s, 2H), 4.69 (d, 2H, *J* = 7.2 Hz), 4.10–3.98 (m, 2H),

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3.61 (s, 2H), 2.91 (dd, 2H, *J* = 16.0, 8.1 Hz), 2.54 (dd, 2H, *J* = 16.0, 8.1 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$): δ/ppm = 154.0, 153.8, 151.9, 145.0, 144.8, 130.2, 118.8, 114.8, 114.0, 105.1, 99.9, 95.5, 81.9, 67.0, 27.2, 15.4; IR (film): $\nu_{max}$ = 3057, 3031, 2932, 2878,1612, 760 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{31}H_{27}O_{12}$ [M - H]$^-$: 591.1503, found: 591.1507.

**Synthesis of bis-8,8´-epicatechinylmethane (3).** To a solution of octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**, 13.1 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2$/C (5%, 40 mg) under hydrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography ($AcOH/MeOH/CH_2Cl_2$ = 1:5:50) over silica gel to afford bis-8,8´-epicatechinylmethane (**3**) as a white amorphous powder (5.3 mg). Yield: 90%; $[\alpha]_D^{25}$ -104.1 (c = 1.5, MeOH); $^1$H NMR (400 MHz, $CD_3OD$): δ/ppm = 6.97 (s, br, 2H), 6.75 (s, br, 4H), 5.98 (s, 2H), 4.78 (s, br, 2H), 4.12 (s, br, 2H), 3.90 (s, 2H), 2.85 (dd, 2H, *J* = 16.6, 4.7 Hz), 2.70 (dd, 2H, *J* = 16.6, 4.7 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$): δ/ppm = 155.8, 155.2, 153.6, 145.8, 131.6, 119.6, 116.0, 115.4, 106.5, 100.4, 96.8, 80.4, 67.0, 29.0, 16.5; IR (film): $\nu_{max}$ = 3065, 3033, 2919, 2873, 1606, 763 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{31}H_{27}O_{12}$ [M - H]$^-$: 591.1503, found: 591.1507.

**Alternative synthesis of talienbisflavan A (1) and bis-8,8´-epicatechinylmethane (3, Scheme 3)**

**Synthesis of tetra-*O*-benzyl epicatechin (20).** To a solution of $Bn_4$-catechin **4** (325.4 mg, 0.5 mmol) in anhydrous dichloromethane (10 mL) were added Dess–Martin periodinane (318.1 mg, 0.75 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for about 16 h until TLC showed the absence of starting material. Subsequently, saturated aqueous $NaHCO_3$ solution (4.2 mL) and 10% aqueous $Na_2S_2O_3$ solution (4.2 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15% ethyl acetate in petroleum ether) over silica gel to afford the ketone as a yellow oil. To a solution of this crude ketone in dry THF (5 mL) was added dropwise L-selectride (0.6 mL, 1.0 M solution in THF, 0.60 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for 4 h, and TLC showed the reaction was complete. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford tetra-*O*-benzyl epicatechin (**20**) as a white solid (244.1 mg). Yield: 70% (2 steps); m.p. = 129–130 °C (lit.,[19] 129.5–130 °C); $[\alpha]_D^{25}$ -27.7 (c = 2.16, EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.48–7.33 (m, 20H), 7.18 (s, 1H), 7.03–7.01 (m, 2H), 6.30 (s, 2H), 5.22 (s, 2H), 5.20 (s, 2H), 5.05 (s, 2H), 5.04 (s, 2H), 4.94 (s, 1H), 4.25 (s, br, 1H), 3.05–2.97 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 158.8, 158.3, 155.3, 149.1, 149.0, 137.3, 137.2, 137.0, 137.0, 128.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.5, 127.3, 127.2, 119.5, 115.3, 113.8, 101.0, 94.8, 94.1, 78.4, 71.5, 71.4, 70.2, 70.0, 66.3, 28.2; IR (film): $\nu_{max}$ = 3030, 1617, 1592, 1512, 1498, 1455, 1441, 1377, 1260, 1217, 1144, 1112, 750, 697 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{43}H_{39}O_6$ [M + H]$^+$: 651.2747, found: 651.2749.

