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ORIGINAL ARTICLE

Syntheses of methylated catechins and theaflavins using 2-nitrobenzenesulfonyl group to protect and deactivate phenol

Tomohiro Asakawa[1], Yusuke Kawabe[1], Atsushi Yoshida[1], Yoshiyuki Aihara[1], Tamiko Manabe[1], Yoshitsugu Hirose[1], Asuka Sakurada[1], Makoto Inai[1], Yoshitaka Hamashima[1], Takumi Furuta[1,2], Toshiyuki Wakimoto[1,3] and Toshiyuki Kan[1]

An efficient and versatile synthetic method for labile polyphenols was established using 2-nitrobenzenesulfonate (Ns) as a protecting group for phenol. This methodology provides regio- and stereoselective access to a range of methylated catechins, such as methylated epigallocatechin gallates, that are not readily available from natural sources. In addition, biomimetic synthesis of theaflavins from catechins was accomplished using Ns protection to minimize undesired side reactions of electron-rich aromatic rings during oxidation, enabling construction of the complex benzotropolone core in a single-step oxidative coupling reaction. Availability of these compounds will aid detailed structure–biological activity relationship studies of catechins.
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INTRODUCTION

Synthetic methods for polyphenols have been extensively studied, because these compounds possess an array of interesting biological activities, including anticancer, antiviral and antimicrobial activities. Nevertheless, only a few efficient and versatile synthetic methods are available, both because the highly polar nature of polyphenols makes handling difficult, and because of the susceptibility of the compounds to oxidation. Protection of the hydroxyl groups of polyphenol is indispensable during usual chemical transformations and also during purification. Thus, selection of a suitable protecting group is critical. In this context, the 2-nitrobenzenesulfonate (Ns) group[1] should be an excellent protecting group for labile polyphenols, because it can be easily removed under mild conditions. Furthermore, its electron-withdrawing nature should enhance the stability of polyphenols during synthetic manipulations. Herein, we report efficient syntheses of a range of methylated catechins (**2** and **3**) and theaflavins (**4** and **5**) by exploiting the Ns group for protection of phenols.

RESULT AND DISCUSSION

Synthesis of methylated cathechins

Epigallocatechin gallate (EGCg: **1**), which has various biological activities, including cancer-preventive, antiviral and antimicrobial activities, is a major component of catechin derivatives derived from tea (Figure 1).[2–4] Recently, various methylated derivatives, such as (−)-3′-methyl-epigallocatechin gallate (3′-Me-EGCg: **2**), have been identified as minor catechins in natural tea leaves and as mammalian metabolites of tea catechins.[4] Because **2** and its regioisomer (4′-Me-EGCg: **3**) exhibit potent inhibitory activities towards type I allergic reactions in mice[5,6] and matrix metalloproteinases,[7,8] it seems likely that other methylated catechin derivatives may also have therapeutic potential.[9–11]

Compounds **2** and **3** are readily available from natural and synthetic sources,[12,13] and investigations of structure–activity relationships have so far been limited to these compounds. However, synthesis of all possible regio- and stereoisomers of the naturally available methylated catechins (EGC: epigallocatechin, GC: gallocatechin, EC: epicatechin and CC: catechin) would allow systematic evaluation of the structure–biological activity relationships. Hence, we are interested in concise synthesis of methylated catechins (**2**, **3** and **6**–**13**). Although synthetic investigations of the catechin skeleton have been reported by many groups,[2] including ours,[14,15] derivation of methylated catechins from natural catechins, such as EGC[16] and other derivatives (GC, EC and CC), which are inexpensive and readily available, should be a convenient and effective strategy.

Our synthetic plan is illustrated in Scheme 1. A key issue is selecting a suitable protecting group for phenol. Although benzyl ether has been employed for catechin synthesis because it is readily deprotectable under hydrogenolysis conditions, ether formation of phenol is often troublesome: for example, epimerization of the 2-position can occur under basic conditions (Scheme 2). To make matters worse, electron-rich aromatics readily undergo undesired electrophilic substitution and unexpected oxidation at the benzylic position. Thus, a major concern in polyphenol synthesis is how to avoid these problems.

[1]School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan; [2]Institute for Chemical Research, Kyoto University, Kyoto, Japan and [3]Faculty of Pharmaceutical Sciences, Hokkaido University, Hokkaido, Japan
Correspondence: Professor T Kan, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan.
E-mail: kant@u-shizuoka-ken.ac.jp
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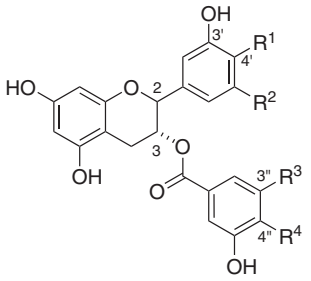
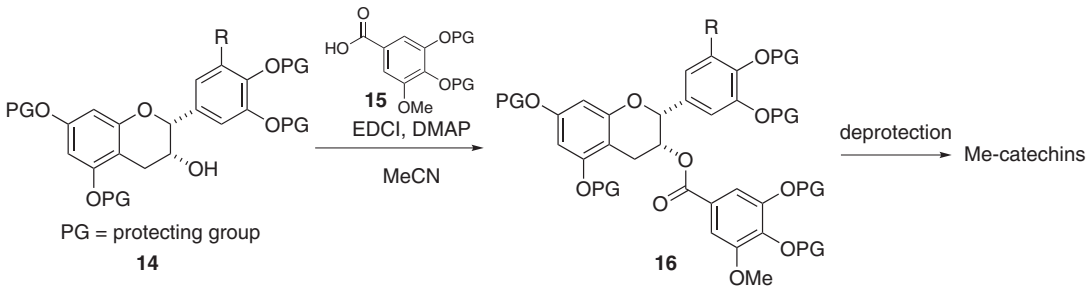
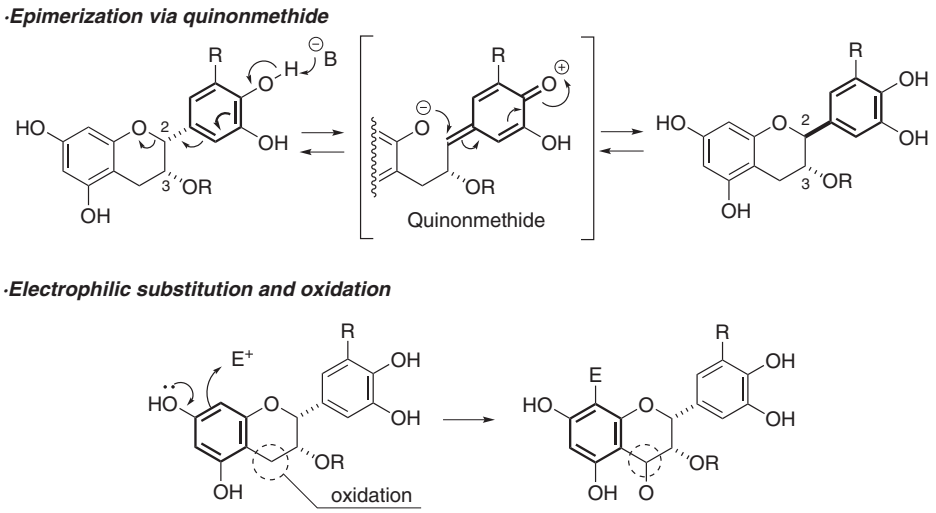


catechines		R^1	R^2	R^3	R^4
(–)-EGCg (**1**):	2,3-*cis*	OH	OH	OH	OH
(–)-3''-Me-EGCg (**2**):	2,3-*cis*	OH	OH	OMe	OH
(–)-4''-Me-EGCg (**3**):	2,3-*cis*	OH	OH	OH	OMe
(–)-3'-Me-EGCg (**6**):	2,3-*cis*	OH	OMe	OH	OH
(–)-4'-Me-EGCg (**7**):	2,3-*cis*	OMe	OH	OH	OH
(–)-3''-Me-ECg (**8**):	2,3-*cis*	OH	H	OMe	OH
(–)-4''-Me-ECg (**9**):	2,3-*cis*	OH	H	OH	OMe
(–)-3''-Me-GCg (**10**):	2,3-*trans*	OH	OH	OMe	OH
(–)-4''-Me-GCg (**11**):	2,3-*trans*	OH	OH	OH	OMe
(+)-3''-Me-CCg (**12**):	2,3-*trans*	OH	H	OMe	OH
(+)-4''-Me-CCg (**13**):	2,3-*trans*	OH	H	OH	OMe

Figure 1 EGCg (**1**) and methylated catechins.



Scheme 1 Plan for practical synthesis of methylated catechins.



Scheme 2 Potential issues in catechin synthesis.

The Ns group should be an excellent protecting group for labile polyphenols because it can be easily deprotected under mild conditions.[1,17–19] Furthermore, the electron-withdrawing nature of the Ns group should improve the stability of polyphenol during synthetic manipulations. A preliminary investigation of deprotection of 4-(((2-nitrophenyl)sulfonyl)oxy)benzyl acetate (**17**) showed that selective deprotection of the Ns group could be achieved in the presence of the ester group (Scheme 3). Thus, protection of phenols with Ns group should be effective for the synthesis of methylated catechins.

Therefore, we next investigated selective incorporation of the methyl group at 3- and 4-OH of allyl gallate (**20**), as shown in Scheme 4. Gallic acid (**19**) was converted to allyl ester **20** by reaction with allyl alcohol and EDCI. Upon treatment of **20** with Li_2CO_3 and methyl iodide, selective deprotonation and alkylation of the most acidic 4-OH proceeded smoothly to give **21**. On the other hand, 3-OH selective alkylation was achieved by utilizing a bridged boronic ester intermediate[20] between the *o*-phenolic hydroxyl groups. After formation of the boronic ester **23** by treating **20** with borax in the presence of NaOH, methylation with Me_2SO_4 and subsequent acidic hydrolysis of the boronic ester exclusively provided **24**. Ns groups were incorporated into the resultant phenols **20**, **21** and **24** by treatment with NsCl and Et_3N. Treatment of the allyl esters with catalytic amounts of $Pd(PPh_3)_4$ and *p*-tolSO_2Na[21] resulted in smooth deprotection of the allyl group to afford the desired **26**, **22** and **25**, respectively.

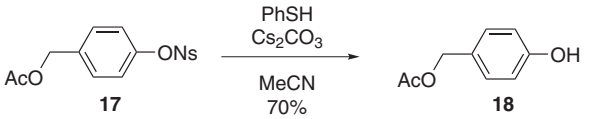
Next, we focused on incorporating gallate derivatives **22** and **25** into protected epigallocatechin derivatives and deprotection of the Ns group (Scheme 5). Protection of EGC (**27**) with the Ns group was carried out with NsCl and Et_3N to provide **28**. Condensation reaction of **28** with **25** and EDCI in the presence of a catalytic amount of DMAP proceeded smoothly to provide the desired **29** in high yield. Similar condensation of **28** and **22** provided the 4′-methylated EGCg derivative **30**. Deprotection of the Ns groups of **29** and **30** was accomplished with the use of thiophenol and cesium carbonate to provide 3′-methylated EGCg (**2**) and 4′-methylated EGCg (**3**), respectively. During this transformation, neither epimerization at the 2-position of the benzopyran ring nor decomposition of gallate ester was observed. A similar protocol provided the desired methylated gallate catechin derivatives **8**–**13** from natural catechin derivatives GC, EC and CC (Table 1).[22]

Then, we turned our attention to selectively introducing a methyl group into the B-ring (Scheme 6). To our knowledge, (–)-EGCg derivatives methylated at the B-ring have not yet been reported, so an SAR study of these compounds should be interesting. We found that a bridged boronic ester intermediate effectively distinguishes the hydroxyl groups at the A-ring and B-ring. Treatment of **27** with three equivalents of NsCl and excess H_3BO_3 in the presence of NaOH[23] resulted in regioselective sulfonylation to afford predominantly 3′,5,7-Ns-EGCg (**32**).

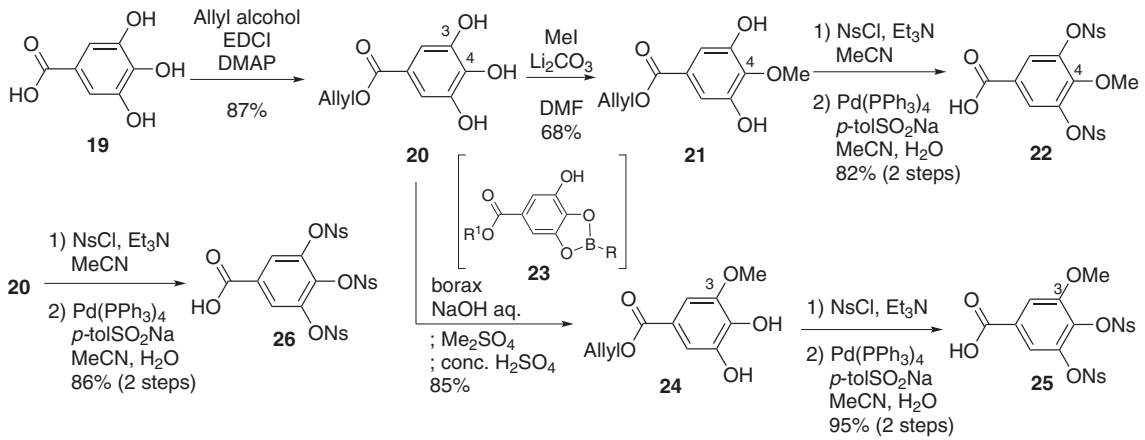
Next, selective incorporation of the TBDPS group at the less hindered hydroxyl group (5′-OH) was accomplished by treating **32** with TBDPSCl and Et_3N to give **33** (Scheme 7). The 4′-Me-EGCg derivative was prepared by methylation of **33** with diazomethane, condensation of **35** with Ns-protected gallic acid **26**,[24] and stepwise deprotection of TBDPS group and Ns group, affording 4′-Me-EGCg (**7**).

3′-Me-EGCg (**6**) and 3′,3′-diMe-EGCg (**38**) were also synthesized from **33**. Protection of **33** with Ns proceeded at the 4′-hydroxyl group. Deprotection of the TBDPS group and incorporation of a methyl group afforded **37**. Although condensation of **37** with **26** and deprotection of Ns groups readily provided 3′-Me-EGCg (**6**), we chose to employ a modified preparation with double-methylated derivatives. After condensation of **37** and **25**, deprotection of Ns groups was accomplished using 2-aminothiophenol (**39**) instead of thiophenol to afford 3′,3′-diMe- EGCG (**38**; Table 1).[25,26] For a review on recent progress in the synthesis of the advantage of this method is that **39** is odorless compared with thiophenol. Furthermore, the by-product, 2-(2-nitrophenylthio)aniline (**40**), can be easily removed by washing the ethereal layer with 1 M HCl solution.

