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Tetrahedron
Tetrahedron 61 (2005) 7703–7711

Asymmetric total synthesis of B-ring modified (−)-epicatechin gallate analogues and their modulation of β-lactam resistance in *Staphylococcus aureus*

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Received 20 April 2005; revised 10 May 2005; accepted 26 May 2005

Available online 20 June 2005

Abstract—Two enantiomerically pure B-ring modified analogues of (−)-epicatechin gallate were synthesised and their modulation of β-lactam resistance using three strains of methicillin resistant *Staphylococcus aureus* (BB 568, EMRSA-15 and EMRSA-16) evaluated. Sub-inhibitory concentrations (12.5 and 25 mg/L) of the two analogues fully sensitised each of the three MRSA strains to oxacillin, reducing the MIC to less than 0.5 mg/L, identical to levels achieved with ECg. Lower concentrations demonstrated that the position and degree of hydroxylation of the B-ring is important for activity.

1. Introduction

The benefits to health of green tea (*Camellia sinensis*) are well documented[1] and are attributable, in the main, to polyphenolic constituents that include (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECg) and (−)-epigallocatechin gallate (EGCg), the four most abundant catechins present in green tea (~10% of dry weight, Fig. 1).[2] In addition to their capacity to inhibit the development of tumours,[3] catechins possess weak anti-bacterial properties[4] and catechin gallates are able to reduce the resistance of the opportunistic human pathogen *Staphylococcus aureus* to a wide spectrum of β-lactam antibiotics, such as methicillin, oxacillin and flucloxacillin.[5] Strains of methicillin-resistant *S. aureus* (MRSA) have emerged in recent years as a major cause of hospital-acquired infection and the difficulty in treating these infections is compounded by the fact that they are often also resistant to a wide range of other antibiotics.[6] The recent introduction of two novel antibacterial agents, quinupristin/dalfopristin and linezolid, has provided efficacious and safe therapeutic options for MRSA but there remains an urgent need for new treatments of these infections, in particular with agents that suppress or abrogate the emergence of drug resistance.

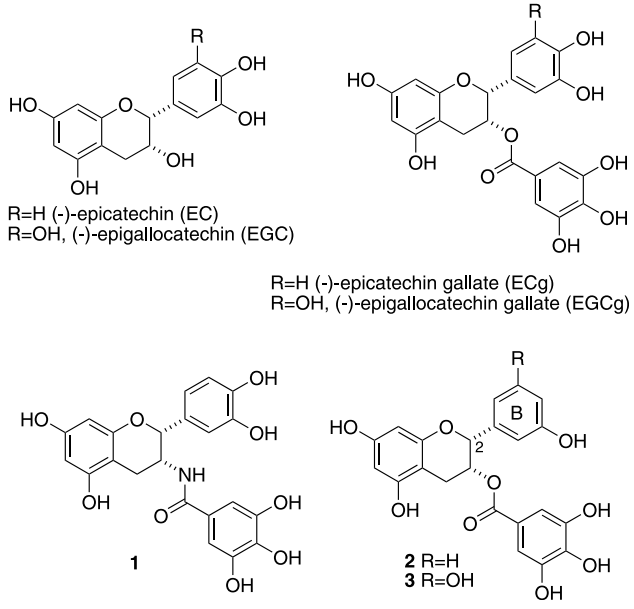

Figure 1.

The resistance modifying capacity of catechin gallates raises the possibility that such molecules could be used in combination with β-lactam agents that are currently of limited use in the treatment of MRSA infections. Naturally occurring catechin gallates, such as the potent modifier ECg,[7] are rapidly degraded in vivo to inactive products due

Keywords: Epicatechin gallate; Asymmetric synthesis; Oxacillin; MRSA.
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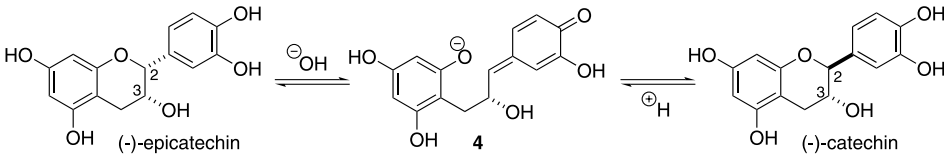
doi:10.1016/j.tet.2005.05.086