**Synthesis of octa-*O*-benzyl bis-8,8´-epicatechinylmethane (17).** To a solution of tetra-*O*-benzyl epicatechin (**20**, 100 mg, 0.15 mmol) in dichloromethane (0.15 mL) were added paraformaldehyde (4.5 mg, 0.15 mmol) and $Hf(OTf)_4$ (1.16 mg, 0.0015 mmol). The resulting mixture was stirred at room temperature for 0.5 h. Water was poured into the solution, and the mixture was extracted with ethyl acetate (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**) as a colourless oil (92.9 mg). Yield: 92%; $[\alpha]_D^{25}$ -28.4 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.46–7.11 (m, 40H), 6.93 (s, 2H), 6.84 (d, 2H, *J* = 8.2 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.21 (s, 2H), 5.22–5.11 (m, 14H), 4.75 (d, 2H, *J* = 13.1 Hz), 4.33 (s, 2H), 4.17 (s, 2H), 4.00 (s, 2H), 3.01 (d, 2H, *J* = 17.0 Hz), 2.82 (dd, 2H, *J* = 17.3, 3.9 Hz); $^{13}$C NMR (100 MHz,$CDCl_3$): δ/ppm = 156.2, 155.3, 153.4, 148.6, 148.4, 137.7, 137.4, 137.4, 137.2, 132.1, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 127.3, 127.2, 119.6, 114.7, 113.6, 111.5, 101.0, 91.8, 77.8, 71.2, 71.1, 70.5, 70.0, 66.1, 26.9, 17.6; IR (film): $\nu_{max}$ = 3541, 1617, 1592, 1512, 1498, 1453, 1441, 1377, 1263, 1217, 1144, 1112, 750, 697 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ [M + H]$^+$: 1313.5410, found: 1313.5418.

**Synthesis of ester 21.** To a suspension of tri-*O*-benzyl gallic acid (135.38 mg, 0.31mol) and one drop of DMF in anhydrous dichloromethane (3 mL) was added oxalyl chloride (0.5 mL) at room temperature with agitation under nitrogen atmosphere. The reaction mixture was stirred under reflux for 3 h. The excess oxalyl chloride and solvent were removed by distillation. The residue was dried under vacuum for 3 h, and was then added dropwise to a solution of tetra-*O*-benzyl epicatechin (**20**, 100 mg, 0.15 mmol) and DMAP (18.77 mg, 0.015 mmol) in dichloromethane (2 mL) at zero temperature. The resulting mixture was stirred at room temperature for 12 h, and was then added with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) over silica gel to afford ester **21** as a white solid (131.9 mg). Yield: 80%; m.p. = 45–47 °C (lit.,[20] 45–47 °C); $[\alpha]_D^{25}$ -87.0 (c = 3.45, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.36 (ddd, 35H, *J* = 7.7, 16.5 Hz, *J* = 25.1Hz), 7.23 (s, 2H), 7.08 (s, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 8.1 Hz), 6.41 (s, 1H), 6.37 (s, 1H), 5.65 (s, 1H), 5.12 (s, 4H), 5.05 (d, 8H, *J* = 11.4 Hz), 4.96 (s, 1H), 4.80 (d, 1H, *J* = 11.7 Hz), 4.69 (d, 1H, *J* = 11.7 Hz), 3.15 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ/ppm = 165.0, 158.8, 158.0, 155.7, 152.3, 149.0, 148.9, 137.2, 137.0, 136.8, 136.5, 131.1, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.5, 127.4, 120.0, 114.8, 113.7, 109.1, 100.9, 94.6, 93.9, 75.0, 71.2, 71.0, 70.2, 70.0, 68.5, 29.7; IR (film): $\nu_{max}$ = 3090, 3064, 3032, 2930, 2872, 1715, 1619, 1592, 1499, 1454, 1429, 1373, 1327, 1266, 1215, 1145, 1112, 1028, 910, 860, 812, 735, 696 cm$^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{71}H_{61}O_{10}$ [M + H]$^+$: 1073.4265, found: 1073.4266.

