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Structure–activity study of *epi*-gallocatechin gallate (EGCG) analogs as proteasome inhibitors

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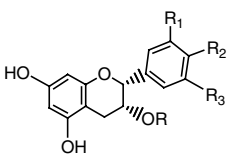
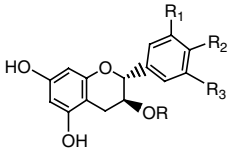
Abstract—The structure–activity relationship of a number of synthetic green tea polyphenol analogs involving modifications of A ring and B ring of *epi*-gallocatechin gallate (EGCG) as proteasome inhibitors has been examined. It was found that in B ring, a decrease in the number of OH groups led to decreased potency. Introduction of a hydrophobic benzyl group into the 8 position of A ring did not significantly affect the proteasome-inhibitory potency.

1. Introduction

Regular drinking of green tea has been associated with reduced risk of several forms of cancer.[1,2] The biological effects of green tea are often attributed to the polyphenols, in particular, the catechins.[3] A number of catechins have been identified in green tea infusions.[4,5] They are (−)-*epi*-afzelechin (EZ, **1**), (+)-catechin (C, **2**), (−)-*epi*-catechin (EC, **3**), (−)-gallocatechin (GC, **4**), (−)-*epi*-gallocatechin (EGC, **5**), their respective 3-gallate esters (−)-EZG (**6**), (+)-CG (**7**), (−)-ECG (**8**), (−)-GCG (**9**) and (−)-EGCG (**10**). Although a number of cancer-related proteins are affected by tea polyphenols, the exact mechanism of tea-mediated cancer prevention is not known.[2] Recently, we proposed that inhibition of proteasome may be a key mechanism in the cancer prevention activity of green tea[2,6] (Fig. 1).



1: R=R_1=R_3=H, R_2=OH
3: R=R_1=H, R_2=R_3=OH
5: R=H, R_1=R_2=R_3=OH
6: R=gallate, R_1=R_3=H, R_2=OH
8: R=gallate, R_1=H, R_2=R_3=OH
10:R=gallate, R_1=R_2=R_3=OH



2: R=R_1=H, R_2=R_3=OH
4: R=H, R_1=R_2=R_3=OH
7: R=gallate, R_1=H, R_2=R_3=OH
9: R=gallate, R_1=R_2=R_3=OH

Figure 1. Various catechins in green tea.

The proteasome is responsible for the degradation of most cellular proteins via the ubiquitin/proteasome-dependent degradation pathway and plays an important role in the up-regulation of cell proliferation and down-regulation of cell death. The eukaryotic proteasome contains three known activities: chymotrypsin-like mediated by the β5-subunit, trypsin-like by the β2-subunit and the caspase-like by the β1-subunit.[7] Proteasome inhibitors have been considered as potential anticancer drugs.[8] Indeed, MLN-341 (formerly PS-341), a dipeptidyl boronic compound and a potent and selective inhibitor of the chymotrypsin-like activity of the 20S proteasome, has recently been approved for the treatment of hematological malignant neoplasms.[9] In the case of natural green tea polyphenols, it was reported that the naturally occurring ester bond-containing green tea polyphenols,

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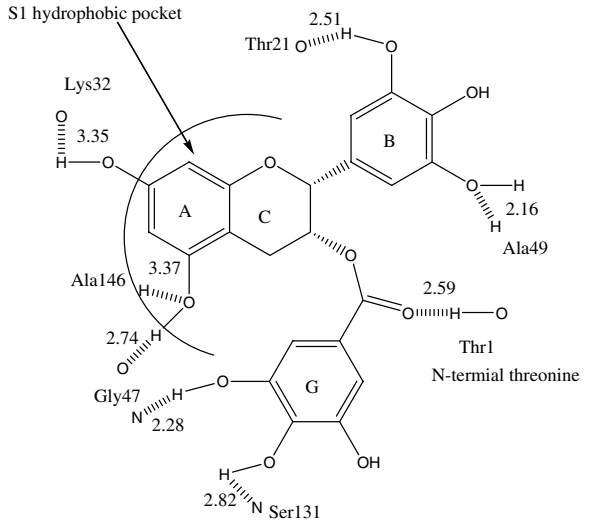
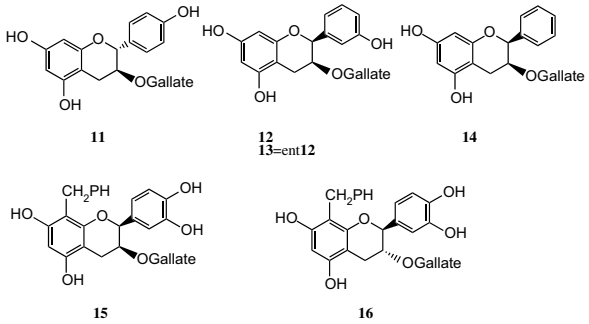


Figure 2. Docking model of (−)-EGCG in the β5-subunit of 20S proteasome. The number is distance in Å for the H-bond indicated.

such as EGCG, GCG and ECG, possess the ability to inhibit proteasome activity in vitro and in vivo.[6] In contrast, the polyphenols without the gallate ester function, such as EGC, GC and EC, are not inhibitors of proteasome.[6] Through our synthetic efforts, we have recently prepared the natural (−)-EGCG,[10] (−)-GCG,[11] (−)-ECG[12] and (+)-CG[12] as well as their respective enantiomers.[10–12] Unexpectedly, it was found that the unnatural enantiomers were equally or more potent as the natural compounds in inhibiting the chymotrypsin-like activity of proteasome.[11] A mechanistic model, with in silico docking calculations, to account for their inhibition of proteasome has been proposed.[11] In this model, the polyphenol gallate ester, for example, (−)-EGCG, binds to the active site of the β5-subunit of 20S proteasome. The A ring of (−)-EGCG acts as the phenyl ring of a phenylalanine mimic, binding to the hydrophobic S1 pocket of the β5-subunit (Fig. 2). The ester bond of (−)-EGCG is then in reasonable proximity (about 3.18 Å) from the N-terminal Thr (Thr 1) OH function, which is responsible for the protease catalytic activity. Inhibition is then due to the irreversible transfer of the gallate moiety from (−)-EGCG to the hydroxy oxygen of Thr 1. This model has successfully accounted for the similar activities of the natural and unnatural enantiomers by recognizing the pseudo-symmetry of the B and G (gallate) rings in the active site.[13] It is also consistent with subsequent structure–activity studies, which showed that both the A and C rings were necessary for the proteasome inhibition activity but the oxygen in C ring can be replaced with the CH_2 isostere.[14]

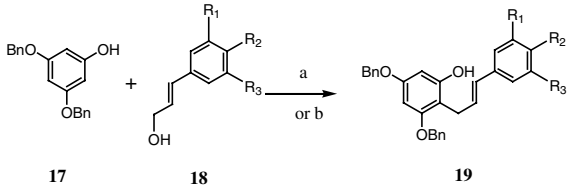
In this study, we intend to probe the structure–activity relationship on the following two issues. Firstly, how critical is the various OH substituents in the B ring? In order to answer this question, the four gallate analogs **11**–**14**, which are not present in natural green tea catechins, have been prepared and their biological activities compared with compounds **6**–**10**. Secondly, since the A ring is embedded in the hydrophobic region of the β5-subunit of 20S proteasome, what is the effect of the presence of a hydrophobic substituent in the A ring in affecting the biological activity? To answer this point, we have prepared the two benzyl compounds **15** and **16** and examined their biological activities.