Scheme 1.

to the presence of esterase-susceptible linkage groups.[8] In addition, ECg and other catechin gallates are also known to undergo C-2 epimerisation in hot water or dilute hydroxide.[9–11] We have determined that the presence of the galloyl moiety is essential for β-lactam resistance modification by ECg.[7] In order to prevent the esterase-mediated removal of the galloyl moiety from catechin gallates, the initial step in the metabolism of these molecules, we have designed, synthesised and evaluated an amide ECg analogue **1** (Fig. 1) in which the hydrolytically susceptible ester bond was replaced with an inherently more stable amide linkage.[12] This compound reduced the oxacillin resistance of MRSA strains to levels that are comparable to those achieved with ECg.[12] In order to further improve the pharmacological profile of ECg, we have examined the effect of the degree of hydroxylation of the B-ring (Fig. 1) on modification of β-lactam resistance in MRSA: although the mechanism of modification is at present only partially understood, it is likely to involve a reduction in efficiency of membrane-associated cell wall synthesis as a result of intercalation of ECg into the staphylococcal cytoplasmic membrane.[13] Recent work has shown that catechins in the nanomole range are able to modulate the structure and function of model membranes due to their capacity to partition into the phospholipid palisade.[14] Galloyl catechins bound more avidly than either EC or EGC to small unilamellar vesicles produced from phosphatidyl choline, and ECg had a greater affinity for the membrane bilayer than EGCg.[14] The relative affinity of catechins for membrane bilayers is reflected in their capacity to modulate β-lactam resistance and their partition coefficients in *n*-octanol-saline. ECg differs from EGCg only by the absence of a hydroxyl function at one of the other *meta*- position of the B-ring; we surmised that a further reduction in the degree of hydroxylation of the B-ring would enhance anti-MRSA effects by increasing the affinity of these analogues for lipid bilayers.

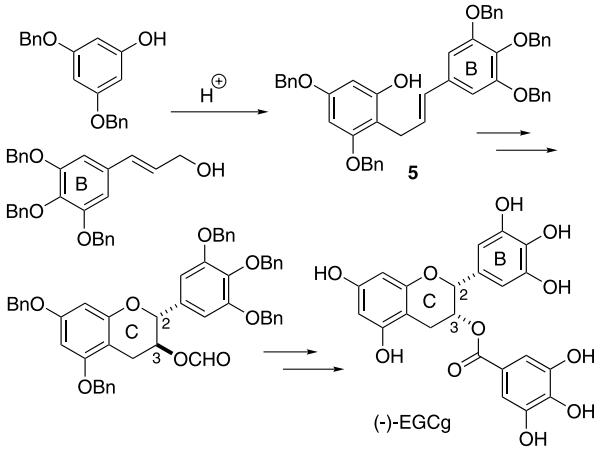
The facility for epimerization may also be due to the extent of hydroxylation of the aromatic B-ring. Rate measurements of epimerization of tea catechins in tea infusion indicated that the presence of hydroxyl groups on the B-ring of catechin structures promoted epimerization.[11] The most reasonable mechanism for epimerization involves the intermediate quinine methide **4**, proposed by Mehta and Whalley,[15] which is also supported by the fact that epimerization only affects the stereochemistry at C-2. (Scheme 1).[16] It has also been noted that under basic reaction conditions epimerization of epicatechin type molecules (2,3-*cis*) reaches an equilibrium in which the catechin type skeleton (2,3-*trans*) predominates.[10]

We proposed that a further reduction in the degree of hydroxylation of the B-ring would enhance anti-MRSA effects by increasing the affinity of these analogues for lipid bilayers. Specifically, modified ECg molecule **2** that did not possess the *para*-hydroxyl group would also be less prone to epimerization via a quinine methide-like intermediate due to the removal of this anchimeric substituent. We have synthesized this compound (**2**) in enantiomerically pure form, as well as the 3,5-dihydroxy B-ring (**3**) to compare their capacity to suppress the resistance of MRSA isolates to the β-lactam antibiotic oxacillin.