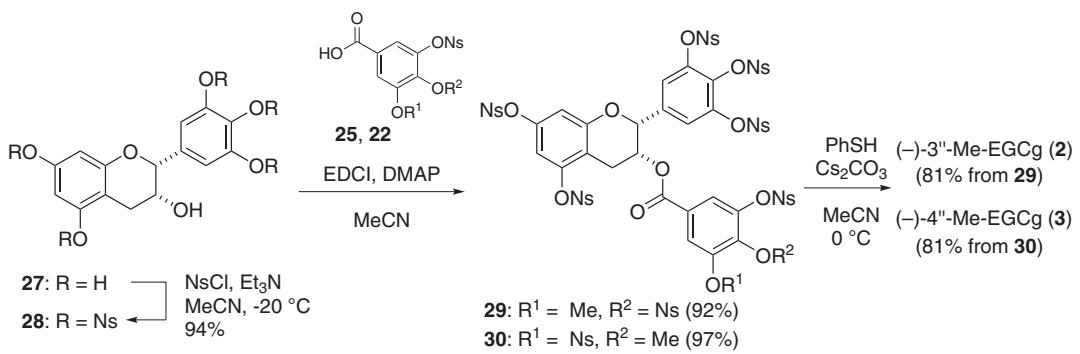
Combining the selective methylation strategies for the B- and D-rings of EGCg should provide access to several types of double-methylated EGCg derivatives. Furthermore, this regioselective modification of EGCg should be applicable for alkylation as well as acylation; thus, it should be possible to apply this synthetic strategy to



Scheme 3 Selective deprotection of *O*-Ns group.

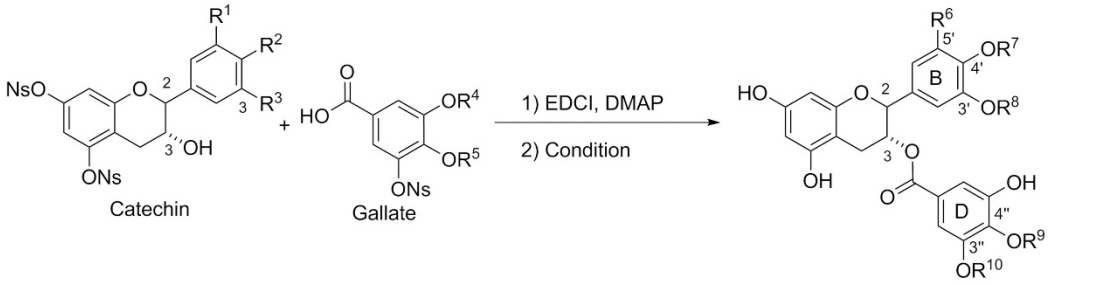


Scheme 4 Synthesis of selectively methylated gallic acids.

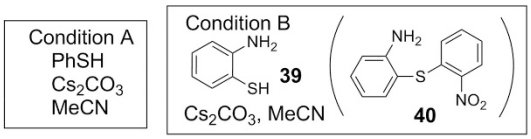


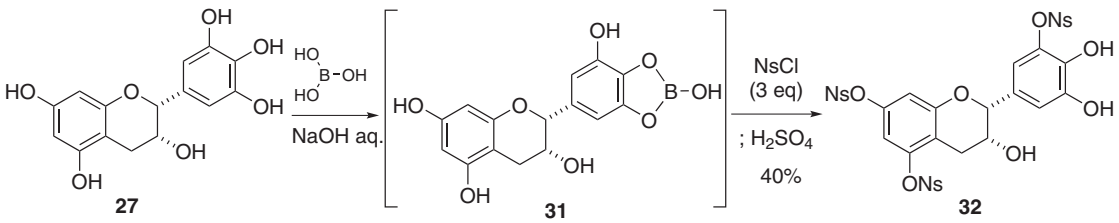
Scheme 5 Synthesis of 3′-Me-EGCg (**2**) and 4′-Me-EGCg (**3**).

Table 1 Versatile synthesis of methylated catechins



Entry	Catechin	Gallate	Condition	Product	Yield(%)
1	**35** : R^1 = ONs, R^2 = OMe R^3 = OTBDPS, 2,3-*cis*	**26** : $R^{4,5}$ = Ns	1) TBAF, AcOH THF 2) Conditon A	4'-Me-EGCg (**7**) : R^6 = OH, R^7 = Me $R^{8,9,10}$ = H, 2,3-*cis*	70
2	**37** : R^1 = OMe $R^{2,3}$ = ONs, 2,3-*cis*	**26** : $R^{4,5}$ = Ns	Condition A	3'-Me-EGCg (**6**) : R^6 =OH, R^8 =Me $R^{7,9,10}$ = H, 2,3-*cis*	63
3	**37** : R^1 = OMe $R^{2,3}$ = ONs, 2,3-*cis*	**25** : R^4 = Me R^5 = Ns	Condition B	3',3"-diMe-EGCg (**38**) : R^6 = OH, $R^{8,10}$ = Me $R^{7,9}$ = H, 2,3-*cis*	52
4	**41** : R^1 = H, $R^{2,3}$ = ONs 2,3-*cis*	**25** : R^4 = Me R^5 = Ns	Condition A	3"-Me-ECg (**8**) : R^6 = H, $R^{7,8,9}$ = H R^{10} = Me, 2,3-*cis*	84
5	**41** : R^1 = H, $R^{2,3}$ = ONs 2,3-*cis*	**22** : R^4 = Ns R^5 = Me	Condition A	4"-Me-ECg (**9**) : R^6 = H, $R^{7,8,10}$ = H R^9 = Me, 2,3-*cis*	83
6	**42**: R^1 = OH, $R^{2,3}$ = ONs 2,3-*trans*	**25** : R^4 = Me R^5 = Ns	Condition A	3"-Me-GCg (**10**) : R^6 = OH, $R^{7,8,9}$ = H R^{10} = Me, 2,3-*trans*	75
7	**42**: R^1 = OH, $R^{2,3}$ = ONs 2,3-*trans*	**22** : R^4 = Ns R^5 = Me	Condition A	4"-Me-GCg (**11**) : R^6 = OH, $R^{7,8,10}$ = H R^9 = Me, 2,3-*trans*	71
8	**43** : R^1 = H, $R^{2,3}$ = ONs 2,3-*trans*	**25** : R^4 = Me R^5 = Ns	Condition A	3"-Me-CCg (**12**) : R^6 = H, $R^{7,8,9}$ = H R^{10} = Me, 2,3-*trans*	73
9	**43** : R^1 = H, $R^{2,3}$ = ONs 2,3-*trans*	**22** : R^4 = Ns R^5 = Me	Condition A	4"-Me-CCg (**13**) : R^6 = H, $R^{7,8,10}$ = H R^9 = Me, 2,3-*trans*	79





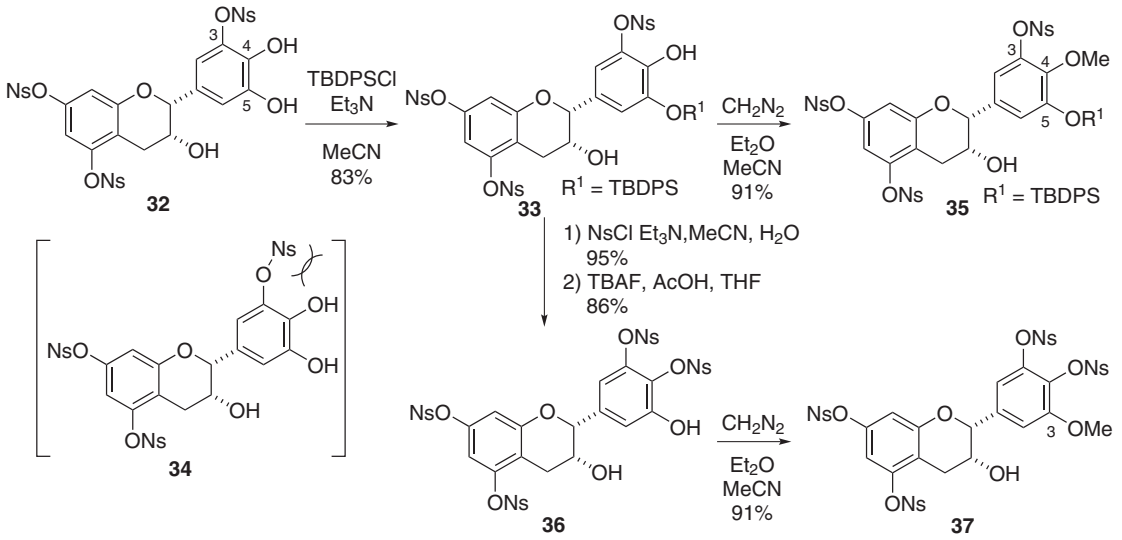
Scheme 6 Selective incorporation of Ns group via bridged boronic ester intermediate.

other natural catechins (GC, EC and C) to construct a diverse catechin library.

Synthesis of theaflavins

Theaflavin (**4**) is an oxidative dimer of catechin derivatives (Figure 2),[27–30] which is found in black tea. It has a number of biological activities.[31] Although many synthetic studies of catechin derivatives have been reported,[32–34] there are only a few reports of the synthesis of **4** by means of enzymatic oxidation.[32,35]

Recently, Nakatsuka and Yanase's group reported a novel oxidative coupling of *o*-quinone **45** and pyrogallol derivative **46** based on their proposed biosynthetic pathway,[35] as shown in Scheme 8. Although their model reaction proceeded in excellent yield, its application to the synthesis of theaflavin has not been reported to date. This is probably because oxidation precursors and theaflavin itself are unstable under strongly oxidizing conditions. We envisioned that the application of our Ns group[16–19] for protecting reactive phenols would enable efficient synthesis of theaflavins from catechins.



Scheme 7 Synthesis of selectively methylated epigallocatechin.

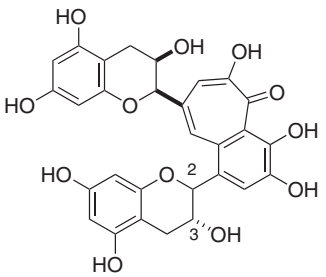
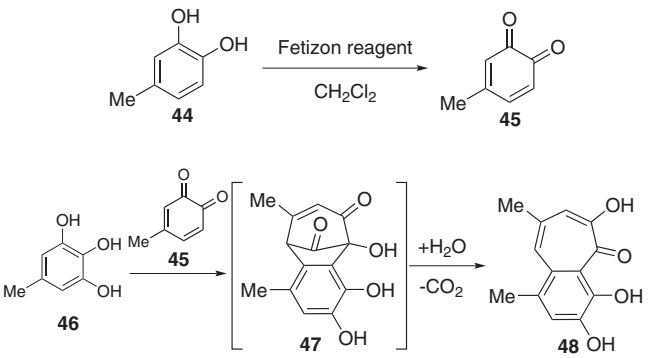


Figure 2 Structures of theaflavine (**4**) and neotheaflavine (**5**).



Scheme 8 Coupling reaction of *o*-quinone **45** and pyrogallol derivative **46** reported by Nakatsuka and Yanase.

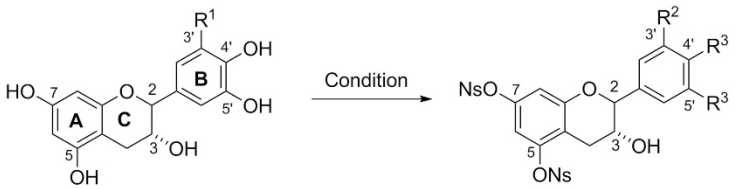
For the synthesis of theaflavin, we initially investigated selective incorporation of the Ns group into the A-ring of CC (**49**), EC (**50**) and EGC (**27**), as shown in Table 2.

Regioselective protection of the A-ring with a Ns group was performed utilizing the bridged boronic ester intermediate **54**[11] between neighboring phenolic hydroxyl groups on the B-ring (Scheme 9). Thus, after formation of the boronic ester by treatment of **27** with boronic acid in the presence of NaOH, reaction with two equivalents of NsCl and subsequent acidic hydrolysis of boronic ester exclusively provided **53** (Table 2, entry 3). Although the boronic ester intermediate of **27** possesses a remaining phenolic hydroxyl group on the B-ring, steric hindrance appears to prevent reaction with NsCl. Similar reactions of **49** and **50** proceeded smoothly to provide **51** and **52** (entries 1 and 2).

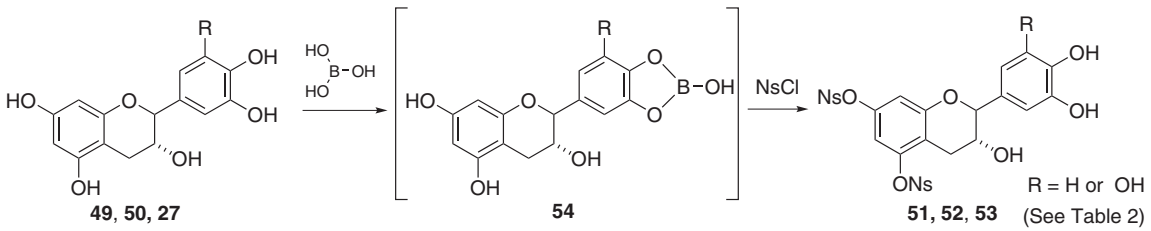
Having succeeded in selective protection of the A-ring, the next challenge is oxidation of the catechol group in **51** and **52**. First, we optimized the oxidation conditions using **51**, which is derived from less expensive **49**. As shown in Scheme 10, the best result was obtained by oxidation with $Pb(OAc)_4$ in MeCN at 0 °C, affording the desired quinone **55** in good yield. Utilizing $Pb(OAc)_4$ as an oxidant has the advantage that lead derivatives can be easily removed from the reaction medium by celite filtration after completion of the reaction. Furthermore, the electron-withdrawing nature of the Ns group would enhance the stability of the A-ring during the reaction with the strong oxidant $Pb(OAc)_4$. Although other various oxidants (such as Fetizon reagent and $PhI(OAc)_2$) were tested, they did not efficiently provide the *o*-quinone for the next reaction without the need for purification.

Next, we tested the coupling reaction of quinone **55** with pyrogallol derivative **53** (Scheme 11). As quinone **55** was labile during purification, crude **55** was used directly for the coupling reaction. Gratifyingly, treatment of three equivalents of **55** with **53** in a mixture of MeCN and CH_2Cl_2, followed by addition of H_2O, provided the desired **56** in moderate yield. Considering the reaction mechanism shown in Scheme 12, at least two equivalents of *o*-quinone should theoretically be consumed in the two oxidation steps (**58**–**59** and **61**–**62**). Furthermore, addition of MS3A to the reaction mixture before the addition of H_2O was essential for efficient conversion. MS3A might have a significant role in the oxidation step from **58** to **59**, although the mechanism involved remains to be established. After separation from **51** (generated by reduction of **55**), deprotection of the Ns group of **56** was accomplished by treatment with thiophenol and cesium carbonate to provide neotheaflavin (**5**). No decomposition of the reactive benzotropolone ring was observed during the coupling and deprotection processes.