2. Results and discussion

2.1. Enantioselective syntheses of *epi*-4′-deoxycatechin gallate (12 and 13) and *epi*-3′,4′-dideoxycatechin gallate (14)

In all our previously reported syntheses of EGCG and other catechins, a Friedel–Crafts reaction was used to build up the connection between A ring (**17**) and B ring (**18**) (Scheme 1).[10–13] The same Friedel–Crafts coupling reaction was used in the syntheses of *epi*-afzelechin gallate (**6**) and afzelechin gallate (**11**).[15] It was noted however that the yields of coupling reactions declined as the number of alkoxy groups in the B ring diminished (Table 1). When the same coupling reaction was carried out with 3′-benzyloxycinnamyl alcohol (**18d**) or cinnamyl alcohol (**18e**), the product yields were so low that rendered the reaction impractical for the synthesis of **12**–**14**. The low yields in the latter two cases were probably due to the absence of *para* alkoxy group, which was needed to stabilize the carbenium ion intermediate necessary for the Friedel–Crafts reaction. Alternative method for the construction of the fragment **19** was sought. We attempted the Mitsunobu reaction using the standard conditions of triphenylphosphine and di-isopropyl azodicarboxylate (DIAD) in toluene in the hope of getting the ether **20**, which may then undergo the Claisen rearrangement to the desired **19**. Much to our delight, compound **19** was obtained directly under the Mitsunobu conditions in reasonable yield. The reaction was not subject to electronic effect, and the yields for **19d** and **19e** were the same as those for **19a**–**c** (Table 1). The intermediate **20** was confirmed by carrying out the Mitsunobu reaction of **18d′** (Scheme 2). A mixture of products was obtained, which included **19d**, **20** and **21**.



Scheme 1. Friedel–Crafts versus Mitsunobu condensation: (a) H_2SO_4/SiO_2/CH_2Cl_2, rt; (b) Ph_3P/DIAD/toluene, −20 °C.

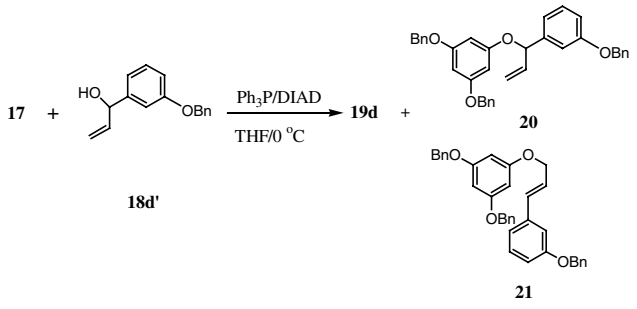
Table 1. Yields of Friedel–Crafts versus Mitsunobu reactions between **17** and **18** to give **19** (Scheme 1)

	R_1	R_2	R_3	Friedel–Crafts[a] yield (%)	Mitsunobu[b] yield (%)
19a	OBn	OBn	OBn	60	48
19b	OBn	OBn	H	47	50
19c	H	OBn	H	37	53
19d	OBn	H	H	10	60
19e	H	H	H	8	62

[a] $H_2SO_4/SiO_2/CH_2Cl_2$, rt.
[b] Ph_3P/DIAD/toluene, −20 °C.

Compound **20** could be isolated by flash chromatography at 0 °C but rearranged readily at room temperature on silica gel to **19d**.

With compounds **19d** and **19e** at hand, the syntheses of **12**, **13** and **14** followed more or less the path previously used (Scheme 3).[10] Steroselective Sharpless dihydroxylation, using AD-mix-α as the oxidant, was performed on the TBS protected **19d** and **19e**, and then deprotection to give compounds (+)-**22d** and (+)-**22e**, respectively, with *S*,*S* configuration. Reaction of (+)-**22d** with triethyl formate and PPTS gave the acetal **23d**. Conversion of **23d** to the benzopyran skeleton could not be achieved with PPTS at 60 °C, the conditions previously used for the synthesis of EGCG.[10] This is again because of the absence of *para* alkoxy group in the B ring to facilitate the nucleophilic opening of the acetal function at the benzylic position. Alternatively, compound **23d** reacted with acetyl bromide at 0 °C to give the bromo compound **24d**, which then cyclized in acetone with K_2CO_3 as base to produce (+)-**25d** with *cis* *S*,*S* configuration. Evidently, two S_N2 substitution reactions must have occurred at the benzylic carbon giving an overall retention of configuration at that centre. The same cyclization method was used to synthesize (+)-**25e**. Esterification of **25d** or **25e** with 3,4,5-tris(benzyloxy)benzoyl chloride, followed by hydrogenolysis gave the desired compounds **12** and **14** in overall yield of 14% and 15%, respectively. When compound **19d** was converted to the dihydroxy compound (−)-**22d** with AD-mix-β, and the same reaction sequence was followed, **13** was obtained. It had the same NMR spectra as the (+)-enantiomer **12** but with opposite optical rotation.



Scheme 2. Isolation of intermediate **20**.

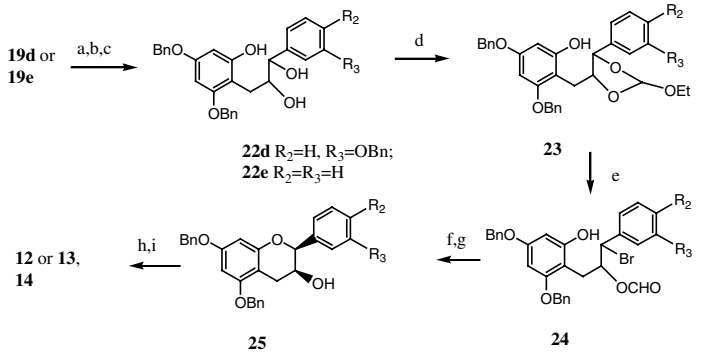
2.2. Enantioselective syntheses of 8-benzyl-*epi*-catechin gallate (15) and 8-benzylcatechin gallate (16)

In order to synthesize compounds **15** and **16**, the precursor compound **27** was required. Providently, compound 27 was a by-product in the preparation of the starting materials **17** (Scheme 4) used in the previous syntheses of green tea catechins.[10–13,15] In the literature synthesis of **17**,[10,16] ethanethiol was used to debenzylate 1,3,5-tribenzyloxybenzene (**26**). The reaction yielded at various times low yield of **17** (11%) with a substantial amount of **27** (56%). We eventually traced the low yield of **17** to the volatility of ethanethiol, which easily escaped the reaction mixture under reflux conditions. Changing the debenzylation agent with the higher boiling *n*-butanethiol, the reaction gave consistently **17** as the major product (64% yield) with **27** (16%) as the minor component.