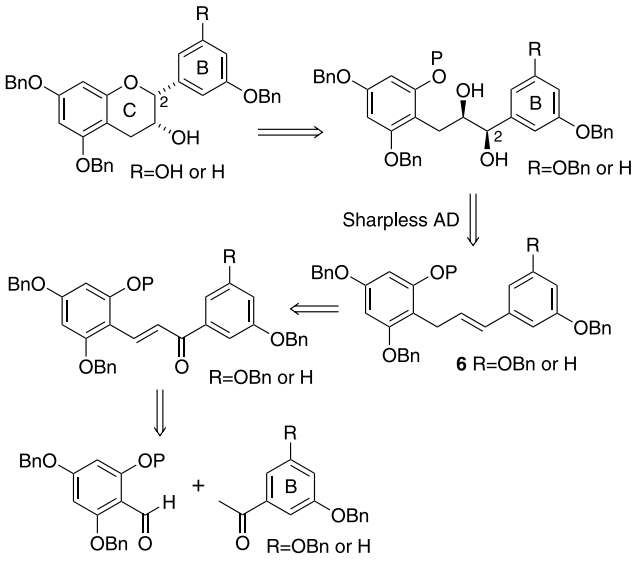
2. Chemical synthesis

We desired a flexible total synthesis that would allow access to analogues of ECg with respect to the number and location of the hydroxyl groups and also to individual stereoisomers. During the initial stages of our work there appeared two total syntheses of EGCg,[17,18] both forming the gallate ester bond at a late stage in the synthesis. The synthesis[15] by Li and Chan was enantioselective based upon the Sharpless asymmetric dihydroxylation[19] of **5** followed by subsequent cyclisation via an *ortho* ester to give the C-ring catechin 2,3-*trans* stereochemistry (Scheme 2).[15] Using a published stereochemical inversion of the C-3 hydroxyl of catechin derivatives,[20] oxidation of the C-3 hydroxyl group and reduction furnished the epicatechin 2,3-*cis* stereochemistry.

Our attempts at an analogous route using a 3-hydroxylated or 3,5-dihydroxylated B-ring failed at the acid induced coupling stage in an attempt to give the analogue of **5**. Presumably the *para*-oxygen functionality is important for the success of this coupling. It was also noted in Li and Chan's work[17] that under cyclisation conditions to give directly the *cis*-2,3 C-ring, the integrity at the benzylic C-2 position was compromised by the oxygenation of the B-ring, again most probably due to the *para*-hydroxyl group. We decided to access **6**, the 3-hydroxylated and 3,5-dihydroxylated B-ring analogue of **5** (Scheme 3), by using an aldol



Scheme 2.