Table 2 Regioselective incorporation of Ns group into the A-ring of catechins



Entry	*Catechin*	*Condition*	*Product*	*Yield(%)*
1	**49** : R^1 = H, 2,3-*trans*	exess $B(OH)_3$, NaOH aq. (pH 9.0); NsCl (2 eq), toluene	5,7-Ns-CC (**51**): R^2 =H, R^3 = OH	70
2	**50** : R^1 = H, 2,3-*cis*	exess $B(OH)_3$, NaOH aq. (pH 9.0); NsCl (2 eq), toluene	5,7-Ns-EC (**52**): R^2 =H, R^3 = OH	63
3	**27** : R^1 = OH, 2,3-*cis*	exess $B(OH)_3$, NaOH aq. (pH 9.0); NsCl (2 eq), toluene	5,7-Ns-EGC (**53**): R^2, R^3 = OH	52
4	**27** : R^1 = OH, 2,3-*cis*	exess $B(OH)_3$, NaOH aq. (pH 9.0); NsCl (3 eq), toluene	5,7,3'-Ns-EGC(**32**): R^2 =ONs, R^3 = OH	40
5	**27** : R^1 = OH, 2,3-*cis*	NsCl, Et_3N, MeCN, -20 °C	5,7,3',4',5'-Ns-EGC(**28**): R^2, R^3 = ONs	94



Scheme 9 Regioselective incorporation of Ns group into the A-ring.

This benzotropolone ring-forming reaction was also applicable to the synthesis of theaflavin (**4**) and its derivatives, as shown in Scheme 13. Upon treatment of Ns-protected epicatechin (**52**) with $Pb(OAc)_4$, the desired oxidation reaction proceeded smoothly to provide the *o*-quinone **63**. The coupling reaction with **53** was carried out without purification of the *o*-quinone intermediate **63** to give benzotropolone intermediate **64**. Finally, deprotection of Ns group afforded theaflavin (**4**).[36] The lower yield of **4** in comparison with **5** might be a result of instability of the *o*-quinone intermediate derived from *cis*-benzopyran **52**.

This oxidation–coupling strategy was also applied to the coupling between pyrogallol (**65**) and gallate **66** to give **67** and **68**, respectively (Table 3). As compounds similar to **68**, which is derived from oxidative coupling with gallate derivatives, have been isolated from tea,[8] this method would be useful to synthesize derivatives for SAR study.

In summary, we have shown that the Ns group is an excellent protecting group for labile polyphenols; it can be easily deprotected under mild conditions, and its electron-withdrawing nature improves the stability of polyphenol during synthetic manipulations. Utilizing the Ns group to protect phenols and to block undesired oxidation reactions, we were able to develop an efficient and practical method for regio- and stereoselective methylation of catechins and theaflavins. Further applications, as well as structure–biological activity relationship studies of the synthesized derivatives, are under investigation in our laboratory.

EXPERIMENTAL SECTION

General experimental details

NMR [^{1}H NMR (270 MHz), ^{13}C NMR (68 MHz)] spectra were determined on a JEOL EX-270 instrument (Tokyo, Japan), and [^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)] spectra were determined on JEOL α-500 instrument (Tokyo, Japan). Chemical shifts for ^{1}H NMR were reported in p.p.m. downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were referenced to solvent peaks: δ_C 77.0 for $CDCl_3$, δ_C 29.8 for acetone-d_6, δ_C 118.3 for CD_3CN and δ_C 49.0 for CD_3OD. HR-MS were obtained on either JEOL MStation JMS-700 or JMS-GCmate II (Tokyo, Japan). Fast atom bombardment (FAB) mass spectra were obtained with a mixture of 3-nitrobenzylalcohol and magic bullet as a matrix.

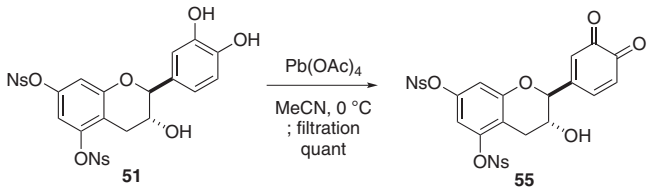
Analytical TLC was performed on Merck (Tokyo, Japan) precoated analytical plates, 0.25-mm thick, silica gel 60 F_{254}. Preparative TLC separations were made on 7 × 20-cm plates prepared with a 0.25-mm layer of Merck silica gel 60 F_{254}. Compounds were eluted from the adsorbent with 10% methanol in chloroform. Column chromatography was carried out with KANTO CHEMICAL (Tokyo, Japan) Silica Gel 60 N (spherical, neutral) 63–210 μm. Reagents and solvents were commercial grades and were used as supplied with following exceptions: dichloromethane, diethylether, *n*-hexane, tetrahydrofuran and toluene, dried over molecular sieves 4A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Experimental procedures and characterization data

*Allyl gallate (**20**).* To a mixture of gallic acid monohydrate (50.0 g, 266 mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

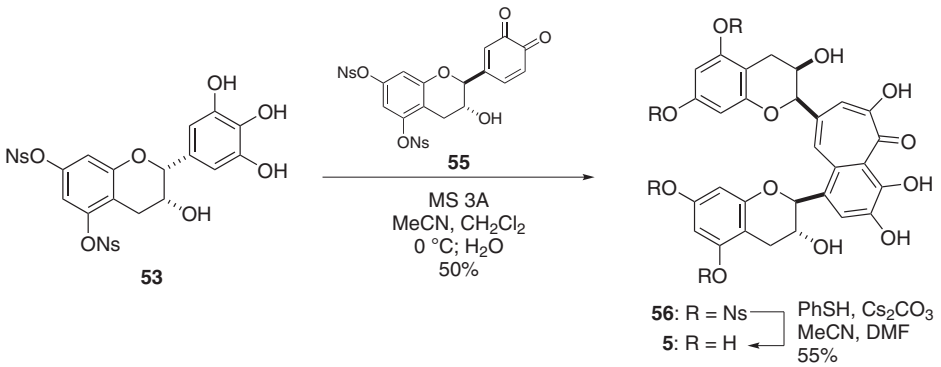
(EDCI) (61.2 g, 319 mmol) and 4-Dimethylaminopyridine (DMAP) (3.25 g, 26.6 mmol) was added allyl alcohol (200 ml) at room temperature, then heated at 60 °C for 4 h. The resulting mixture was quenched with 2 N HCl and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to afford **20** (48.7 g, 87%) as a light tan solid. HR-MS (FAB) calculated for $C_{10}H_{11}O_5$ $[M+H]^+$211.0606, found 211.0593; IR (neat) 3367, 1701, 1610, 1388, 1256, 1198 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.13 (2H, s), 5.97–6.11 (1H, m), 5.37 (1H, dq, $J_{1,2}=17.1$, 1.8 Hz), 5.22 (1H, dq, $J_{1,2}=10.6$, 1.8 Hz), 4.71 (2H, dt, $J_{1,2}=5.5$, 1.8 Hz); ^{13}C NMR (68 MHz, acetone-d_6) δ 166.3, 146.0, 138.8, 133.9, 121.7, 117.6, 109.8, 65.4.

*Allyl 3,5-dihydroxy-4-methoxybenzoate (**21**).* To a suspension of **20** (1.50 g, 7.15 mmol) in N,N-dimethylformamide (DMF) (20 ml) were added Li_2CO_3 (1.32 g, 17.9 mmol) and methyl iodide (1.11 ml, 17.9 mmol) at 50 °C. The mixture was stirred at 50 °C for 20 h. The reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (1–3% MeOH in CH_2Cl_2) to afford **21** (1.83 g, 68%) as a colorless solid. HR-MS (FAB) calculated for $C_{11}H_{12}O_5$ $[M]^+$ 224.0685, found 224.0705; IR (neat) 3369, 1701, 1597, 1524, 1375, 1234, 1193 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, s), 5.97–6.05 (1H, m), 5.40 (1H, dq, $J_{1,2}=17.2$, 1.4 Hz), 5.22 (1H, dq, $J_{1,2}=10.4$, 1.4 Hz), 4.79 (2H, dt, $J_{1,2}=5.5$, 1.4 Hz), 3.97 (3H, s); ^{13}C NMR (68 MHz, acetone-d_6) δ 166.1, 151.3, 133.8, 126.4, 117.8, 109.9, 109.8, 65.7, 60.6.

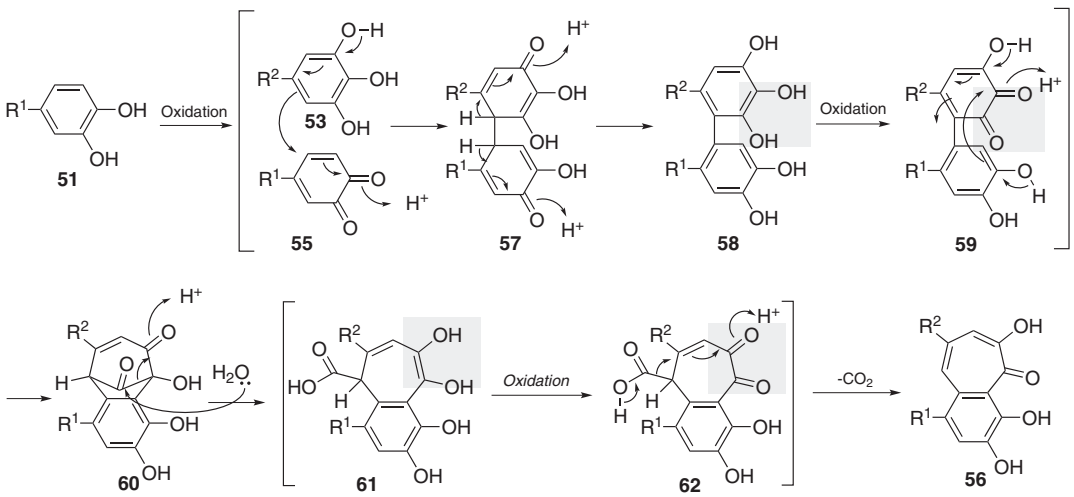


Scheme 10 Oxidation of **51** to *o*-quinone **55**.

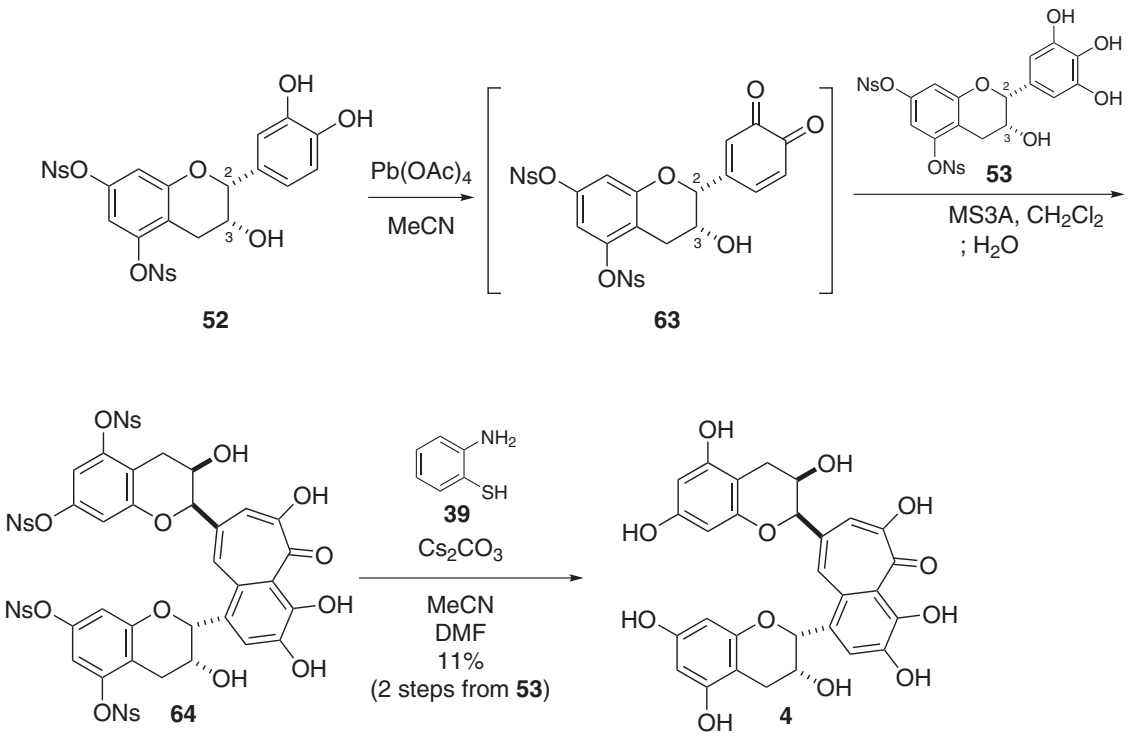
*3,5-Di(2-nitrobenzenesulfoxy)-4-methoxybenzoic acid (**22**).* To a solution of **21** (400 mg, 1.79 mmol) in MeCN (4 ml) were added triethylamine (1.12 ml, 8.04 mmol) and 2-nitrobenzenesulfonyl chloride (872 mg, 3.93 mmol) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction mixture was quenched with 2 M HCl and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2) to afford crude (954 mg) as a colorless amorphous. To a suspention of *p*-toluenesulfinic acid (343 mg, 1.92 mmol) in H_2O (16 ml) were added a solution of the crude and tetrakis(triphenylphosphine) palladium (0) (92.0 mg, 800 µmol) in THF (32 ml) at room temperature. The mixture was stirred at room temperature for 1 h. To the resulting mixture were added CH_2Cl_2 and H_2O, and then organic layer was extracted with H_2O. The combined aqueous phases were acidified with 2 M HCl (up to pH 3.0) and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford **22** (743 mg, 82%, two steps) as a colorless solid. HR-MS (FAB) calculated for $C_{20}H_{15}N_2O_{13}S_2$ $[M+H]^+$555.0016, found 555.0017; IR (neat) 3026, 1703,



Scheme 11 Synthesis of neotheaflavin (**5**) by oxidative coupling reaction of **53** and **55**.

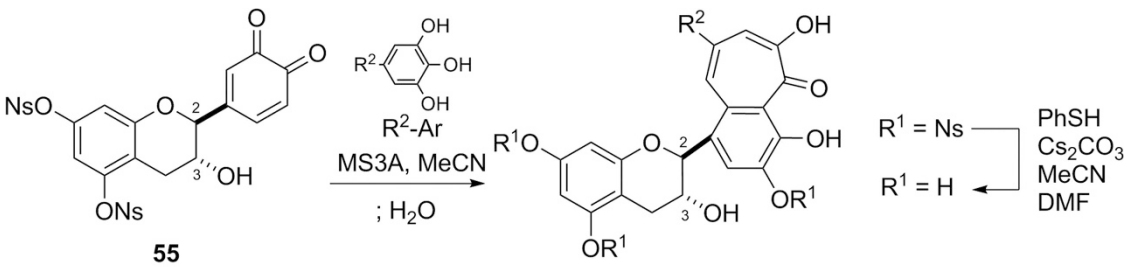


Scheme 12 Proposed mechanism of the coupling reaction of quinone and pyrogallol according to Nakatsuka and Yanase.