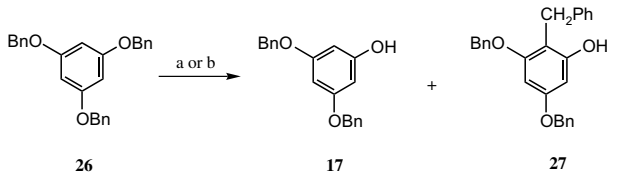
Friedel–Crafts coupling of **27** with **18b** gave a fair yield (46%) of the coupled product **28**. The conversion of **28** to compounds **15** and **16** was accomplished by following the sequence of reactions outlined in Scheme 5 without difficulties.

2.3. Proteasome inhibition

We then tested whether these synthetic compounds can inhibit the proteasomal chymotrypsin-like activity of purified 20S prokaryotic proteasome, using (−)-EGCG



Scheme 3. Reagents and conditions: (a) TBSCl/imidazole/DMF, rt; (b) AD-mix-α/$MeSO_2NH_2$/H_2O/*t*-BuOH/CH_2Cl_2/0 °C; (c) TBAF/THF, rt; (d) $CH(OEt)_3$/PPTS/CH_2Cl_2, rt; (e) AcBr/CH_2Cl_2/0 °C; (f) K_2CO_3/acetone, rt; (g) K_2CO_3/MeOH; (h) 3,4,5-tri(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (i) H_2/$Pd(OH)_2$/MeOH/THF, rt.



Scheme 4. Preparation of compound **27**: (a) EtSH/NaH/DMF, 150 °C; (b) BuSH/NaH/DMF, 150 °C.

as a positive control.[6,11,12] The results are summarized in Table 2. By comparing the IC_{50}s of the series: (−)-EGCG (0.30), (−)-ECG (0.58), (−)-EZG (2.69), **12** (0.84) and **14** (4.56), all with the same absolute configurations at the two stereogenic centres, one can conclude that as the number of OH group in the B ring diminishes, the inhibition activity declines. Furthermore, comparing (−)-EZG with compound **12**, the *meta* OH is more effective than the *para* OH group in enhancing inhibition activity. This result is consistent with the model in Figure 2 where there is H-bonding between the *meta* OH with the amino acids in the active site. The nearly equal potencies of compound **12** and its enantiomer **13** agree with all our previous observation that the natural polyphenols and their synthetic enantiomers have nearly equal activities in the inhibition of proteasome.[11,12] Because **14** without OH group in B ring still inhibits the proteasomal chymotrypsin-like activity mediated by β5-subunit though with reduced potency (Table 2), it suggests to us that interaction of Thr21 and Ala49 of β5 to the two OH groups in B ring of EGCG (Fig. 2) might not be essential for the proteasome-inhibitory activity, but may be required for improving the potency of EGCG. Compound **14**, as well as other analogs, will be docked to the β5-subunit to validate this prediction. As for hydrophobic substitution in the A ring, compounds **15** and **16** were found to be slightly more active than the counterparts (+)-ECG and (−)-CG or the natural (+)-CG. This suggests that the hydrophobic benzyl substitution at the C-8 position of A ring did not significantly affect the proteasome-inhibitory potency. This may be due to the rather large steric size of the benzyl group. Substitution with alkyl groups of different sizes will be required to explore the dimension of this hydrophobic pocket.

Several of these compounds have also been tested in cultured tumour cells. We found that they moderately inhibited cellular proteasome activity and induced apoptosis in a portion of tumour cells.[17] These data suggest that although these compounds act as proteasome inhibitors in vivo, their potency is decreased probable due to their decreased stability.[17]

3. Conclusions

We have studied thus far the structure–activity relationship in the inhibition of proteasome by green tea polyphenols by modifications of A, C and B rings as well as the stereochemistry of the two stereogenic centres. The results appear to be consistent with the model proposed with the polyphenol binding to the active site of β5-subunit of 20S proteasome. Remained unexplored is the variation in the structure in the gallate (G) ring. This will be the subject of another study.[18]

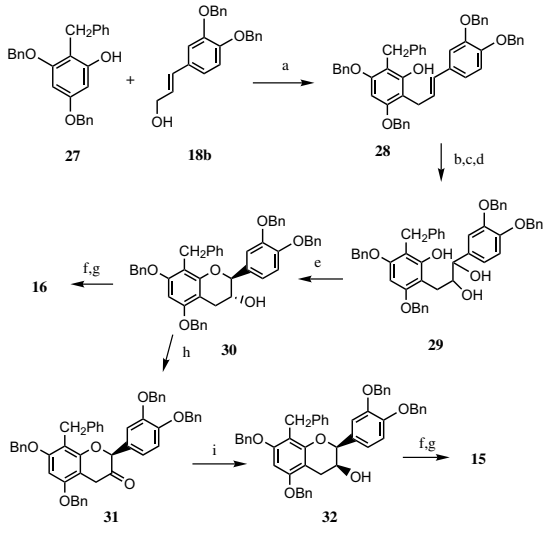
Table 2. Effects of natural and synthetic tea polyphenols on 20S prokaryotic proteasome activities

Compound	IC_{50} (μM)	Reference
(−)-EGCG, **10**	0.30	This work
(−)-ECG, **8**	0.58	Ref. 12
(+)-CG, **7**	0.73	Ref. 12
(−)-EZG, **6**	2.69	This work
(+)-ZG, **11**	4.56	This work
12	0.84	This work
13	1.22	This work
14	4.56	This work
(+)-ECG	0.73	Ref. 12
15	0.39	This work
(−)-CG	0.75	Ref. 12
16	0.59	This work

4. Experimental

4.1. General

The starting materials and reagents, purchased from commercial suppliers, were used without further purification. Literature procedures were used for the preparation of 3,5-bis(benzyloxy)phenol (**17**),[10,16] 3,4,5-tris(benzyloxy)benzoic acid,[10] silica gel supported H_2SO_4,[10] (*E*)-3,4-bis(benzyloxy)cinnamyl alcohol (**18b**)[12] and (*E*)-3-(benzyloxy)cinnamyl alcohol (**18d**).[4] Anhydrous THF was distilled under nitrogen from sodium benzophenone ketyl. Anhydrous methylene chloride was distilled under nitrogen from CaH_2. Anhydrous DMF was distilled