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**Synthesis of ester 19.** To a solution of ester **21** (100 mg, 0.09 mmol) in anhydrous dichloromethane (0.09 mL) were added paraformaldehyde (2.7 mg, 0.09 mmol) and $Hf(OTf)_4$ (3.49 mg, 0.0045 mmol). The resulting mixture was stirred at room temperature for 2 h, added with water, extracted with ethyl acetate (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether) over silica gel to afford ester **19** as a yellow oil (87.2 mg). Yield: 85%; $[\alpha]_D^{25}$ -105.0 (c= 1.0, $CDCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35–7.17 (m, 70H), 7.05 (d, 4H, *J* = 7.1 Hz), 6.84 (s, 2H), 6.69 (d, 2H, *J* = 8.1 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.19 (s, 2H), 5.38 (s, 2H), 5.08–4.94 (m, 26H), 4.73–4.65 (m, 4H), 4.24 (s, 2H), 2.99–2.96 (m, 4H); $^{13}C$ NMR(100 MHz, $CDCl_3$): δ/ppm = 165.2, 156.3, 154.9, 153.7, 152.3, 148.7, 148.5, 142.8, 137.4, 137.3, 137.1, 136.5, 131.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.3, 127.1, 119.9, 114.5, 113.7, 111.7, 109.5, 101.1, 91.6, 75.0, 71.2, 71.2, 70.6, 70.0, 68.6, 29.7; IR (film): $\nu_{max}$ = 3065, 3028, 2934, 2870, 1718, 1614, 1590, 1499, 1446, 1428, 1371, 1322, 1269, 1119, 868, 813, 735, 694 $cm^{-1}$. HRMS (ESI) *m/z*: calcd for $C_{143}H_{120}O_{20}Na$ $[M + Na]^+$: 2179.8271, found: 2179.8268.

## Conclusions

In summary, we described a newly developed $Hf(OTf)_4$-catalyzed direct regioselective methylenation of catechin derivatives, which is employed to the first asymmetric total syntheses of talienbisflavan A and bis-8,8′-epicatechinylmethane as well as a facile synthesis of bis-8,8′-catechinylmethane. This direct regioselective methylenation reaction together with efficient hydrogenolysis of well-desighed natural product precursors could facilitate the preparation of sufficient quantities of these natural products for biological and medical studies. Further applications of these strategies for the synthesis of other bioactive natural products with related skeletons are under investigation, and will be reported in due course.

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## Graphical Abstract

Asymmetric total synthesis of talienbisflavan A

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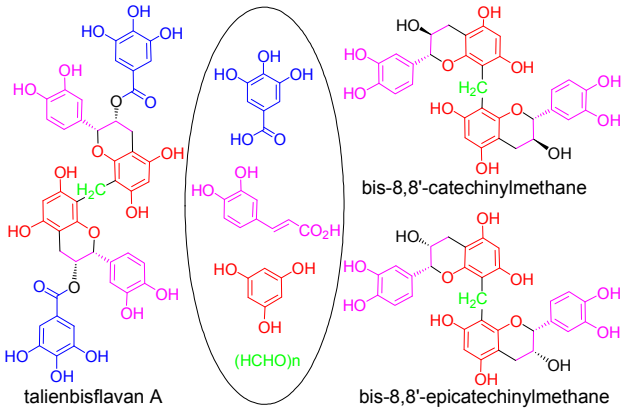


The first asymmetric total syntheses of talienbisflavan A and bis-8,8′-epicatechinylmethane as well as a facile synthesis of bis-8,8′-catechinylmethane has been accomplished from readily available starting materials by using a newly developed direct regioselective methylenation of catechin derivatives as one of the key steps.