Scheme 13 Synthesis of theaflavin (**4**).

Table 3 Synthesis of benzotropolone derivatives



Entry	*R^2-Ar*	*Product*	*Yield (%) (2 steps from R^2-Ar)*
1	**65**: R^2 = H	**67**	13
2	**66**: R^2 =CO_2Me	**68**	24

1546, 1392, 1307, 1190, 1006 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.94–8.18 (8H, m), 7.78 (2H, s), 3.72 (3H, s); ^{13}C NMR (68 MHz, acetone-d_6) δ 164.8, 150.5, 143.4, 137.7, 132.6, 128.5, 127.0, 126.2, 125.6, 62.7.

*Allyl 4,5-dihydroxy-3-methoxybenzoate (**24**).* To a suspension of **20** (300 mg, 1.43 mmol) in H_2O (20 ml) was added sodium tetraborate decahydrate (1.40 g, 3.67 mmol), then the mixture was stirred at room temperature for 1 h. After stirring, dimethyl sulfate (0.523 ml, 5.53 mmol) and 6.5 M NaOH (25 ml) were added to the reaction mixture, which was stirred at room temperature for 12 h. The reaction mixture was acidified with concentrated H_2SO_4 (up to pH 2.0) and stirred at room temperature for 1 h. The resulting mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated to afford **24** (320 mg, 85%) as a colorless solid. HR-MS (FAB) calculated for $C_{11}H_{12}O_5$[M+H]$^+$224.0685, found 224.0705; IR (neat) 3371, 1710, 1602, 1531, 1382, 1246, 1192 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.23 (1H, d, J=2.0 Hz), 7.16 (1H, d, J =2.0 Hz), 5.98–6.10 (1H, m), 5.36 (1H dq, $J_{1,2}$=17.1, 1.5 Hz), 5.21 (1H, dq, $J_{1,2}$=10.4, 1.5 Hz), 4.73 (2H, dt, $J_{1,2}$=5.5, 1.5 Hz), 3.87 (3H, s); ^{13}C NMR (68 MHz, acetone-d_6) δ 166.3, 148.5, 145.8, 139.7, 133.8, 121.6, 1177.8, 111.6, 105.7, 65.6, 56.5.

*4,5-Di(2-nitrobenzenesulfoxy)-3-methoxybenzoic acid (**25**).* In a similar manner to that used to prepare **22**, treatment of **24** gave **25** (95%, two steps) as a colorless solid. HR-MS (FAB) calculated for $C_{20}H_{15}N_2O_{13}S_2$ [M+H]$^+$555.0016, found 555.0017; IR (neat) 3008, 1705, 1556, 1385, 1194, 1078, 970 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.90–8.13 (8H, m), 7.68 (1H, d, J=2.0 Hz), 7.52 (1H, d, J=2.0 Hz), 3.72 (3H, s); ^{13}C NMR (68 MHz, acetone-d_6) δ 165.4, 154.5, 143.3, 137.8, 137.0, 133.9, 133.6, 132.2, 131.5, 130.5, 128.5, 126.2, 125.9, 117.2, 113.7, 57.1.

*3,4,5-Tri(2-nitrobenzenesulfoxy)benzoic acid (**26**).* In a similar manner to that used to prepare **22**, treatment of **20** gave **26** (86%) as a colorless solid. HR-MS

(FAB) calculated for $C_{25}H_{15}N_3O_{17}S_3Na$ $[M+Na]^+$747.9461, found 747.9468; IR (neat) 3437, 1701, 1541, 1400, 1305, 1193, 1091, 1014 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.15–7.85 (14H, m); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.5, 148.5, 148.1, 143.0, 138.2, 137.4, 137.1, 133.3, 132.0, 131.8, 131.2, 128.3, 126.9, 125.6, 124.0.

*5-((2R,3R)-3-Hydroxy-5,7-bis(2-nitrophenylsulfonyloxy)chroman-2-yl)benzene-1,2,3-triyl tris(2-nitrobenzenesulfonate) (**28**).* To a solution of **27** (100 mg, 0.327 mmol) in MeCN (20 ml) were added triethylamine (0.453 ml, 3.27 mmol) and 2-nitrobenzenesulfonyl chloride (362 mg, 1.63 mmol) at −20 °C. The mixture was stirred at −20 °C for 1.5 h. The reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2) to afford **28** (377 mg) as a colorless amorphous. HR-MS (FAB) calculated for $C_{45}H_{30}N_5O_{27}S_5$ $[M+H]^+$1231.9732, found 1231.9751; $[\alpha]^D_{20}$ = −5.33 (*c* 1.00, acetone); IR (neat) 3406, 1701, 1618, 1589, 1542, 1421, 1388, 1362, 1305, 1222, 1193, 1114, 1008 cm^{-1}; ^1H NMR (270 MHz, CD_3CN) δ 7.70–8.05 (20H, m), 7.24 (2H, s), 6.66 (1H, d, *J* = 2.6 Hz), 6.44 (1H, d, *J* = 2.6 Hz), 5.01 (1H, m), 4.05 (1H, m), 3.04 (1H, br s), 2.88–2.72 (2H, m); ^{13}C NMR (68 MHz, CD_3CN) δ 156.5, 149.5, 149.2, 148.9, 148.3, 143.5, 141.1, 138.0, 137.9, 137.7, 135.2, 134.1, 134.1, 134.0, 133.8, 133.1, 133.0, 132.8, 132.6, 129.3, 128.2, 127.9, 127.5, 126.4, 126.3, 122.1, 118.3, 115.7, 110.7, 109.9, 78.3, 64.2, 29.3.

*5-(2R,3R)-5,7-Bis(2-nitrophenylsulfonyloxy)-2-(3,4,5-tris(2-nitrophenylsulfonyloxy) phenyl) chroman-3-yl-3-methoxy-4,5-bis(2-nitrophenylsulfonyloxy)benzoate (**29**).* **28** (700 mg, 0.568 mmol), **25** (628 mg, 1.14 mmol), EDCI (327 mg, 1.70 mmol) and DMAP (13.9 mg, 0.114 mmol) were dissolved in CH_3CN (3 ml) and stirred at room temperature for 16 h. The resulting mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (25% hexane in CH_2Cl_2) to afford **29** (925 mg, 92%) as a colorless amorphous. $[\alpha]^D_{20}$ = −73.1 (*c* 0.85, acetone); HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$1789.9383, found 1789.9386; IR (neat) 1708, 1618, 1593, 1545, 1419, 1394, 1366, 1305, 1193, 1121, 1001 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.80–8.14 (28H, m), 7.54 (2H, s), 7.34 (1H, d, *J* = 2.0 Hz), 7.23 (1H, d, *J* = 2.0 Hz), 6.97 (1H, d, *J* = 2.6 Hz), 6.66 (1H, d, *J* = 2.6 Hz), 5.73–5.78 (1H, m), 5.65 (1H, s), 3.59 (3H, s), 3.30 (1H, dd, $J_{1,2}$ = 17.5, 4.3 Hz), 3.23 (1H, dd, $J_{1,2}$ = 17.5, 3.3 Hz); ^{13}C NMR (68 MHz, acetone-d_6) δ 162.1, 155.6, 150.2, 148.7, 148.4, 147.8, 142.6, 141.0, 140.8, 138.5, 137.1, 137.0, 136.9, 133.1, 133.0, 133.0, 132.9, 132.3, 132.0, 131.9, 131.8, 127.6, 127.5, 127.4, 127.2, 126.9, 126.7, 125.4, 125.4, 125.3, 124.8, 124.7, 124.7, 122.5, 113.7, 110.4, 109.7, 76.4, 67.7, 62.0, 26.0.

*(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4,5-dihydroxy-3-methoxybenzoate (**2**).* To a suspension of Cs_2CO_3 (3.61 g, 11.3 mmol) in MeCN (6 ml) were added thiophenol (1.16 ml, 5.75 mmol) and **29** (800 mg, 0.452 mmol) at 0 °C. The mixture was stirred at room temperature for 3.5 h. The reaction was quenched with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (7% MeOH in CH_2Cl_2) to afford **2** (174 mg, 81%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ $[M+Na]^+$495.0904, found 495.0873; $[\alpha]^D_{20}$ = −186.2 (*c* 1.00, 50% acetone in H_2O); IR (neat) 3327, 1701, 1610, 1340, 1229 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.05 (1H, d, *J* = 1.9 Hz), 7.01 (1H, d, *J* = 1.9 Hz), 6.50 (2H, s), 5.96 (1H, d, *J* = 2.6 Hz), 5.95 (1H, d, *J* = 2.6 Hz), 5.49 (1H, m), 5.00 (1H, s), 3.81 (3H, s), 2.99 (1H, dd, $J_{1,2}$ = 17.5, 4.3 Hz), 2.86 (1H, dd, $J_{1,2}$ = 17.5, 3.0 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.7, 157.9, 157.8, 157.2, 149.0, 146.8, 146.0, 140.6, 133.7, 130.9, 121.5, 111.9, 106.8, 106.3, 99.4, 96.5, 95.8, 78.5, 70.4, 56.6, 26.6.

*5-(2R,3R)-5,7-Bis(2-nitrophenylsulfonyloxy)-2-(3,4,5-tris(2-nitrophenylsulfonyloxy) phenyl) chroman-3-yl-4-methoxy-3,5-bis(2-nitrophenylsulfonyloxy)benzoate (**30**).* In a similar manner to that used to prepare **29**, treatment of **28** with **22** gave **30** (97%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$1789.9383, found 1789.9386; $[\alpha]^D_{20}$ = −73.1 (*c* 0.85, acetone); IR (neat) 1708, 1618, 1593, 1545, 1419, 1394, 1366, 1305, 1193, 1121, 1001 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.80–8.14 (28H, m), 7.57 (2H, s), 7.46 (2H, s), 6.98 (1H, d, *J* = 2.6 Hz), 6.66 (1H, d, *J* = 2.6 Hz), 5.74 (1H, m), 5.60 (1H, s), 3.63 (3H, s), 3.28 (1H, dd, $J_{1,2}$ = 17.5, 4.3 Hz), 3.10 (1H, dd, $J_{1,2}$ = 17.5, 3.3 Hz); ^{13}C NMR (126 MHz, acetone-d_6) δ 162.2, 155.3, 150.2, 148.8, 148.4, 148.2, 147.7, 142.9, 142.7, 138.7, 137.2, 136.9, 136.9, 134.4, 133.2, 133.1, 133.1, 133.0, 132.3, 132.1, 132.0, 131.7, 131.6, 128.3, 127.8, 127.1, 126.9, 126.6, 125.5, 125.5, 125.4, 124.9, 124.8, 121.2, 113.8, 110.4, 109.9, 75.9, 67.4, 61.9, 26.0.

*(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,5-dihydroxy-4-methoxybenzoate (**3**).* In a similar manner to that used to prepare **2**, treatment of **30** gave **3** (81%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ $[M+Na]^+$495.0904, found 495.0896; $[\alpha]^D_{20}$ = −171.5 (*c* 1.20, 50% acetone in H_2O); IR (neat) 3367, 1701, 1604, 1348, 1236 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 6.91 (2H, s), 6.49 (2H, s), 5.95 (2H, s), 5.53 (1H, m), 4.97 (1H, s), 3.81 (3H, s), 2.99 (1H, dd, $J_{1,2}$ = 17.5, 4.6 Hz), 2.84 (1H, dd, $J_{1,2}$ = 17.5, 2.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 167.2, 157.9, 157.8, 157.2, 151.5, 146.7, 141.1, 133.8, 130.7, 126.6, 110.3, 106.8, 99.3, 96.5, 95.9, 78.5, 70.3, 60.7, 26.8.

*(2R,3R)-2-(3,4-Dihydroxy-5-(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**32**).* To a solution of boric acid (4.64 g, 80.3 mmol) and NaOH (800 mg) in H_2O (160 ml) was added **27** (492 mg, 1.61 mmol) and the resulting solution was adjusted to pH 9.0. Then, 2-nitrobenzenesulfonyl chloride (1.06 g, 4.83 mmol) in toluene (16 ml) was added dropwise over 30 min and stirred at room temperature for 3 h. The reaction was quenched with 2 M HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (1–3% MeOH in CH_2Cl_2) to afford **32** (560 mg, 40%) as a pale yellow solid. HR-MS (FAB) calculated for $C_{33}H_{23}N_3O_{19}S_3Na$ $[M+Na]^+$883.9986, found 883.9965; $[\alpha]^D_{20}$ = +10.6 (*c* 1.28, acetone); IR (neat) 3422, 1701, 1618, 1591, 1541, 1440, 1388, 1358, 1305, 1191, 1111, 995 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 7.80–8.20 (12H, m), 6.99 (1H, d, *J* = 2.3 Hz), 6.71 (1H, d, *J* = 2.3 Hz), 6.62 (1H, d, *J* = 2.3 Hz), 6.50 (1H, d, *J* = 2.3 Hz), 4.99 (1H, m), 4.22 (1H, m), 2.80–2.98 (2H, m); ^{13}C NMR (68 MHz, acetone-d_6) δ 157.3, 149.5, 148.2, 147.3, 138.9, 138.2, 137.8, 137.0, 133.9, 133.6, 133.3, 133.0, 132.9, 132.6, 130.2, 129.5, 128.4, 127.7, 126.3, 126.2, 125.8, 116.0, 114.1, 113.4, 110.3, 109.1, 79.4, 64.8, 29.6.

*(2R,3R)-2-(3-tert-Butyldiphenylsilyloxy-4-hydroxy-5-(2-nitrophenylsulfonyloxy) phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**33**).* To a solution of **32** (200 mg, 0.182 mmol) in MeCN (0.4 ml) were added triethylamine (0.196 ml, 1.09 mmol) and TBDPSCl (197 mg, 0.545 mmol) at −20 °C, then the resulting solution was stirred at −20 °C for 3 h. The reaction mixture was quenched with 2 M HCl and extracted with CH_2Cl_2. The combined organic phases were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (50% ethyl acetate in hexane) to afford **33** (211 mg, 83%) as a pale yellow solid. HR-MS (FAB) calculated for $C_{33}H_{23}N_3O_{19}S_3Na$ $[M+Na]^+$1122.1163, found 1122.1191; $[\alpha]^D_{20}$ = −0.68 (*c* 1.35, acetone); IR (neat) 3448, 1707, 1618, 1591, 1544, 1441, 1388, 1364, 1305, 1193, 1112, 997 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ, 7.36–8.13 (23H, m), 6.77 (1H, d, *J* = 2.0 Hz), 6.51 (1H, d, *J* = 2.0 Hz), 6.43 (1H, d, *J* = 2.0 Hz), 6.37 (1H, d, *J* = 2.0 Hz), 4.58 (1H, m), 3.73 (1H, m), 2.82–2.86 (2H, m), 1.09 (9H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.4, 148.3, 147.1, 144.4, 140.1, 136.4, 135.9, 135.8, 135.5, 135.4, 135.3, 132.6, 132.3, 132.3, 132.1, 130.6, 130.6, 128.1, 127.7, 125.0, 124.9, 124.8, 116.0, 114.3, 113.9, 110.0, 109.1, 64.6, 28.0, 26.6, 19.5.