Scheme 5. Reagents and conditions: (a) $H_2SO_4/SiO_2/CH_2Cl_2$, rt; (b) TBSCl/imidazole/DMF, rt; (c) AD-mix-β/$MeSO_2NH_2/H_2O$/*t*-BuOH/CH_2Cl_2/0 °C; (d) TBAF/THF, rt; (e) $CH(OEt)_3$/PPTS/CH_2Cl_2, 60 °C; (f) 3,4,5-tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (g) H_2/$Pd(OH)_2$/MeOH/THF, rt; (h) Dess–Martin periodinane/CH_2Cl_2, rt; (i) L-Selectride/THF, −78 °C to rt.

under vacuum from CaH_2. Reaction flasks were flame-dried under a stream of N_2. All moisture-sensitive reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silica-gel 60 (70–230 mesh). The melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were measured with TMS as an internal standard when $CDCl_3$ or acetone-d_6 were used as solvent. High-resolution (ESI) MS spectra were recorded using a QTOF-2 Micromass spectrometer.

4.2. 2-Benzyl-3,5-bis(benzyloxy)phenol (27)

Butanethiol (19 g, 216 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 2.4 g, 100 mmol) in dry DMF (120 mL) at 0 °C. After 1 h, 1,3,5-tribenzyloxybezene (24 g, 60 mmol) was added in 10 batches and the mixture was heated to 150 °C for 1.5 h. After the reaction was cooled, water (500 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (benzene) to give the product **17** as white solid (9.3 g, 64%) after recrystallization from carbon tetrachloride and product **27** as white solid (3.0 g, 16%) after recrystallization from EtOAc and hexane.

When ethanethiol was used instead of butanethiol, the mixture was heated to 150 °C for 1.5 h while excess ethanethiol was distilled off in the first 10 min. The reaction mixture was work up as the above procedure to afford 56% of **27** and 11% **17**. Compound **27** was identified by mp 107–109 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.23 (m, 15H), 6.25 (d, $J = 2.2$ Hz, 1H), 6.07 (d, $J = 2.2$ Hz, 1H), 4.96 (s, 2H), 4.92 (s, 2H), 3.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.4, 157.9, 154.9, 140.7, 136.7, 136.6, 128.4, 128.2, 128.1, 127.8, 127.5, 127.3, 127.0, 125.6, 108.5, 94.7, 93.3, 70.2, 69.9, 28.3; HRMS (ESI) calcd for $C_{27}H_{24}O_3Na$ (M+Na) 419.1623, found 419.1645.

4.3. (*E*)-3-[2,4-Bis(benzyloxy)-5-benzyl-6-hydroxyphenyl]-1-[3,4-bis(benzyloxy)phenyl]propene (28)

At rt under an N_2 atmosphere, 25% H_2SO_4/SiO_2 (1.6 g, 4 mmol) was added in one batch to the stirred mixture of 2-benzyl-3,5-bis(benzyloxy)phenol (3.96 g, 10 mmol) and (*E*)-3,4-bis(benzyloxy)cinnamyl alcohol (3.46 g, 10 mmol) in dry CH_2Cl_2 (80 mL). The resulting mixture was stirred at rt overnight. After filtration and evaporation, the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/7 v/v) and recrystalized from EtOAc and *n*-hexane to give a white solid, (3.4 g, 46.0% yield): mp 93–95 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.22 (m, 30H), 6.92 (s, 1H), 6.79 (s, 1H), 6.78 (d, $J = 4.0$ Hz, 1H), 6.35 (A of AB, $J = 15.8$ Hz, 1H), 6.26 (s, 1H), 6.13–6.07 (B of ABt, $J = 15.8$, 5.0 Hz, 1H), 5.08 (s, 2H), 5.07 (s, 2H), 4.99 (s, 4H), 4.02 (s, 2H), 3.55 (d, $J = 5.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.1, 155.6, 154.0, 148.9, 148.2, 141.1, 137.2, 137.1, 131.0, 130.1, 128.5, 128.4, 128.2, 127.8, 127.7, 127.6, 127.3, 127.2, 127.1, 126.5, 125.7, 119.7, 114.9, 112.4, 109.6, 107.3, 91.4, 71.1, 70.5, 70.3, 28.8, 26.6; HRMS (ESI): calcd for $C_{50}H_{44}O_5Na$ (M+Na) 747.3086, found 747.3096.

4.4. (−)-(1*R*,2*R*)-3-[2,4-Bis(benzyloxy)-5-benzyl-6-hydroxy-phenyl]-1-[3,4-bis(benzyloxy)phenyl]propane-1,2-diol ((−)-29)

The propene **28** (3.4 g, 4.6 mmol) was dissolved in dry DMF (30 mL), and to this solution imidazole (1.03 g, 15.2 mmol) and TBSCl (1.2 g, 7.8 mmol) were added successively. The resulting mixture was stirred at rt for 3 days, and then saturated Na_2CO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatograph on silica gel (*n*-hexane and EtOAc = 9/1 v/v) to afford [3,5-bis(benzyloxy)-6-benzyl-2-[3-[3,4-bis(benzyloxy)phenyl]allyl]phenoxy]-*tert*-butyldimethylsilane. This material was used in the next step without further purification.

AD-mix-β (13.0 g) and methanesulfonamide (0.87 g) were dissolved in a solvent mixture of *t*-BuOH (50 mL) and H_2O (50 mL). The resulting mixture was stirred at rt for 5 min, then the mixture was cooled to 0 °C and a solution of [3,5-bis(benzyloxy)-6-benzyl-2-[3-[3,4-bis(benzyloxy)phenyl]allyl]phenoxy]-*tert*-butyldimethylsilane in dichloromethane (50 mL) was added. After the mixture had been stirred overnight, two more batches of AD-mix-β (13.0 g each) and methanesulfonamide (0.87 g each) were added in each 24 h intervals. After another 24 h of stirring at 0 °C, TLC showed that the reaction was completed. Then a 10% $Na_2S_2O_3$ solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatograph on silica gel (*n*-hexane and EtOAc = 4/1 v/v) to afford [3,5-bis(benzyloxy)-6-benzyl-2-[3-[3,4-bis(benzyloxy)phenyl]-1,2-dihydroxyl-propyl]phenoxy]-*tert*-butyldimethylsilane. The resulting compound was dissolved in THF (75 mL), and TBAF (10 mL, 1 M in THF) was added. The resulting mixture was stirred at rt for 4 h, and saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc, and the organic layers were combined, dried (MgSO4) and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/2 v/v) and then recrystallized from EtOAc and hexane to give a white solid (2.4 g, 67% yield) (−)-**29**: mp 157–159 °C; $[\alpha]_D$ −5.5 ($c = 1.1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.09 (m, 25H), 6.91 (d, $J = 1.6$ Hz, 1H), 6.77 (m, 2H), 6.17 (s, 1H), 5.06 (s, 4H), 4.98 (s, 2H), 4.82 (AB, $J = 11.9$ Hz, 2H), 4.42 (d, $J = 6.6$ Hz, 1H), 4.05 (s, 2H), 3.91 (br, 1H), 2.93 (A of ABt, $J = 14.5$, 3.2 Hz, 1H), 2.72 (B of ABt, 14.5, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.4, 155.6, 155.3, 148.9, 148.8, 142.1, 137.2, 137.1, 137.0, 133.5, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.3, 127.2, 127.1, 126.7, 125.3, 119.9, 114.5, 113.6, 112.1, 111.2, 106.7, 90.9, 77.2, 76.7, 71.1, 70.9, 70.3, 70.2,

29.1, 26.8; HRMS (ESI) calcd for $C_{50}H_{46}O_7Na$ (M+Na) 781.3141, found 781.3110.

4.5. (−)-(2*S*,3*R*)-*trans*-5,7-Bis(benzyloxy)-8-benzyl-2-[3,4-bis-(benzyloxy)phenyl]chroman-3-ol ((−)-30)

To a suspension of (−)-**29** (2.4 g, 3.1 mmol) in 1,2-dichloroethane (50 mL) was added triethyl orthoformate (1 mL), followed by PPTS (450 mg, 1.8 mmol). The mixture was stirred at rt for 20 min until the solid dissolved. The mixture was then heated to 55 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was dissolved in DME (30 mL) and MeOH (30 mL), K_2CO_3 (450 mg) was added. The mixture was stirred at rt overnight. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1/3 v/v) to afford the desired product as white solid (1.8 g, 77% yield): mp 145–146 °C; $[\alpha]_D$ −20.1 (c = 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.15 (m, 25H), 6.93 (d, J = 1.6 Hz, 1H), 6.88 (A of AB, J = 8.3 Hz, 1H), 6.82 (B of ABt, J = 8.3, 1.6 Hz, 1H), 6.24 (s, 1H), 5.13 (s, 2H), 5.02 (s, 2H), 5.00 (s, 2H), 4.98 (s, 2H), 4.63 (d, J = 8.1 Hz, 1H), 4.04 (AB, J = 14.2 Hz, 2H), 3.86 (m, 1H), 3.10 (A of ABt, J = 5.6, 16.4 Hz, 1H), 2.67 (B of ABt, J = 9.0, 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 155.8, 155.5, 152.9, 148.9, 148.8, 142.2, 137.2, 137.1, 137.0, 136.9, 131.2, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.4, 127.2, 127.1, 127.0, 125.2, 120.2, 114.5, 113.2, 110.2, 102.4, 91.1, 81.2, 71.1, 70.9, 70.4, 69.9, 68.2, 28.6, 27.6. HRMS (ESI) calcd for $C_{50}H_{44}O_6Na$ (M+Na) 763.3036, found 763.3032.

4.6. (+)-(2*R*)-5,7-Bis(benzyloxy)-8-benzyl-2-[3,4-bis(benzyloxy)-phenyl]chroman-3-one ((−)-31)

Dess–Martin periodinane (6.3 mL, 15% g/mL in CH_2Cl_2, 2.2 mmol) was added in one batch to a stirred solution of (−)-**30** (900 mg, 1.2 mmol) in CH_2Cl_2 (30 mL) under an N_2 atmosphere. The mixture was stirred at rt for about 2 h till TLC showed the absence of starting material. Subsequently, saturated $NaHCO_3$ solution (15 mL) and 10% $Na_2S_2O_3$ aqueous solution (15 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (benzene) and then recrystallized in $CHCl_3$ and ether to afford the desired compound (770 mg, 86%): mp 143–145 °C, $[\alpha]_D$ −17.1 (c = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.07 (m, 25H), 6.89 (s, 1H), 6.84 (AB, J = 8.5 Hz, 2H), 6.33 (s, 1H), 5.13–5.04 (m, 6H), 5.02 (s, 1H), 4.99 (s, 2H), 4.05 (AB J = 14.2 Hz, 2H), 3.67 (AB, J = 20.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 205.8, 156.5, 154.8, 152.5, 149.0, 148.7, 141.7, 137.1, 136.9, 136.8, 136.5, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.3, 127.1, 125.4, 120.0, 114.5, 113.2, 111.9, 102.4, 92.6, 82.9, 71.0, 70.5, 70.2, 34.0, 28.8; HRMS (ESI) calcd for $C_{50}H_{42}O_6Na$ (M+Na) 761.2879, found 761.2843.

4.7. (+)-(2*S*,3*S*)-*cis*-5,7-Bis(benzyloxy)-8-benzyl-2-[3,4-bis-(benzyloxy)phenyl]chroman-3-ol ((+)-32)

Under an N_2 atmosphere, the ketone (−)-**31** (700 mg, 0.95 mmol) was dissolved in dry THF (15 mL), and the solution was cooled to −78 °C. Then L-Selectride (1.5 mL, 1 M solution in THF, 1.5 mmol) was added dropwise. The resulting solution was stirred at −78 °C for 8 h. When TLC showed the reaction was completed, saturated $NaHCO_3$ aqueous solution (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAC/benzene) and then recrystallized with ethanol and EtOAC to afford the desired product (630 mg, 90%) as a white solid: mp 129–131 °C, $[\alpha]_D$ +5.3 (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.07 (m, 25H), 7.05 (s, 1H), 6.93 (AB, J = 8.4 Hz, 2H), 6.26 (s, 1H), 5.15 (s, 2H), 5.02 (s, 2H), 5.00 (s, 4H), 4.92 (br s, 1H), 4.20 (br s, 1H), 4.10 (AB, J = 14.5 Hz, 2H), 3.07 (A of AB, J = 17.2 Hz, 1H), 2.92 (B of ABt, J = 17.2, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.2, 155.9, 152.8, 148.9, 148.5, 142.1, 137.2, 137.1, 137.0, 131.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.4, 127.2, 125.2, 118.9, 114.9, 112.9, 110.2, 101.1, 91.4, 78.0, 71.2, 71.0, 70.5, 70.0, 66.1, 28.6, 28.2; HRMS (ESI) calcd for $C_{50}H_{44}O_6Na$ (M+Na) 763.3036 found 763.3024.