*(2R,3R)-2-(3-tert-Butyldiphenylsilyloxy-4-methoxy-5-(2-nitrophenylsulfonyloxy) phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**35**).* To a solution of **33** (125 mg, 0.110 mmol) in MeCN (1 ml) were added diazomethane (Et_2O solution) until color of the solution became yellow at 0 °C. The resulting solution was stirred at 0 °C for 10 min. The reaction was quenched with acetic acid and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (50% ethyl acetate in hexane) to afford **35** (115 mg, 91%) as a pale yellow solid. HR-MS (FAB)

calculated for $C_{33}H_{23}N_3O_{19}S_3Na$ [M+Na]$^+$1136.1320, found 1136.1298; $[\alpha]^D_{20}=-9.17$ (*c* 1.25, acetone); IR (neat) 3420, 1709, 1618, 1591, 1550, 1441, 1391, 1360, 1308, 1196, 1113, 997 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ, 8.08–7.36 (22H, m), 6.71 (1H, d, $J=2.4$ Hz), 6.50 (1H, d, $J=2.4$ Hz), 6.43 (1H, d, $J=2.4$ Hz), 6.40 (1H, d, $J=2.4$ Hz), 4.58 (1H, m), 3.84 (3H, s), 3.71 (1H, m), 2.89 (1H, dd, $J_{1,2}=17.7$, 2.4 Hz), 2.89 (1H, dd, $J_{1,2}=17.7$, 4.0 Hz), 1.09 (9H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.3, 150.3, 148.6, 148.3, 147.1, 143.1, 135.9, 135.8, 135.5, 135.4, 135.3, 132.6, 132.3, 132.3, 132.1, 132.0, 131.9, 131.8, 130.4, 130.3, 128.2, 128.0, 128.0, 125.0, 124.9, 124.7, 117.8, 114.1, 113.9, 110.0, 109.1, 64.5, 61.3, 28.0, 26.4, 19.5.

*(2R,3R)-2-(3-tert-Butyldiphenylsilyloxy-4-methoxy-5-(2-nitrophenylsulfonyloxy) phenyl)-5,7-bis(2-nitrophenylsulfonyloxy)-chroman-3-yl-3,4,5-tris(2-nitrophenyl-sulfonyloxy)benzoate (**69**)*. In a similar manner to that used to prepare **29**, treatment of **35** with **26** gave **69** (86%) as a colorless solid. HR-MS (FAB) calculated for $C_{75}H_{56}N_6O_{35}SiS_6Na$ [M+Na]$^+$1843.0778, found 1843.0771; $[\alpha]^D_{20}=-42.3$ (*c* 1.00, acetone); IR (neat) 1711, 1618, 1591, 1545, 1442, 1391, 1364, 1308, 1193, 1114, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–8.03 (34H, m), 6.68 (1H, d, $J=1.9$ Hz), 6.67 (1H, d, $J=1.9$ Hz), 6.60 (1H, d, $J=2.0$ Hz), 6.26 (1H, d, $J=2.0$ Hz), 5.04 (1H, m), 4.64 (1H, m), 3.70 (3H, s), 2.95 (1H, dd, $J_{1,2}=18.0$, 4.6 Hz), 2.80 (1H, dd, $J_{1,2}=18.0$, 1.5 Hz), 1.02 (9H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 161.4, 155.1, 150.1, 148.6, 148.4, 148.2, 148.2, 148.0, 147.4, 143.6, 143.1, 143.1, 139.0, 136.3, 136.3, 136.1, 135.9, 135.4, 135.3, 133.0, 132.9, 132.7, 132.6, 132.3, 132.1, 131.9, 131.9, 131.7, 131.1, 130.4, 130.4, 129.2, 128.9, 128.0, 128.0, 127.8, 127.7, 127.4, 125.4, 125.1, 125.0, 124.8, 124.1, 117.6, 114.3, 112.4, 110.2, 110.0, 67.4, 61.3, 26.5, 26.3, 19.5.

*(2R,3R)-2-(3-Hydroxy-4-methoxy-5-(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy)-chroman-3-yl-3,4,5-tris(2-nitrophenylsulfonyloxy)benzoate (**70**)*. To a solution of **69** (400 mg, 0.220 mmol) and acetic acid (0.0377 ml, 0.661 mmol) in tetrahydrofuran (THF) (4.6 ml) was added TBAF (1.0 M solution in THF, 0.266 ml, 0.266 mmol) at 0 °C, then the resulting solution was stirred at 0 °C for 15 min. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford crude **70** (320 mg) as a colorless solid. The crude **70** was used in the next step without further purification. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.62–8.07 (24H, m), 7.57 (2H, s), 6.83 (1H, d, $J=1.8$ Hz), 6.82 (1H, d, $J=1.8$ Hz), 6.69 (1H, d, $J=1.8$ Hz), 6.65 (1H, d, $J=1.8$ Hz), 5.50 (1H, m), 4.06 (1H, m), 3.80 (3H, s), 3.19 (1H, dd, $J_{1,2}=18.3$, 4.3 Hz), 3.03 (1H, dd, $J_{1,2}=18.3$, 4.3 Hz)

*(2R,3R)-2-(3,5-Dihydroxy-4-methoxyphenyl)-5,7-dihydroxychroman-3-yl 3,4,5-trihydroxybenzoate (**7**)*. In a similar manner to that used to prepare **2**, treatment of crude **70** gave **7** (77%, 2 steps) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ [M+Na]$^+$ 495.0904, found 495.0942; $[\alpha]^D_{20}=-147.6$ (*c* 1.00, 50% acetone in H_2O); IR (neat) 3346, 1701, 1608, 1357, 1234 cm^{-1}; ^{1}H NMR (270 MHz, CD_3OD) δ 6.84 (2H, s), 6.43 (2H, s), 5.87 (2H, s), 5.44 (1H, m), 4.89 (1H, m), 3.66 (3H, s), 2.90 (1H, dd, $J_{1,2}=17.1$, 4.6 Hz), 2.75 (1H, dd, $J_{1,2}=17.1$, 2.3 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.6, 157.8, 157.0, 151.3, 146.2, 136.3, 136.0, 135.8, 129.8, 121.5, 110.3, 107.1, 99.4, 96.6, 95.9, 78.4, 69.8, 60.8, 26.8.

*(2R,3R)-2-(3-tert-Butyldiphenylsilyloxy-4,5-bis(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**71**)*. In a similar manner to that used to prepare **28**, treatment of **33** gave **71** (95%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{56}H_{44}N_4O_{23}SiS_4Na$ [M+Na]$^+$1307.0946, found 1307.0963; $[\alpha]^D_{20}=-9.25$ (*c* 0.84, acetone); IR (neat) 1709, 1618, 1591, 1548, 1440, 1391, 1360, 1306, 1196, 1113, 997 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ, 7.36–8.13 (26H, m), 6.60 (1H, d, $J=2.0$ Hz), 6.43 (1H, d, $J=2.0$ Hz), 6.42 (1H, d, $J=2.0$ Hz), 6.35 (1H, d, $J=2.0$ Hz), 4.51 (1H, m), 3.58 (1H, m), 2.88 (2H, m), 2.76 (1H, dd, $J=17.5$, 4.0 Hz), 1.08 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 150.7, 148.5, 148.3, 148.3, 148.2, 146.9, 142.4, 136.5, 136.0, 136.0, 135.9, 135.5, 135.4, 135.3, 132.8, 132.6, 132.6, 132.4, 132.4, 132.2, 132.1, 132.0, 131.7, 131.2, 131.0, 130.5, 130.4, 130.1, 128.0, 127.5, 125.1, 124.9, 124.6, 117.5, 113.8, 112.6, 109.9, 64.2, 60.4, 27.9, 26.0, 19.4.

*(2R,3R)-2-(3-Hydroxy-4,5-bis(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**36**)*. In a similar manner to that used to prepare **70**, treatment of **71** gave **36** (86%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{39}H_{26}N_4O_{23}S_4Na$ [M+Na]$^+$1068.9768, found 1068.9788; $[\alpha]^D_{20}=-1.41$ (*c* 1.80, acetone); IR (neat) 3429, 1701, 1612, 1591, 1543, 1438, 1389, 1364, 1194, 1113, 999 cm^{-1}; ^{1}H NMR (270 MHz, acetone-d_6) δ, 8.13–7.86 (16H, m), 7.17 (1H, d, $J=2.0$ Hz), 6.78 (1H, d, $J=2.0$ Hz), 6.74 (1H, d, $J=2.0$ Hz), 6.50 (1H, d, $J=2.0$ Hz), 5.12 (1H, m), 4.29 (1H, m), 2.98–2.90 (2H, m); ^{13}C NMR (125 MHz, acetone-d_6) δ 156.2, 151.6, 148.7, 148.6, 148.5, 148.4, 147.4, 142.3, 139.2, 137.1, 136.8, 136.0, 133.1, 132.9, 132.9, 132.8, 132.2, 132.2, 132.1, 131.9, 131.4, 130.1, 130.0, 127.8, 127.4, 126.8, 125.5, 125.5, 125.3, 125.1, 115.2, 114.9, 112.2, 109.7, 108.6, 78.3, 63.7, 29.8.

*(2R,3R)-2-(3-Methoxy-4,5-bis(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**37**)*. In a similar manner to that used to prepare **35**, treatment of **36** gave **37** (91%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{40}H_{28}N_4O_{23}S_4Na$ [M+Na]$^+$1082.9925, found 1082.9946; $[\alpha]^D_{20}=-3.18$ (*c* 0.56, acetone); IR (neat) 3451, 1701, 1618, 1591, 1541, 1439, 1389, 1356, 1306, 1194, 1113, 999 cm^{-1}; ^{1}H NMR (270 MHz, acetone-d_6) δ 8.13–7.90 (16H, m), 7.30 (1H, d, $J=2.0$ Hz), 6.94 (1H, d, $J=2.0$ Hz), 6.77 (1H, d, $J=2.6$ Hz), 6.51 (1H, d, $J=2.6$ Hz), 5.21 (1H, m), 4.37 (1H, m), 3.64 (3H, s), 2.98–2.94 (2H, m); ^{13}C NMR (68 MHz, acetone-d_6) δ 156.2, 153.3, 148.7, 148.6, 148.5, 148.3, 147.4, 142.2, 139.6, 137.1, 137.0, 136.8, 136.0, 133.1, 133.0, 132.9, 132.7, 132.2, 132.0, 131.9, 131.3, 130.8, 130.0, 127.9, 127.5, 126.8, 125.5, 125.5, 125.4, 125.1, 115.1, 113.4, 110.7, 109.8, 108.7, 78.5, 63.6, 54.2, 29.8.

*(2R,3R)-2-(3-Methoxy-4,5-bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy)-chroman-3-yl 3-methoxy-4,5-bis(2-nitrophenylsulfonyloxy) benzoate (**72**)*. **37** (20.0 mg, 0.0188 mmol), **25** (20.9 mg, 0.0377 mmol), EDCI (10.8 mg, 0.0563 mmol), DMAP (0.2 mg, 1.9 μmol) were dissolved in MeCN (0.25 ml) and the resulting solution was stirred at room temperature for 17 h. Then, the reaction mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford crude **72** as a colorless solid. The crude **72** was used in the next step without further purification. ^{1}H NMR (270 MHz, acetone-d_6) δ, 8.17–7.81 (28H, m, 28H), 7.37 (1H, d, $J=2.0$ Hz, 1H), 7.31 (1H, d, $J=2.0$ Hz), 7.24 (1H, d, $J=2.0$ Hz), 7.04 (1H, d, $J=2.0$ Hz), 6.96 (1H, d, $J=2.0$ Hz), 6.66 (1H, d, $J=2.0$ Hz), 5.82–5.77 (1H, m, 1H), 5.59–5.56 (1H, m, 1H), 3.60 (3H, s), 3.48 (3H, s), 3.32 (1H, dd, $J_{1,2}=17.8$, 4.0 Hz), 3.15 (1H, dd, $J_{1,2}=17.8$, 2.0 Hz).

*(2R,3R)-2-(4,5-Dihydroxy-3-methoxyphenyl)-5,7-dihydroxychroman-3-yl 3,4-dihydroxy-5-methoxybenzoate (**38**)*. In a similar manner to that used to prepare **2**, treatment of **72** with 2-aminothiophenol gave **38** (63%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{24}H_{23}O_{11}$ [M+H]$^+$487.1240, found 487.1229; $[\alpha]^D_{20}=-218.1$ (*c* 0.04, 50% acetone in H_2O); IR (neat) 3285, 1701, 1605, 1364, 1221; ^{1}H NMR (500 MHz, CD_3OD) δ 7.10 (1H, d, $J=2.0$ Hz), 7.02 (1H, d, $J=2.0$ Hz), 6.61 (1H, d, $J=2.0$ Hz), 6.58 (1H, d, $J=2.0$ Hz), 5.96 (2H, s), 5.52 (1H, m), 5.23 (1H, m), 3.79 (3H, s), 3.58 (3H, s), 3.01 (1H, dd, $J_{1,2}=17.1$, 4.6 Hz), 2.86 (1H, dd, $J_{1,2}=17.1$, 1.7 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 165.9, 156.5, 156.5, 148.0, 147.7, 144.9, 144.8, 139.2, 133.4, 129.3, 119.8, 110.6, 107.3, 104.9, 101.7, 98.1, 95.2, 94.4, 77.5, 68.9, 55.1, 54.9, 25.4.

*(2R,3R)-2-(3-Methoxy-4,5-bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy)-chroman-3-yl-3,4,5-tris(2-nitrophenylsulfonyloxy)benzoate (**73**)*. In a similar manner to that used to prepare **29**, treatment of **37** with **26** gave **73** (86%) as a colorless solid. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ [M+Na]$^+$1789.9383, found 1789.9396; $[\alpha]^D_{20}=-37.4$ (*c* 0.38, acetone); IR (neat) 1709, 1618, 1593, 1545, 1442, 1391, 1364, 1308, 1196, 1116, 1006 cm^{-1}; ^{1}H NMR (270 MHz, acetone-d_6) δ 8.20–7.80 (28H, m), 7.69 (2H, s), 7.31 (1H, d, $J=1.3$ Hz), 7.00 (1H, d, $J=1.3$ Hz), 6.96 (1H, d, $J=2.0$ Hz), 6.67 (1H, d, $J=2.0$ Hz), 5.81 (1H, m), 5.56 (1H, m), 3.49 (3H, s), 3.33 (1H, dd, $J_{1,2}=17.8$, 4.0 Hz), 3.13 (1H, dd, $J_{1,2}=17.8$, 2.0 Hz); ^{13}C NMR (68 MHz, acetone-d_6) δ 162.3, 156.4, 154.4, 149.2, 149.1, 148.6, 143.9, 143.3, 138.8, 138.1, 137.9, 137.7, 136.9, 134.1, 133.8, 133.7, 133.4, 133.0, 132.8, 132.5, 132.1, 130.6, 130.4, 129.2, 128.4, 128.0, 127.9, 127.6, 126.4, 126.3, 126.1, 125.8, 124.7, 114.4, 114.0, 111.2, 110.8, 110.5, 77.4, 69.0, 56.9, 26.8.