4.8. (+)-(2*S*,3*S*)-5,7-Bis(benzyloxy)-8-benzyl-2-[3,4-bis-(benzyloxy)-phenyl]chroman-3-yl 3,4,5-tris(benzyloxy)-benzoate ((+)-33)

Under an N_2 atmosphere, a solution of 3,4,5-tris(benzyloxy)benzoic acid (170 mg, 0.39 mmol) was refluxed with oxally chloride (1 mL) in dry CH_2Cl_2 (10 mL) and one drop of DMF for 3 h. The excess oxally chloride and solvent were removed by distillation and the residue was dried under vacuum for 3 h and dissolved in CH_2Cl_2 (2 mL). This solution was added dropwise to a solution of (+)-**32** (150 mg, 0.20 mmol) and DMAP (75 mg, 0.62 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at rt overnight, then saturated $NaHCO_3$ aqueous solution was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc/benzene) to afford the desired compound (215 mg, 91%). Recrystallization in $CHCl_3$ and ether gave a white powder: mp 52–54 °C; $[\alpha]_D$ +37.5 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.10 (m, 42H), 6.99 (t, J = 7.4 Hz, 1H), 6.93 (AB, J = 8.3 Hz, 2H), 6.31 (s, 1H), 5.65 (br s, 1H), 5.13 (br s, 1H), 5.07 (s, 2H), 5.02 (s, 4H), 5.00 (s, 2H), 4.92 (s, 4H), 4.83 (AB, J = 11.8 Hz, 2H), 4.11 (s, 1H), 3.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 165.2, 156.0, 155.9, 153.2, 152.3, 148.8, 148.6, 142.6, 142.2, 137.4, 137.2, 137.0, 136.5, 131.4, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 127.3, 127.2, 125.4, 125.1, 119.4, 114.6, 113.2, 110.3, 109.2, 101.0,

91.2, 75.1, 71.1, 70.5, 70.0, 68.6, 28.7, 26.2; HRMS (ESI) calcd for $C_{78}H_{66}O_{10}Na$ (M+Na) 1185.4554, found 1185.4542.

4.9. (−)-(2*S*,3*R*)-5,7-Bis(benzyloxy)-8-benzyl-2-[3,4-bis-(benzyloxy)phenyl]chroman-3-yl 3,4,5-tris(benzyloxy)-benzoate ((−)-34)

Following the procedure used for the preparation of (−)-**33** but with (−)-**30** as starting material, (−)-(2*S*,3*R*)-5,7-bis(benzyloxy)-8-benzyl-2-[3,4-bis(benzyloxy)phenyl]chroman-3-yl 3,4,5-tris(benzyloxy)benzoate was obtained (90% yield) as a white solid: mp 103–105 °C, $[\alpha]_D$ −9.8 (*c* = 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.11 (m, 42H), 6.90 (s, 1H), 6.77 (m, 2H), 6.27 (s, 1H), 5.42 (m, 1H), 5.18 (d, *J* = 6.3 Hz, 1H), 5.06 (s, 4H), 5.05–4.99 (m, 4H), 4.97 (s, 4H), 4.88 (s, 2H), 4.12 (AB, *J* = 14.1 Hz, 2H), 3.01 (A of ABt, *J* = 16.8, 5.0 Hz, 1H), 2.89 (B of ABt, *J* = 16.8, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.0, 155.9, 155.4, 152.5, 152.3, 148.8, 148.6, 142.3, 142.1, 137.3, 137.1, 137.0, 136.9, 136.5, 131.3, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 125.3, 124.9, 114.6, 112.8, 110.2, 108.9, 101.5, 91.0, 78.0, 75.0, 71.2, 71.1, 71.0, 70.4, 70.0, 69.9, 28.6, 24.0; HRMS (ESI) calcd for $C_{78}H_{66}O_{10}Na$ (M+Na) 1185.4554, found 1185.4573.

4.10. (+)-(2*S*,3*S*)-5,7-Dihydroxy-8-benzyl-2-[3,4-dihydroxy-phenyl]chroman-3-yl 3,4,5-trihydroxybenzoate ((+)-15)

Under an H_2 atmosphere, $Pd(OH)_2/C$ (20%, 400 mg) was added to a solution of (+)-**33** (200 mg, 0.17 mmol) in a solvent mixture of THF/MeOH (1:1 v/v, 20 mL). The reaction mixture was stirred at rt under H_2 for 6 h when 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 chromatograph on silica gel (10%MeOH/CH_2Cl_2, then 20% MeOH/CH_2Cl_2) to afford (+)-8-benzylcatechin gallate ((+)-**16**) (82 mg, 90% yield): mp 243–245 °C (decomposed); $[\alpha]_D$ +123 (*c* = 1.8, acetone); ^1H NMR (acetone-d_6, 400 MHz): δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.26–7.21 (m, 4H), 7.04 (AB, *J* = 8.2 Hz, 2H), 6.31 (s, 1H), 5.75 (br s, 1H), 5.32 (br s, 1 H), 4.22 (AB, *J* = 14.3 Hz, 2H), 3.29 (A of ABt, *J* = 17.4, 4.4 Hz, 1H), 3.17 (B of AB, *J* = 17.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 165.2, 154.2, 154.1, 153.6, 144.9, 144.6, 144.3, 142.6, 137.9, 130.6, 128.4, 127.8, 125.0, 120.9, 118.1, 114.7, 113.7, 109.1, 106.7, 98.0, 95.3, 77.1, 68.3, 25.9; HRMS (ESI) calcd for $C_{29}H_{24}O_{10}Na$ (M+Na) 555.1267, found 555.1279.

4.11. (−)-(2*S*,3*R*)-5,7-Dihydroxy-8-benzyl-2-[3,4-dihydroxyphenyl]chroman-3-yl 3,4,5-trihydroxybenzoate ((−)-16)

Following the procedure for the preparation (+)-**15**, but with (−)-**33** as starting material, (−)-8-benzyl *epi*-catechin gallate ((−)-**16**) was obtained (91% yield): mp 239–241 °C (decomposed); $[\alpha]_D$ −35 (*c* = 2.0, acetone); ^1H NMR (acetone-d_6, 400 MHz): δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.23 (s, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.92–6.86 (m, 2H), 6.34 (s, 1H), 5.56 (m, 1H), 5.35 (d, *J* = 6.2 Hz, 1H), 4.17 (AB, *J* = 14.3 Hz, 2H), 3.12 (A of ABt, *J* = 16.5, 5.2 Hz, 1H), 2.98 (B of ABt, *J* = 16.5. 6.2 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 165.0, 154.1, 153.7, 152.8, 144.9, 144.7, 144.6, 142.2, 137.8, 130.2, 128.3, 127.5, 124.8, 120.5, 117.9, 114.8, 113.2, 108.8, 106.2, 98.2, 95.1, 77.7, 69.4, 23.5; HRMS (ESI) calcd for $C_{29}H_{24}O_{10}Na$ 555.1267, found 555.1285.

4.12. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3-benzyloxyphenyl]propene (9d)

At −20 °C under an N_2 atmosphere, di-isopropyl azocarboxylate (3.03 g, 15 mmol) was added to a solution of (*E*)-3-benzyloxycinnamyl alcohol (2.4 g, 10 mmol), 3,5-bis(benzyloxy)phenol (3.06 g, 10 mmol) and triphenylphosphine (3.93 g, 15 mmol) in dry toluene (100 mL). The mixture was stirred for 1 h, −5 to −20 °C. After evaporation, the residue was purified by chromatography on silica gel (benzene) to give the desired compound as a white solid 3.19 g (60% yield): mp 82–84 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.30 (m, 15H), 7.19–7.15 (t, 7.9 Hz, 1H), 6.93–6.89 (m, 2H), 6.79 (dd, *J* = 7.9, 2.2 Hz, 1H), 6.43 (A of AB, *J* = 15.9 Hz, 1H), 6.33 (B of ABt, *J* = 15.9, 5.6 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 5.17 (s, 1H), 5.01 (s, 2H), 5.00 (s, 2H), 4.97 (s, 2H), 3.57–3.56 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.7, 158.5, 157.7, 155.4, 138.6, 136.8, 136.7, 130.0, 129.2, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 17.3, 127.2, 127.1, 118.9, 113.4, 112.1, 106.7, 94.8, 93.4, 70.1, 69.9, 69.7, 26.2; HRMS (ESI) calcd for $C_{36}H_{32}O_4Na$ (M+Na) 551.2198, found 551.2187.

4.13. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-phenylpropene (19e)

Following the procedure of the preparation of **19d**, cinnamyl alcohol was used as starting material to yield **19e** as a white solid (62% yield); mp 76–78 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.24 (m, 15H), 6.48 (A of AB, *J* = 15.9 Hz, 1H), 6.35 (B of ABt, *J* = 15.9, 5.5 Hz, 1H), 6.27 (d, *J* = 2.1 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 1H), 5.07 (s, 1H), 5.02 (s, 2H), 4.99 (s, 2H), 3.59–3.57 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.5, 157.6, 155.4, 137.0, 136.8, 136.6, 130.2, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.3, 127.0, 126.8, 125.8, 106.6, 94.8, 93.4, 70.1, 69.9, 26.2; HRMS (ESI) calcd for $C_{29}H_{26}O_3Na$ (M+Na) 445.1780, found 445.1793.

4.14. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-3-benzyloxyphenylpropane-1,2-diol ((+)-22d)

Following the procedure used for the preparation of (−)-**29** but with **19d** as starting material and AD-mix-α as dihydroxylation regent, ((+)-**22d**) was obtained (63% yield) as a white solid; mp 120–122 °C; $[\alpha]_D$ +4.4 (*c* = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.20 (m, 14H), 7.07–7.04 (m, 3H), 6.90 (s, 1H),

6.81 (m, 2H), 6.18 (s, 1H), 6.13 (s, 1H), 4.87 (s, 4H), 4.77 (s, 2H), 4.38 (d, J = 6.1 Hz, 1H), 3.94 (m, 1H), 2.87 (A of AB, J = 14.2, 1H), 2.71 (B of ABt, J = 14.2, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.9, 158.7, 157.7, 157.1, 141.9, 136.8, 136.7, 129.5, 128.5, 128.4, 127.9, 127.6, 127.5, 127.4, 126.7, 119.2, 114.5, 113.2, 106.1, 95.7, 93.3, 76.7, 69.9, 69.8, 26.5; HRMS (ESI) calcd for $C_{36}H_{34}O_6Na$ (M+Na) 585.2253, found 585.2293.

Using the same procedure, AD-mix-β was used to afford (−)-**22d** with opposite configuration and identical NMR spectra as the (+)-isomer.

4.15. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-phenylpropane-1,2-diol ((+)-22e)

Following the procedure used for the preparation of (−)-**29** but with **19e** as starting material and AD-mix-α as dihydroxylation regent, (+)-**22e** was obtained (47% yield) as a white solid; mp 121–123 °C; $[\alpha]_D$ +4.7 (c = 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.19 (m, 13H), 7.10 (m, 2H), 6.23 (d, J = 2.3 Hz, 1H), 6.17 (d, J = 2.3 Hz, 1H), 4.94 (s, 2H), 4.82 (AB, J = 11.7 Hz, 2H), 4.47 (d, J = 6.6 Hz, 1H), 3.97 (m, 1H), 2.88 (A of ABt, J = 14.6, 3.6 Hz, 1H), 2.72 (B of ABt, J = 14.6, 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.8, 157.6, 157.0, 140.0, 136.6, 136.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.4, 127.3, 126.8, 126.5, 105.9, 95.6, 93.2, 76.6, 69.8, 69.7, 26.2; HRMS (ESI) calcd for $C_{29}H_{28}O_5Na$ (M+Na) 479.1834, found 479.1841.

4.16. (+)-(2*S*,3*S*)-*cis*-5,7-Bis(benzyloxy)-2-(3-benzyloxyphenyl)chroman-3-ol ((+)-25d)

To a suspension of (1*S*,2*S*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-phenylpropane-1,2-diol (360 mg, 0.79 mmol) in 1,2-dichloroethane (10 mL) was added triethyl orthoformate (170 mg, 1.6 mmol), followed by PPTS (118 mg, 0.47 mmol). The mixture was stirred at rt for 20 min and the solid dissolved, and then evaporated the solvent under vacuum. The residue was dissolved in dry CH_2Cl_2 (10 mL), the solution was cooled to −5 to 0 °C, and AcBr (145 mg, 112 mmol) was added dropwise. The mixture was stirred at −5 to 0 °C for 45 min, distilled the solvent under vacuum. Acetone (15 mL) and K_2CO_3 (160 mg) were added successively. After the mixture was stirred at rt for 6 h, methanol (15 mL) and another batch of K_2CO_3 (160 mg) were added. Then the mixture was stirred at rt overnight. After evaporating the solvent, water (30 mL) was added, extracted with CH_2Cl_2, the combined organic phases was dried ($MgSO_4$) and solvent was distilled under vacuum. The residue was purified by chromatograph on silica gel (*n*-hexane/EtOAc = 3/1 v/v), then recrystallized to give a white solid 170 mg (49%); mp 85–87 °C; $[\alpha]_D$ +37.4 (c = 1.1, ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.31 (m, 16H), 7.18 (br s, 1H), 7.08 (d, J = 7.3 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.30 (d, J = 6.7 Hz, 2H), 5.08 (s, 2H), 5.00 (s, 4H), 4.79 (br s, 1H), 4.26 (br s, 1H), 3.05 (AB, J = 17.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 159.0, 158.7, 158.2, 155.1, 139.8, 136.8, 129.6, 128.5, 127.9, 127.8, 127.5, 127.1, 118.6, 114.2, 112.9, 110.9, 94.6, 94.0, 78.4, 70.0, 69.9, 69.8, 66.3, 28.2; HRMS (ESI) calcd for $C_{36}H_{32}O_5Na$ (M+Na) 567.2147, found 567.2128.