*(2R,3R)-2-(4,5-Dihydroxy-3-methoxyphenyl)-5,7-dihydroxychroman-3-yl 3,4,5-trihydroxybenzoate (**6**).* In a similar manner to that used to prepare **2**, treatment of **73** gave **6** (63%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ $[M+Na]^+$ 495.0904, found 495.0938; $[\alpha]^D_{20} = -148.9$ (*c* 0.325, 50% acetone in H_2O); IR (neat) 3332, 1703, 1618, 1365, 1244 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.05 (1H, d, $J=2.0$ Hz), 7.01 (1H, d, $J=2.0$ Hz), 6.51 (2H, s), 5.97 (1H, d, $J=2.0$ Hz), 5.95 (1H, d, $J=2.0$ Hz), 5.49 (1H, m), 4.99 (1H, m), 3.80 (3H, s), 2.99 (1H, dd, $J_{1,2}=17.1$, 4.6 Hz), 2.86 (1H, dd, $J_{1,2}=17.1$, 3.0 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 166.6, 157.1, 156.5, 148.6, 145.6, 145.3, 135.2, 134.0, 129.8, 129.0, 120.7, 109.5, 108.0, 102.6, 98.6, 95.8, 95.2, 78.2, 69.2, 55.6, 26.2.

*(2R,3R)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrophenylsulfonate) (**41**).* In a similar manner to that used to prepare **28**, treatment of (–)-Epicatechin gave **41** (92%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{39}H_{26}N_4O_{22}S_4$ $[M+H]^+$ 1052.9819, found 1052.9816; $[\alpha]^D_{20} = +3.83$ (*c* 1.06, acetone); IR (neat) 3404, 1705, 1620, 1591, 1550, 1440, 1394, 1346, 1306, 1182, 1110, 999 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.15–7.86 (16H, m), 7.57 (1H, dd, $J_{1,2}=8.6$, 2.0 Hz), 7.39 (1H, d, $J=8.6$ Hz), 7.38 (1H, d, $J=2.0$ Hz), 6.77 (1H, d, $J=2.4$ Hz), 6.51 (1H, d, $J=2.4$ Hz), 5.26 (1H, s), 4.33–4.26 (1H, m), 3.03–2.85 (2H, m); ^{13}C NMR (126 MHz, acetone-d_6) δ 156.2, 148.7, 148.5, 147.4, 140.8, 140.5, 140.1, 137.1, 137.0, 136.9, 136.9, 133.1, 133.1, 133.0, 132.9, 132.2, 132.0, 131.9, 131.7, 127.9, 127.7, 127.5, 127.3, 126.8, 125.5, 125.5, 125.4, 124.2, 122.9, 115.1, 109.7, 108.7, 78.2, 63.7, 29.3.

*(2R,3R)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy) chroman-3-yl 3-methoxy-4,5-bis(2-nitrophenylsulfonyloxy)benzoate (**74**).* In a similar manner to that used to prepare **29**, treatment of **41** with **25** gave **74** (97%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$ 1566.9831, found 1566.9817; $[\alpha]^D_{20} = -32.1$ (*c* 1.00, acetone); IR (neat) 1712, 1618, 1591, 1552, 1423, 1394, 1368, 1304, 1198, 1117, 1009 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 8.15–7.80 (28H, m), 7.62 (1H, dd, $J_{1,2}=8.6$, 2.0 Hz), 7.49 (1H, d, $J=2.0$ Hz), 7.35 (1H, d, $J=2.0$ Hz), 7.32 (1H, d, $J=8.6$ Hz), 7.22 (1H, d, $J=2.0$ Hz), 6.98 (1H, d, $J=2.0$ Hz), 6.66 (1H, d, $J=2.0$ Hz), 5.74 (1H, m), 5.63 (1H, s), 3.61 (3H, s), 3.33 (1H, dd, $J_{1,2}=17.8$, 4.0 Hz), 3.23 (1H, dd, $J_{1,2}=17.8$, 2.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.1, 155.6, 150.2, 148.7, 148.4, 147.8, 142.6, 141.0, 140.8, 138.5, 137.1, 137.0, 136.9, 133.1, 133.0, 133.0, 132.9, 132.3, 132.0, 131.9, 131.8, 127.6, 127.5, 127.4, 127.2, 126.9, 126.7, 125.5, 125.4, 125.4, 125.3, 124.8, 124.7, 124.7, 122.5, 113.7, 110.4, 109.7, 76.4, 67.7, 62.0, 26.0.

*(2R,3R)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,4-dihydroxy-5-methoxybenzoate (**8**).* In a similar manner to that used to prepare **2**, treatment of **74** gave **8** (87%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{10}Na$ $[M+Na]^+$ 479.0954, found 479.0906; $[\alpha]^D_{20} = -194.4$ (*c* 1.10, 50% acetone in H_2O); IR (neat) 3366, 1701, 1608, 1363, 1232 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.07 (1H, d, $J=2.0$ Hz), 7.02 (1H, d, $J=2.0$ Hz), 6.96 (1H, d, $J=2.0$ Hz), 6.80 (1H, dd, $J=7.9$, 2.0 Hz), 6.70 (1H, d, $J=7.9$ Hz), 5.98 (1H, d, $J=2.6$ Hz), 5.97 (1H, d, $J=2.6$ Hz), 5.51 (1H, m), 5.06 (1H, s), 3.81 (3H, s), 3.01 (1H, dd, $J=17.1$, 4.6 Hz), 2.88 (1H, dd, $J=17.1$, 2.6 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.6, 157.9, 157.8, 157.2, 149.0, 146.1, 146.0, 146.0, 140.6, 131.5, 121.5, 119.2, 116.0, 115.1, 111.9, 106.2, 99.3, 96.6, 95.8, 78.5, 70.4, 56.6, 26.7.

*(2R,3R)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy) chroman-3-yl 4-methoxy-3,5-bis(2-nitrophenylsulfonyloxy)benzoate (**75**).* In a similar manner to that used to prepare **29**, treatment of **41** with **22** gave **75** (99%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$ 1566.9831, found 1566.9839; $[\alpha]^D_{20} = -35.4$ (*c* 1.00, acetone); IR (neat) 1714, 1619, 1591, 1557, 1425, 1398, 1368, 1311, 1201, 1111, 1007 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 8.15–7.80 (28H, m, 28H), 7.59 (1H, dd, $J_{1,2}=8.6$, 2.0 Hz), 7.56 (2H, s), 7.40 (1H, d, $J=2.0$ Hz), 7.32 (1H, d, $J=8.6$ Hz), 6.98 (1H, d, $J=2.0$ Hz), 6.65 (1H, d, $J=2.0$ Hz), 5.71 (1H, m), 5.59 (1H, s), 3.69 (3H, s), 3.32 (1H, dd, $J_{1,2}=17.8$, 4.0 Hz), 3.10 (1H, dd, $J_{1,2}=17.8$, 2.0 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.1, 155.6, 150.2, 148.8, 148.5, 147.8, 142.6, 141.0, 140.8, 138.5, 137.0, 136.9, 133.1, 133.0, 132.9, 132.9, 132.3, 132.0, 131.9, 131.8, 127.6, 127.5, 127.4, 127.1, 126.9, 126.7, 125.5, 125.4, 125.3, 125.3, 124.8, 124.7, 124.7, 122.5, 113.7, 110.4, 109.7, 76.4, 67.7, 61.9, 26.0.

*(2R,3R)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,5-dihydroxy-4-methoxybenzoate (**9**).* In a similar manner to that used to prepare **2**, treatment of **75** gave **9** (84%) as a colorless amorphous. $[\alpha]^D_{20} = -217.3$ (*c* 0.75, 50% acetone in H_2O); IR (neat) 3367, 1705, 1605, 1371, 1240 cm^{-1}; HR-MS (FAB) calculated for $C_{23}H_{20}O_{10}Na$ $[M+Na]^+$ 479.0954, found 479.0906; ^1H NMR (270 MHz, CD_3OD) δ 6.93 (1H, d, $J=2.0$ Hz), 6.92 (2H, s), 6.80 (1H, dd, $J_{1,2}=8.0$, 2.0 Hz), 6.70 (1H, d, $J=8.0$ Hz), 5.97 (2H, s), 5.54 (1H, m), 5.04 (1H, s), 3.83 (3H, s), 3.01 (1H, dd, $J_{1,2}=17.8$, 4.6 Hz), 2.85 (1H, dd, $J_{1,2}=17.8$, 2.6 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.1, 157.9, 157.8, 157.2, 151.5, 146.0, 141.1, 131.4, 126.5, 119.3, 116.0, 115.0, 110.3, 99.3, 96.6, 95.9, 78.5, 70.3, 60.7, 26.8.

*5-((2S,3R)-3-Hydroxy-5,7-bis(2-nitrophenylsulfonyloxy)chroman-2-yl)benzene-1,2,3-triyl tris(2-nitrobenzenesulfonate) (**42**).* In a similar manner to that used to prepare **28**, treatment of (–)-gallocatechin gave **42** (94%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{45}H_{30}N_5O_{27}S_5$ $[M+H]^+$ 1231.9732, found 1231.9717; $[\alpha]^D_{20} = -1.61$ (*c* 1.00, acetone); IR (neat) 3406, 1701, 1618, 1589, 1542, 1421, 1388, 1362, 1305, 1222, 1193, 1114, 1008 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.15–7.85 (20H, m), 7.32 (2H, s), 6.74 (1H, d, $J=2.6$ Hz), 6.55 (1H, d, $J=2.6$ Hz), 5.00 (1H, d, $J=7.3$ Hz), 4.75 (1H, d, $J=5.1$ Hz), 3.90–3.97 (1H, m), 2.82 (1H, dd, $J_{1,2}=16.8$, 5.4 Hz), 2.66 (1H, dd, $J_{1,2}=16.8$, 8.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 155.2, 148.7, 148.5, 148.2, 148.0, 147.6, 142.8, 140.2, 137.2, 137.2, 137.1, 136.9, 134.6, 133.2, 133.2, 133.1, 132.9, 132.2, 132.1, 131.9, 131.6, 128.6, 127.3, 127.1, 126.7, 125.5, 121.5, 115.7, 109.7, 109.3, 80.2, 65.6, 27.8.

*5-(2S,3R)-5,7-Bis(2-nitrophenylsulfonyloxy)-2-(3,4,5-tris(2-nitrophenylsulfonyloxy) phenyl) chroman-3-yl-3-methoxy-4,5-bis(2-nitrophenylsulfonyloxy)benzoate (**76**).* In a similar manner to that used to prepare **29**, treatment of **42** with **25** gave **76** (93%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$ 1789.9383, found 1789.9375; $[\alpha]^D_{20} = +4.03$ (*c* 1.25, acetone); IR (neat) 1717, 1618, 1591, 1550, 1419, 1391, 1362, 1305, 1188, 1105, 1000 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.20–7.75 (28H, m), 7.56 (1H, d, $J=2.0$ Hz), 7.39 (2H, s), 7.33 (1H, d, $J=2.0$ Hz), 6.87 (1H, d, $J=2.0$ Hz), 6.66 (1H, d, $J=2.0$ Hz), 5.63 (1H, d, $J=5.8$ Hz), 5.44–5.40 (1H, m), 3.65 (3H, s), 3.06 (1H, dd, $J_{1,2}=17.8$, 6.3 Hz), 2.81 (1H, dd, $J_{1,2}=17.8$, 4.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.7, 154.5, 153.7, 148.7, 148.4, 148.2, 148.2, 148.1, 148.0, 143.2, 142.6, 138.8, 137.4, 137.3, 137.2, 137.0, 136.4, 133.2, 133.2, 133.0, 132.9, 132.2, 132.1, 132.0, 131.9, 131.7, 131.4, 129.6, 129.4, 128.2, 127.66, 127.1, 126.8, 126.6, 125.6, 125.5, 125.4, 125.2, 121.4, 116.4, 113.8, 113.0, 110.0, 109.9, 76.9, 68.7, 56.4, 23.1.

*(2S,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4-dihydroxy-5-methoxybenzoate (**10**).* In a similar manner to that used to prepare **2**, treatment of **76** gave **10** (81%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ $[M+Na]^+$ 495.0904, found 495.0873; $[\alpha]^D_{20} = +13.9$ (*c* 0.30, 50% acetone in H_2O); IR (neat) 3369, 1701, 1611, 1375, 1240 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.07 (1H, d, $J=2.0$ Hz), 7.01 (1H, d, $J=2.0$ Hz), 6.43 (2H, s), 5.96 (1H, d, $J=2.0$ Hz), 5.94 (1H, d, $J=2.0$ Hz), 5.35–5.25 (1H, m), 4.99 (1H, d, $J=6.6$ Hz), 3.81 (3H, s), 2.90 (1H, dd, $J_{1,2}=16.5$, 4.6 Hz), 2.70 (1H, dd, $J_{1,2}=16.5$, 6.0 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.6, 158.1, 157.7, 156.6, 149.1, 147.0, 146.2, 140.7, 134.1, 130.9, 121.5, 111.9, 106.6, 106.2, 99.7, 96.5, 95.6, 79.7, 71.7, 56.7, 24.7.

*5-(2S,3R)-5,7-Bis(2-nitrophenylsulfonyloxy)-2-(3,4,5-tris(2-nitrophenylsulfonyloxy) phenyl) chroman-3-yl-4-methoxy-3,5-bis(2-nitrophenylsulfonyloxy)benzoate (**77**).* In a similar manner to that used to prepare **29**, treatment of **42** with **22** gave **77** as a crude colorless amorphous. The crude **77** was used in the next step without further purification. ^1H NMR (500 MHz, acetone-d_6) δ 8.20–7.80 (28H, m), 7.68 (2H, s), 7.33 (2H, s), 6.86 (1H, d, $J=2.3$ Hz), 6.64 (1H, d, $J=2.3$ Hz), 5.63 (1H, d, $J=5.8$ Hz), 5.37–5.42 (1H, m), 3.67 (3H, s), 3.01 (1H, dd, $J_{1,2}=18.4$, 5.2 Hz), 2.71 (1H, dd, $J_{1,2}=18.4$, 4.6 Hz).

*(2S,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,5-dihydroxy-4-methoxybenzoate (**11**).* In a similar manner to that used to prepare **2**,

treatment of crude **77** gave **11** (71%, two steps) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{11}Na$ $[M+Na]^+$ 495.0904, found 495.0885; $[\alpha]^D_{20}=+13.7$ (*c* 0.25, 50% acetone in H_2O); IR (neat) 3300, 1701, 1604, 1377, 1238 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 6.95 (2H, s), 6.41 (2H, s), 5.96 (2H, s), 5.42–5.35 (1H, m), 5.04 (1H, d, $J=5.9$ Hz), 3.84 (3H, s), 2.80 (1H, dd, $J_{1,2}=16.5$, 5.3 Hz), 2.71 (1H, dd, $J_{1,2}=16.5$, 5.3 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.1, 158.1, 158.0, 157.6, 157.5, 156.3, 151.6, 147.0, 141.3, 134.0, 130.9, 126.5, 110.2, 106.4, 99.5, 79.2, 71.4, 60.7, 23.9.