Using the same procedure, (−)-**22d** was used as starting material to afford (−)-**25d** with opposite configuration and identical NMR spectra as the (+)-isomer.

4.17. (+)-(2*S*,3*S*)-*cis*-5,7-Bis(benzyloxy)-2-phenylchroman-3-ol ((+)-25e)

Following the procedure used for the preparation of (+)-**25d**, but with (+)-**22e** as starting material, (+)-**25e** was obtained (47% yield) as a white solid; mp 60–62 °C; $[\alpha]_D$ +0.9 (c = 1.0, ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.30 (m, 15H), 6.29 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 2.2 Hz, 1H), 5.02 (br s, 1H), 4.99 (s, 4H), 4.25 (br s, 1H), 3.03 (A of ABt, J = 17.2, 1.4 Hz, 1H), 2.96 (B of ABt, J = 17.2, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.7, 158.2, 155.2, 138.1, 136.9, 136.8, 128.5, 128.4, 128.0, 127.9, 127.8, 127.4, 127.1, 126.2, 100.9, 94.6, 94.0, 78.6, 70.0, 69.8, 66.2, 28.2; HRMS (ESI) calcd for $C_{29}H_{26}O_4Na$ (M+Na) 461.1729, found 461.1741.

4.18. (+)-(2*S*,3*S*)-5,7-Bis(benzyloxy)-2-(3-benzyloxyphenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((+)-35)

Following the procedure used for the preparation of (+)-**33** but with (+)-**25d** as starting material, (+)-**35** was obtained (80% yield) as a white solid: mp 107–109 °C, $[\alpha]_D$ +65.1 (c = 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.17 (m, 31H), 7.12 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 6.39 (s, 1H), 6.31 (s, 1H), 5.62 (br s, 1H), 5.14 (br s, 1H), 5.02 (s, 4H), 5.01 (s, 4H), 4.99 (s, 2H), 4.84 (AB, J = 11.4 Hz, 2H), 3.11 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.8, 158.5, 157.7, 155.2, 152.0, 139.1, 137.2, 136.6, 136.5, 136.2, 129.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.4, 127.2, 126.9, 124.7, 118.8, 114.1, 113.0, 108.7, 100.6, 94.4, 93.6, 77.3, 74.8, 70.7, 69.9, 69.7, 69.6, 68.4, 25.7; HRMS (ESI) calcd for $C_{64}H_{54}O_9Na$ (M+Na) 989.3666, found 989.3633.

Using the same procedure, (−)-**25** was used as starting material to afford (−)-**35** with opposite configuration and identical NMR spectra as the (+)-isomer.

4.19. (+)-(2*S*,3*S*)-5,7-Bis(benzyloxy)-2-(3-benzyloxyphenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((+)-36)

Following the procedure used for the preparation of (+)-**33** but with (+)-**25e** as starting material, (+)-**36** was obtained (82% yield) as a white solid: mp 130–132 °C, $[\alpha]_D$ +2.9 (c = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.24 (m, 30H), 7.19 (s, 2H), 6.39 (d, J = 2.2 Hz, 1H), 6.31 (d, J = 2.2 Hz, 1H), 5.60 (br s, 1H), 5.16 (br s, 1H), 5.07 (s, 2H), 5.03 (s, 2H), 5.02 (s, 2H), 5.01 (s, 2H), 4.99 (s, 2H), 3.10 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.9, 158.5, 157.7, 155.3, 152.0, 142.0, 137.5, 137.1, 136.6, 136.5, 136.3, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 126.9, 126.2, 124.7, 108.7, 100.6, 94.3, 93.6, 77.4, 74.8,

70.7, 69.9, 69.7, 68.5, 25.7; HRMS (ESI) calcd for $C_{57}H_{48}O_8Na$ (M+Na) 883.3247, found 883.3212.

4.20. (+)-(2*S*,3*S*)-5,7-Dihydroxy-2-(3-hydroxyphenyl)-chroman-3-yl 3,4,5-trihydroxybenzoate ((+)-12)

Following the procedure for the preparation (+)-**15**, but with (+)-**35** as starting material, compound (+)-**12** was obtained (90% yield): mp 251–253 °C (decomposed); $[\alpha]_D$ +141 ($c = 3.5$, ethanol); ^1H NMR (acetone-d_6, 400 MHz): δ 7.31–7.19 (m, 3H), 7.18 (s, 2H), 6.89 (dd, $J = 8.0$, 1.7 Hz, 1H), 6.24 (s, 1H), 6.23 (s, 1H), 5.76 (br s, 1H), 5.37 (br s, 1H), 3.26 (A of ABt, $J = 17.4$, 4.6 Hz, 1H), 3.13 (B of ABt, $J = 17.4$, 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.9, 156.7, 156.4, 156.1, 155.6, 144.6, 140.0, 137.4, 128.7, 120.5, 117.4, 114.2, 113.2, 108.7, 97.7, 76.9, 68.1, 25.406; HRMS (ESI) calcd for $C_{22}H_{18}O_9Na$ (M+Na) 449.0849, found 449.0833.

Using the same procedure, (−)-**35** was used as starting material to afford (−)-**13** with opposite configuration and identical NMR spectra as the (+)-isomer.

4.21. (+)-(2*S*,3*S*)-5,7-Dihydroxy-2-phenylchroman-3-yl 3,4,5-trihydroxybenzoate ((+)-14)

Following the procedure for the preparation (+)-**15**, but with (+)-**36** as starting material, compound (+)-**14** was obtained (90% yield): mp 258–260 °C (decomposed); $[\alpha]_D$ +13.9 ($c = 3.5$, ethanol); ^1H NMR (acetone-d_6, 400 MHz): δ 7.73–7.71 (m, 2H), 7.49–7.45 (m, 2H), 7.41–7.38 (m, 1H), 7.17 (s, 2H), 6.24 (d, $J = 2.2$ Hz, 1H), 6.23 (d, $J = 2.2$ Hz, 1H), 5.76 (br s, 1H), 5.44 (br s, 1H), 3.27 (A of ABt, $J = 17.4$, 4.5 Hz, 1H), 3.14 (B of ABt, $J = 17.4$, 1.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.7, 156.6, 156.3, 155.7, 144.7, 138.5, 137.6, 127.6, 127.3, 126.3, 120.4, 108.7, 97.7, 95.4, 94.6, 77.0, 68.1, 25.3; HRMS (ESI) calcd for $C_{22}H_{18}O_8Na$ (M+Na) 433.0899, found 433.0904.

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