*(2R,3S)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-3-hydroxychroman-5,7-diyl bis(2-nitrophenylsulfonate) (**43**)*. In a manner similar to that used to prepare **28**, treatment of (+)-catechin gave **43** (94%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{39}H_{26}N_4O_{22}S_4$ $[M+H]^+$ 1052.9819, found 1052.9843; $[\alpha]^D_{20}=+8.54$ (*c* 1.00, acetone); IR (neat) 3498, 1713, 1618, 1595, 1545, 1419, 1392, 1350, 1304, 1191, 1112, 1015 cm^{-1}; ^1H NMR (270 MHz, CD_3CN) δ 8.07–8.01 (4H, m), 7.91–7.71 (12H, m), 7.33–7.23 (3H, m), 6.74 (1H, d, $J=2.5$ Hz), 6.57 (1H, d, $J=2.5$ Hz), 4.83 (1H, d, $J=7.3$ Hz), 3.98 (1H, m), 2.98 (1H, dd, $J_{1,2}=17.0$, 5.0 Hz), 2.80 (1H, dd, $J_{1,2}=17.0$, 8.0 H); ^{13}C NMR (68 MHz, CD_3CN) δ 156.1, 149.3, 149.1, 148.9, 148.5, 141.8, 141.6, 140.7, 137.8, 137.7, 133.9, 133.8, 133.7, 133.1, 132.8, 132.7, 132.6, 128.4, 128.2, 128.0, 127.4, 126.2, 126.2, 125.4, 123.2, 116.3, 110.6, 110.1, 81.1, 66.1, 27.7.

*(2R,3S)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy) chroman-3-yl 3-methoxy-4,5-bis(2-nitrophenylsulfonyloxy)benzoate (**78**)*. In a similar manner to that used to prepare **29**, treatment of **43** with **25** gave **78** (74%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$ 1566.9831, found 1566.9819; $[\alpha]^D_{20}=+22.4$ (*c* 1.07, acetone); IR (neat) 1718, 1618, 1591, 1554, 1417, 1385, 1356, 1304, 1184, 1119, 1000 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.17–7.85 (28H, m), 7.54 (1H, d, $J=2.3$ Hz), 7.49 (1H, dd, $J=8.6$, 2.3 Hz), 7.39 (1H, d, $J=8.6$ Hz), 7.32 (1H, d, $J=2.3$ Hz), 7.31 (1H, d, $J=2.3$ Hz), 6.89 (1H, d, $J=2.0$ Hz), 6.65 (1H, d, $J=2.0$ Hz), 5.59 (1H, d, $J=5.8$ Hz), 5.46–5.42 (1H, m), 3.65 (3H, s), 3.04 (1H, dd, $J_{1,2}=17.2$, 5.2 Hz), 2.77 (1H, dd, $J_{1,2}=17.2$, 4.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.7, 154.8, 153.8, 148.7, 148.5, 148.4, 148.2, 148.1, 148.0, 142.6, 141.3, 141.1, 138.6, 137.2, 137.2, 137.1, 137.0, 136.4, 135.2, 133.2, 133.1, 133.0, 133.0, 132.9, 132.3, 131.9, 131.9, 131.8, 131.4, 129.6, 129.5, 127.6, 127.5, 127.3, 127.1, 126.9, 126.6, 125.6, 125.5, 125.5, 125.4, 125.4, 125.2, 125.1, 122.3, 116.3, 113.9, 112.9, 110.1, 109.8, 77.1, 68.9, 56.4, 23.2.

*(2R,3S)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,4-dihydroxy-5-methoxybenzoate (**12**)*. In a similar manner to that used to prepare **2**, treatment of **78** gave **12** (99%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{10}Na$ $[M+Na]^+$ 479.0954, found 479.0994, $[\alpha]^D_{20}=+142.5$ (*c* 0.34, 50% acetone in H_2O); IR (neat) 3331, 1705, 1612, 1385, 1231 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.07 (1H, d, $J=2.0$ Hz), 7.01 (1H, d, $J=2.0$ Hz), 6.86 (1H, d, $J=2.0$ Hz), 6.71–6.76 (2H, m), 5.97 (1H, d, $J=2.0$ Hz), 5.94 (1H, d, $J=2.0$ Hz), 5.28–5.37 (1H, m), 5.03 (1H, d, $J=6.6$ Hz), 3.82 (3H, s), 2.92 (1H, dd, $J_{1,2}=16.5$, 5.3 Hz), 2.71 (1H, dd, $J_{1,2}=16.5$, 7.3 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.4, 158.2, 157.7, 156.7, 149.0, 146.4, 146.2, 140.7, 131.4, 121.4, 119.4, 116.2, 114.7, 111.9, 106.2, 99.8, 96.5, 95.6, 79.7, 71.2, 56.7, 25.1.

*(2R,3S)-2-(3,4-Bis(2-nitrophenylsulfonyloxy)phenyl)-5,7-bis(2-nitrophenylsulfonyloxy) chroman-3-yl 4-methoxy-3,5-bis(2-nitrophenylsulfonyloxy)benzoate (**79**)*. In a similar manner to that used to prepare **29**, treatment of **43** with **22** gave **79** (89%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{65}H_{41}N_7O_{39}S_7Na$ $[M+Na]^+$ 1566.9831, found 1566.9825; $[\alpha]^D_{20}=+21.0$ (*c* 1.10, acetone); IR (neat) 1705, 1618, 1593, 1554, 1418, 1395, 1365, 1315, 1177, 1119, 1011 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.18–7.88 (28H, m), 7.67 (2H, s), 7.45 (1H, dd, $J=8.6$, 2.3 Hz), 7.39 (1H, d, $J=8.6$ Hz), 7.26 (1H, d, $J=2.3$ Hz), 6.88 (1H, d, $J=2.0$ Hz), 6.65 (1H, d, $J=2.0$ Hz), 5.58 (1H, d, $J=5.2$ Hz), 5.43–5.39 (1H, m), 3.69 (3H, s), 3.00 (1H, dd, $J_{1,2}=17.8$, 5.8 Hz), 2.66 (1H, dd, $J_{1,2}=17.8$, 4.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.2, 154.7, 150.3, 148.8, 148.5, 148.5, 148.4, 148.1, 148.1, 142.6, 141.3, 141.1, 138.5, 137.2, 137.2, 137.1, 137.1, 137.0, 133.1, 133.0, 132.9, 132.3, 132.0, 131.9, 131.8, 131.8, 127.6, 127.5, 127.3, 127.0, 126.9, 126.6, 125.6, 125.5, 125.4, 125.1, 124.8, 122.1, 113.8, 110.1, 109.9, 77.0, 68.6, 61.9, 22.9.

*(2R,3S)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,5-dihydroxy-4-methoxybenzoate (**13**)*. In a similar manner to that used to prepare **2**, treatment of **79** gave **13** (89%) as a colorless amorphous. HR-MS (FAB) calculated for $C_{23}H_{20}O_{10}Na$ $[M+Na]^+$ 479.0954, found 479.0994; $[\alpha]^D_{20}=+110.6$ (*c* 0.80, 50% acetone in H_2O); IR (neat) 3367, 1701, 1604, 1367, 1234 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 6.94 (2H, s), 6.83 (1H, s), 6.72 (2H, s), 5.97–5.93 (2H, m), 5.41–5.34 (1H, m), 5.05 (1H, d, $J=5.9$ Hz), 3.84 (3H, s), 2.85 (1H, dd, $J_{1,2}=16.5$, 5.3 Hz), 2.71 (1H, dd, $J_{1,2}=16.5$, 6.6 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 167.1, 158.2, 157.6, 156.5, 151.6, 146.3, 146.3, 131.3, 126.5, 119.3, 116.2, 114.4, 110.2, 99.6, 96.5, 95.6, 79.3, 71.5, 60.7, 24.5.

*5,7–Di-O-(2–nitrobenzenesulfonyl)catechin (**51**)*. To a solution of boric acid (100 g, 1.6 mol) and NaOH (20 g) in H_2O (1300 ml) was added **49** (10.0 g, 34.5 mmol) and the resulting solution was adjusted to pH 9.0 by the addition of 1 M NaOH. Then, 2-nitrobenzenesulfonyl chloride (15.3 g, 69.0 mmol) in toluene (220 ml) was added dropwise over 30 min and the mixture was stirred at room temperature for 7 h. The reaction was quenched with 1 M HCl and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (1–3% MeOH in CH_2Cl_2) to afford **51** (15.9 g, 70%) as a pale yellow amorphous solid. HR-MS (ESI) calculated for $C_{27}H_{20}N_2O_{14}S_2Na$ $[M+Na]^+$ 683.0248, found 683.0281; $[\alpha]^{20}_D=+13.3$ (*c* 1.0, acetone) IR (neat) 3398, 1701, 1618, 1591, 1545, 1439, 1389, 1366, 1196, 1110, 1032, 997, 780 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.09–8.00 (3H, m), 7.98–7.75 (5H, m), 6.78 (1H, d, $J=8.0$ Hz), 6.73 (1H, dd, $J_{1,2}=6.5$, 2.0 Hz), 6.60 (1H, dd, $J_{1,2}=8.0$, 2.0 Hz), 6.55 (1H, d, $J=2.0$ Hz), 4.85 (1H, d, $J=6.0$ Hz), 4.39 (1H, d, $J=4.0$ Hz), 4.10–4.05 (1H, m), 2.66 (1H, dd, $J_{1,2}=17.0$, 7.5 Hz), 2.53 (1H, dd, $J_{1,2}=17.0$, 5.0 Hz); ^{13}C NMR (126 MHz, acetone-d_6) δ 157.1, 149.5, 149.2, 149.0, 148.5, 148.4, 145.9, 145.8, 137.8, 137.7, 133.8, 133.6, 133.0, 132.5, 130.8, 128.2, 127.6, 126.2, 126.2, 119.1, 116.5, 116.0, 114.5, 110.3, 109.3, 82.7, 66.2, 27.6.

*5,7–Di-O-(2–nitrobenzenesulfonyl)epicatechin (**52**)*. In a similar manner to that used to prepare **51**, treatment of **50** (5.0 g) gave **52** (7.1 g, 63%) as a pale yellow amorphous solid. HR-MS (ESI) calculated for $C_{27}H_{20}N_2O_{14}S_2Na$ $[M+Na]^+$ 683.0248, found 683.0255; $[\alpha]^{20}_D=+6.5$ (*c* 1.00, acetone); IR (neat) 3421, 1691, 1617, 1385, 1195, 1110, 997, 781 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.17-8.08 (4H, m, 4H), 8.06–8.01 (2H, m, 2H), 8.00–7.91 (2H, m), 7.91 (1H, br s), 7.88 (1H, br s), 7.00 (1H, br s), 6.79 (2H, br s), 6.77 (1H, d, $J=2.0$ Hz), 6.47 (1H, d, $J=2.0$ Hz), 5.02 (1H, br s), 4.30–4.20 (1H, m), 4.06 (1H, d, $J=4.5$ Hz), 3.00–2.85 (2H, m); ^{13}C NMR (126 MHz, acetone-d_6) δ 157.0, 148.7, 148.5, 147.5, 144.8, 144.7, 136.9, 133.1, 132.9, 132.2, 131.8, 130.0, 127.6, 126.9, 125.5, 125.4, 118.5, 115.3, 114.8, 114.4, 109.6, 108.2, 79.5, 64.3, 29.1.

*5,7–Di-O-(2–nitrobenzenesulfonyl)epigallocatechin (**53**)*. In a similar manner to that used to prepare **51**, treatment of **27** (4.0 g) gave **53** (4.6 g, 52%) as a brown amorphous solid. HR-MS (ESI) calculated for $C_{27}H_{20}N_2O_{15}S_2Na$ $[M+Na]^+$ 699.0197, found 699.0191; $[\alpha]^{20}_D=+4.1$ (*c* 1.00, acetone); IR (neat) 3342, 1701, 1620, 1591, 1547, 1441, 1385, 1368, 1194, 1111, 997, 781 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.20–7.75 (8H, m), 7.34 (1H, s), 7.00 (1H, br s), 6.75 (1H, d, $J=2.5$ Hz), 6.51 (2H, s), 6.47 (1H, d, $J=2.0$ Hz), 4.96 (1H, br s), 4.26–4.20 (1H, m), 4.01 (1H, d, $J=4.5$ Hz), 2.93 (1H, dd, $J_{1,2}=16.5$, 4.0 Hz), 2.53 (1H, dd, $J_{1,2}=16.5$, 4.0 Hz); ^{13}C NMR (126 MHz, acetone-d_6) δ 157.7, 149.4, 148.2, 146.1, 137.7, 133.8, 133.6, 133.2, 133.0, 132.6, 130.0, 128.3, 127.6, 126.2, 126.2, 110.3, 108.9, 106.7, 80.1, 65.1, 30.0.

*(2R,3R)-5,7,5,7-Tetra-O–(2-nitrobenzenesulfonyl)neotheaflavin (**56**)*. To a solution of **50** (1.0 g, 1.5 mmol) in MeCN (15 ml) was added $Pb(OAc)_4$ (806 mg, 4.5 mmol) at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. The reaction mixture was added to benzene, and then the mixture was filtered through a pad of celite. Then, the filtrate was evaporated under reduced pressure, and the resulting crude product was used in the next reaction without further purification.

The crude product **55** was dissolved in MeCN/CH_2Cl_2 (1:4, 25 ml). To this solution were added MS3A (1.0 g) and Ns-epigallocatchin (**53**) (342 mg, 505 μmol) in MeCN/CH_2Cl_2 (1:4, 10 ml) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. After the addition of H_2O, the mixture was stirred for 5 min at room temperature. The reaction mixture was filtered, and

then the filtrate was extracted with AcOEt, the organic phase was washed with H_2O, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2:MeOH = 98:2) to afford **56** (327 mg, 50%) as an orange amorphous solid. HR-MS (ESI) calculated for $C_{53}H_{36}N_4O_{28}S_4Na$ $[M+Na]^+$ 1327.0291, found 1327.0284; $[\alpha]^{20}_D = -6.6$ (*c* 0.20, acetone); IR (neat) 3352, 1701, 1618, 1591, 1541, 1477, 1437, 1384, 1361, 1232, 1190, 1106, 1058, 1030, 995 850, 775, 736 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.18–7.86 (16H, m), 7.51 (1H, s), 7.47 (1H, s), 6.88 (1H, s), 6.83 (1H, br s), 6.63 (1H, d, $J = 2.0$ Hz), 6.53 (1H, d, $J = 2.0$ Hz), 5.85 (1H, br s), 5.17 (1H, s), 4.49 (1H, s), 4.31–2.98 (1H, m), 3.10 (1H, dd, $J_{1,2} = 17.5$, 2.5 Hz), 3.05 (1H, dd, $J_{1,2} = 17.5$, 2.5 Hz), 2.80 (1H, dd, $J_{1,2} = 17.0$, 7.5 Hz), 2.65–2.50 (1H, br s); ^{13}C NMR (125 MHz, acetone-d_6) δ 184.8, 156.9, 156.7, 154.5, 151.2, 149.2, 149.2, 149.1, 149.0, 148.8, 148.4, 148.1, 146.3, 137.6, 137.6, 137.5, 133.8, 133.7, 133.7, 133.6 132.9, 132.8, 132.5, 132.3, 130.4, 129.7, 128.1, 128.0, 127.9, 127.5, 127.3, 126.2, 126.1, 126.1, 126.1, 121.6, 118.6, 116.3, 115.7, 110.5, 110.3, 109.7, 109.4, 82.0, 69.7, 66.5, 64.7, 55.2, 29.6, 29.5.

*Neotheaflavin (**5**).* To a suspension of Cs_2CO_3 (223 mg, 0.17 mmol) and thiophenol (0.17 ml, 1.7 mmol) in MeCN/DMF(1:2, 2.7 ml) was added the solution of **56** in MeCN (3.0 ml) at 0 °C and the reaction mixture was stirred at the same temperature for 2.0 h. The reaction was quenched with 1 M HCl aqueous and extracted with AcOEt. The organic phase was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 9:1) to afford **5** (53.1 mg, 55%) as a orange amorphous solid. HR-MS (ESI) calculated for $C_{29}H_{24}O_{12}Na$ $[M+Na]^+$ 587.1159, found 587.1130; $[\alpha]^{20}_D = -122.1$ (*c* 0.20, acetone); IR (neat) 3362, 1699, 1622, 1607, 1506, 1472, 1429, 1361, 1236, 1193, 1143, 1099, 1076, 1046, 1012, 823 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.80 (1H, br s), 8.26 (1H, s), 7.77 (1H, s), 7.66 (1H, s), 6.06 (1H, s), 6.03 (1H, s), 5.95 (1H, s), 5.94 (1H, s), 5.60 (1H, d, $J = 5.0$ Hz), 5.01 (1H, s), 4.36 (1H, br s), 4.12–4.06 (1H, m), 3.00–2.75 (3H, m), 2.63 (1H, dd, $J_{1,2} = 16.0$, 9.0 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 184.9, 157.7, 157.5, 157.4, 157.1, 156.7, 156.6, 154.4, 150.6, 146.3, 134.9, 132.3, 130.9, 128.7, 122.4, 121.7, 119.3, 100.8, 99.3, 96.4 96.3, 95.6, 95.4, 81.7, 79.3, 69.5, 66.7, 30.6, 29.4. Analytical data for neotheaflavin (**5**) in ref. 16.

*(2R,3R)-5,7,5,7-Tetra-O–(2-nitrobenzenesulfonyl)theaflavin (**64**).* To a solution of **52** (500 mg, 757 mmol) in MeCN (7 ml) was added $Pb(OAc)_4$ (268 mg, 605 mmol) at 0 °C. The resulting suspension was stirred for 10 min at the same temparature. The reaction mixture was added benzene (20 ml), and then the mixture was filtered with celite pad. Then the filtrate was evaporated under reduced pressure, and the resulting crude product was used in the next reaction without further purification.

The crude product **63** was dissolved in MeCN/CH_2Cl_2 (1:4, 12 ml). The solution was added MS3A (300 mg), Ns-epigallocatchin **53** (171 mg, 252 mmol) in MeCN/CH_2Cl_2 (1:4, 4 ml) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. After the addition of H_2O, the mixture was stirred for 5 min at room temperature. The reaction mixture was filtered, and then the filtrate was extracted with AcOEt, the organic phase was washed with H_2O, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel column (CH_2Cl_2:MeOH = 9:1) to afford mixture of **64** and **52** as an orange amorphous solid, and the mixture of product was used in the next reaction without further purification. HR-MS (ESI) calculated for $C_{53}H_{36}N_4O_{28}S_4Na$ $[M+Na]^+$ 1327.0291, found 1327.0245.

*Theaflavine (**4**).* To a solution of the crude **64** (249 mg) in MeCN/DMF (1:2, 3.0 ml) were added Cs_2CO_3 (257 mg, 789 mmol) and thiophenol **39** (0.09 ml, 879 mmol) at 0 °C and the reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with 1 N HCl aqueous and extracted with AcOEt. The organic layer was evaporated under reduced pressure and the residue was purified by HPLC to afford Theaflavin (**4**) (16 mg, 11% for two steps) as an orange amorphous solid. HR-MS (ESI) calculated for $C_{29}H_{24}O_{12}Na$ $[M+Na]^+$ 587.1159, found 587.1164; $[\alpha]^{20}_D = -274.8$ (*c* 0.20, acetone); IR (neat) 3275, 1691, 1624, 1600, 1507, 1460, 1419, 1352, 1230, 1197, 1138, 1089, 1060, 1041, 1010, 891, 805, 706 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.94 (1H, s), 7.81 (1H, s), 7.33 (1H, s), 6.00 (1H, d, $J = 2.0$ Hz), 5.97 (1H, d, $J = 2.0$ Hz), 5.95 (1H, d, $J = 2.0$ Hz), 5.94 (1H, d, $J = 2.0$ Hz), 5.62 (1H, s), 4.86 (1H, s), 4.47–4.41 (1H, m), 4.32–4.25 (1H, m), 2.96 (1H, dd, $J_{1,2} = 17.0$, 4.0 Hz), 2.93 (1H, dd, $J_{1,2} = 17.0$, 4.0 Hz), 2.82 (1H, br d, $J = 16.0$ Hz), 2.80 (1H, br d, $J = 16.0$ Hz); ^{13}C NMR (126 MHz, CD_3OD) δ 184.7, 157.0, 156.9, 156.6, 156.4, 156.1, 156.1, 155.4, 149.8, 145.2, 133.4, 130.2, 127.7, 125.0, 122.7, 120.9, 117.1, 99.0, 98.4, 95.5, 94.8, 94.3, 80.0, 75.9, 65.3, 64.4, 28.6, 28.1. Analytical data for theaflavin (**4**) in ref. 16.

*(2R,3S)-3-Hydroxy-2-(3,4,6-trihydroxy-5-oxo-5H-benzo[7]annulen-1-yl)chroman-5,7-diyl bis(2-nitrobenzenesulfonate) (**80**).* To a solution of **51** (100 mg, 152 μmol) in MeCN (2 ml) was added $Pb(OAc)_4$ (53.7 mg, 121 μmol) at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. To the reaction mixture was added benzene (6.7 ml), and then the mixture was filtered through a pad of celite. Then, the filtrate was evaporated under reduced pressure, and the resulting crude product was used in the next reaction without further purification.

The crude product **55** was dissolved in MeCN/CH_2Cl_2 (1:4, 1.65 ml). To this solution were added MS3A (30 mg) and pyrogallol **65** (19 mg, 150 μmol) in MeCN/CH_2Cl_2 (1:4, 0.50 ml) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. After the addition of H_2O, the mixture was stirred for 5 min at room temperature. The reaction mixture was filtered, and then the filtrate was extracted with AcOEt, the organic phase was washed with H_2O and evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 98:2) to afford **80** (19.5 mg) as a orange amorphous solid. HR-MS (ESI) calculated for $C_{32}H_{22}N_2O_{16}S_2Na$ $[M+Na]^+$ 777.0320, found 777.0269; $[\alpha]^{20}_D = +52.9$ (*c* 0.20, acetone); IR (neat) 3420, 1554, 1384, 1195, 1111, 997 cm^{-1}; ^1H NMR (500 MHz, methanol-d_4) δ 8.15–7.90 (8H, m), 7.88 (1H, d, $J = 12.0$ Hz), 7.47 (1H, s), 7.25 (1H, d, $J = 9.2$ Hz), 6.90 (1H, dd, $J_{1,2} = 12.0$, 9.2 Hz), 6.79 (1H, d, $J = 2.3$ Hz), 6.60 (1H, d, $J = 2.3$ Hz), 5.75 (1H, d, $J = 6.2$ Hz), 4.31–4.24 (1H, m), 2.82 (1H, dd, $J_{1,2} = 16.9$, 7.7 Hz), 2.65 (1H, dd, $J_{1,2} = 16.9$, 4.3 Hz); ^{13}C NMR (126 MHz, acetone-d_6) δ 157.0, 148.9, 148.4, 145.8, 145.8, 137.7, 137.6, 133.7, 133.6, 133.0, 132.5, 130.8, 128.1, 127.5, 126.2, 126.1, 119.1, 116.5, 116.0, 114.4, 110.3, 109.3, 82.6, 66.1, 27.5.

*3,4,6-Trihydroxy-1-((2R,3S)-3,5,7-trihydroxychroman-2-yl)-5H-benzo[7]annulen-5-one (**67**).* To a suspension of Cs_2CO_3 (40.0 mg, 53.0 μmol) and thiophenol (55 μl, 0.53 mmol) in MeCN/DMF(1:2, 0.9 ml) was added solution of the crude of **80** in MeCN (1.0 ml) at 0 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with 1 M HCl aqueous and extracted with AcOEt. The organic phase was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 9:1) to afford **67** (15.9 mg, 78%) as a orange amorphous solid. HR-MS (ESI) calculated for $C_{20}H_{16}O_8Na$ $[M+Na]^+$ 407.0737, found 407.0748; $[\alpha]^{20}_D = -24.8$ (*c* 0.20, acetone); IR (neat) 3319, 1602, 1411, 1327, 1253, 1070, 825 cm^{-1}; ^1H NMR (500 MHz, methanol-d_4) δ 7.84 (1H, d, $J = 12.5$ Hz), 7.60 (1H, s), 7.15 (1H, d, $J = 9.1$ Hz), 6.80 (1H, dd, $J_{1,2} = 12.5$, 9.1 Hz), 6.79 (1H, d, $J = 2.3$ Hz), 6.60 (1H, d, $J = 2.3$ Hz), 5.75 (1H, d, $J = 6.2$ Hz), 4.20–4.13 (1H, m), 2.86 (1H, dd, $J_{1,2} = 16.3$, 5.3 Hz), 2.62 (1H, dd, $J_{1,2} = 16.1$, 8.5 Hz); ^{13}C NMR (126 MHz, methanol-d_4) δ 186.3, 158.0, 157.7, 156.7, 156.6, 151.9, 147.1, 131.5, 130.0, 124.1, 122.9, 122.6, 118.6, 100.7, 96.7, 95.5, 80.2, 68.9, 49.7, 28.9.

*Methyl 3,4,6-trihydroxy-1-((2R,3S)-3-hydroxy-5,7-bis(((2-nitrophenyl)sulfonyl) oxy) chroman-2-yl)-5-oxo-5H-benzo[7]annulene-8-carboxylate (**81**).* To a solution of **51** (200 mg, 303 μmol) in MeCN (3 ml) was added $Pb(OAc)_4$ (161 mg, 363 μmol) at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. The reaction mixture was added to benzene, and then the mixture was filtered through a pad of celite. Then, the filtrate was evaporated under reduced pressure, and the resulting crude product was used in the next reaction without further purification.

The crude product **55** was dissolved in MeCN/CH_2Cl_2 (1:4, 5.0 ml). To the solution were added MS3A (200 mg) and methyl gallate (**66**) (18.6 mg, 101 μmol) in MeCN/CH_2Cl_2 (1:4, 2.0 ml) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. After the addition of H_2O, the mixture was stirred for 5 min at room temperature. The reaction mixture was filtered, and then the filtrate was extracted with AcOEt, the organic phase was washed with H_2O and evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2:MeOH = 98:2) to afford **81** (40.6 mg, 50%) as a orange amorphous solid. HR-MS (ESI) calculated for $C_{34}H_{24}N_2NaO_{18}S_2$ $[M+Na]^+$ 835.0358, found 835.0343; $[\alpha]^{20}_D = +9.6$ (*c* 0.20, acetone); IR (neat)

3369, 1701, 1385, 1248, 1195, 1111, 999, 781 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.88 (1H, s), 8.12–7.93 (8H, m), 7.76 (1H, s), 7.58 (1H, s), 6.82 (1H, d, J = 2.3 Hz), 6.61 (1H, d, J = 2.3 Hz), 5.62 (1H, d, J = 7.5 Hz), 4.33–4.26 (1H, m), 3.84 (1H, s), 2.90 (1H, m), 2.74 (1H, dd, $J_{1,2}$ = 17.2, 8.6 Hz);^{13}C NMR (126 MHz, acetone-d_6) δ 186.8, 168.5, 157.6, 155.4, 153.1, 150.3, 150.1, 149.9, 149.7, 149.4, 138.7, 134.7, 134.5, 134.3, 133.9, 133.6, 133.5, 129.1, 129.0, 128.3, 127.2, 127.1, 125.1, 123.6, 123.1, 117.5, 116.8, 111.4, 110.8, 82.1, 67.5, 54.3, 31.4.

*Methyl 3,4,6-trihydroxy-5-oxo-1-((2R,3S)-3,5,7-trihydroxychroman-2-yl)-5H-benzo[7] annulene-8-carboxylate (**68**).* To a suspension of Cs_2CO_3 (52.1 mg, 64.1 μmol) and thiophenol (66 μl, 641 μmol) in MeCN/DMF(1:2, 0.9 m;) was added solution of **81** in MeCN (1.0 ml) at 0 °C and the reaction mixture was stirred at the same temperature for 30 min. The reaction was quenched with 1 M HCl aqueous and extracted with AcOEt. The organic phase was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 9:1) to afford **68** (13.4 mg, 47%) as a orange amorphous solid. HR-MS (ESI) calculated for $C_{22}H_{18}O_{10}Na$ $[M+Na]^+$ 465.0792, found 465.0795; $[\alpha]^{20}_D$ = –44.6 (*c* 0.20, acetone); IR (neat) 3346, 1701, 1608, 1225 cm^{-1}; ^1H NMR (500 MHz, methanol-d_4) δ 8.92 (1H, s), 7.69 (1H, s), 7.62 (1H, s), 5.97 (1H, d, J = 1.7 Hz), 5.91 (1H, d, J = 1.7 Hz), 5.34 (1H, d, J = 8.0 Hz), 4.35–4.13 (1H, m), 3.82 (1H, s), 2.97 (1H, dd, $J_{1,2}$ = 16.1, 5.7 Hz), 2.61 (1H, dd, $J_{1,2}$ = 16.0, 9.2 Hz); ^{13}C NMR (126 MHz, methanol-d_4) δ 186.8, 181.9, 158.1, 157.7, 156.6, 155.0, 152.4, 149.7, 134.6, 134.4, 128.7, 124.0, 123.5, 112.8, 115.9, 100.8, 96.7, 95.5, 81.3, 69.1, 53.5, 29.7.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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