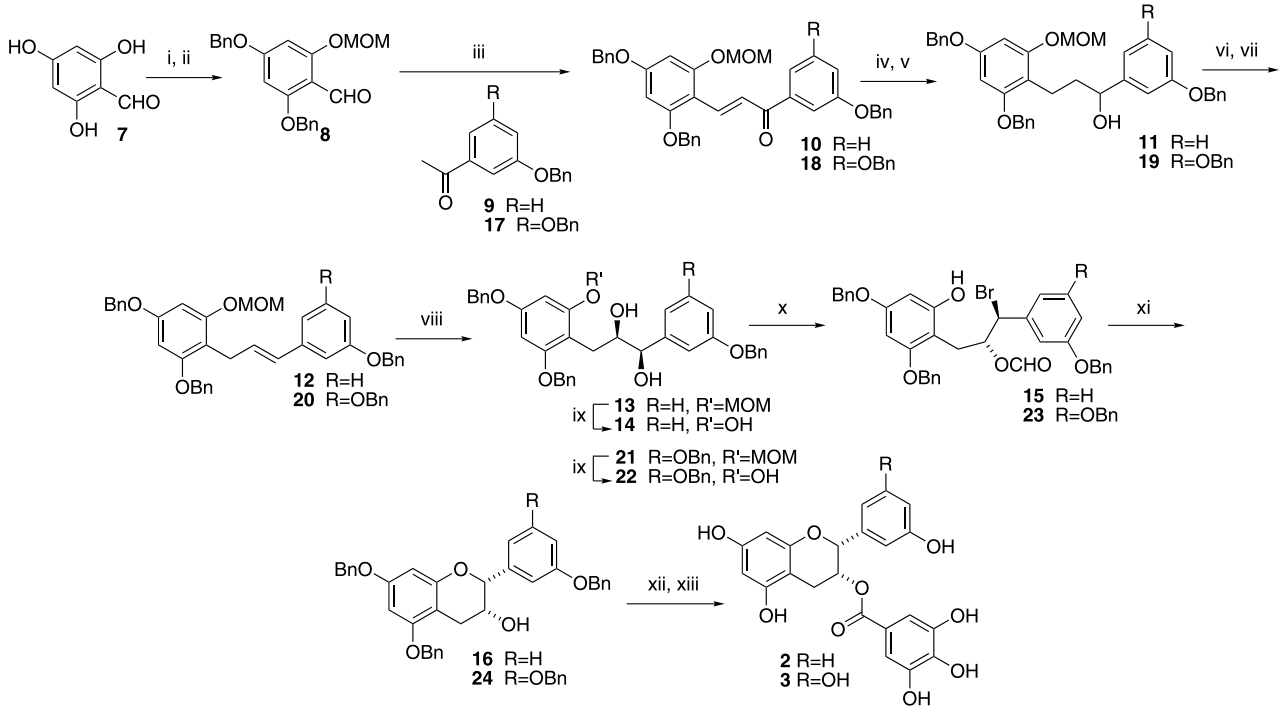


Scheme 3. Retrosynthesis.

dehydration/reduction protocol. We were confident that the reported loss of stereochemical integrity at C-2 upon cyclisation to form the C-ring would be impeded due to the lack of B-ring *para*-oxygenation. Both of the published syntheses[17,18] had shown that global debenzylation was high yielding and so we opted to use the benzyl protecting group except for the orthogonal protecting group P. Our retrosynthesis is detailed in Scheme 3.

Selective 2,4-benzylation[21] of 2,4,6-trihydroxybenzaldehyde (**7**), by treatment with K_2CO_3 and BnBr, was followed by standard MOM protection of the remaining 6-hydroxyl group to give **8** (Scheme 4). We planned that the MOM group would be orthogonal to the benzyl groups and could be selectively removed under acidic conditions that may facilitate cyclisation to form the C-ring. Condensation[22] of **8** with 3-benzyloxyacetophenone (**9**) gave enone **10** uneventfully in good yield. Reduction of the enone system to the alcohol and subsequent elimination to give the alkene was surprisingly capricious. Protocols for one step reduction[23] of the enone to the alcohol gave mixtures of reduction products and it was more efficient for material throughput to perform a two step reduction of the enone alkene with catechol borane[24] and then the resultant ketone with $NaBH_4$. Direct dehydration using acidic reagents was prohibited due to the lability of the MOM ether. The use of activating dehydration reagents; Burgess' reagent and DCC,[25] were slow and unable to give complete conversion. Elimination was achieved by conversion of the benzyl alcohol **11** to the corresponding bromide and then heating in the presence of DBU. The overall reductive isomerisation of enone **10** to alkene **12** was achieved in a four steps with an overall yield of 42% (Scheme 4).

Dihydroxylation of **12** using AD-mix-β®[19] gave **13** with an initial 75% ee (65%).[26] Recrystallisation gave a 48% isolated yield of enantiomerically pure **13**. Removal of the MOM ether (3 M HCl) gave triol **14**, but attempts at direct acid catalysed cyclisation (3 M HCl) proved impossible.



Scheme 4. Reagents: (i) K_2CO_3, BnBr, DMF, rt, 16 h, 69%; (ii) NaH, MOMCl, THF 0 °C to rt, 88%; (iii) KOH aq. (50%), EtOH, THF, rt, 16 h, R=H 69%, R=OBn 94%; (iv) Catechol borane, THF, −78 °C to rt, R=H 86% crude, R=OBn 86% crude; (v) $NaBH_4$, MeOH, rt, R=H 99% crude, R=OBn 99% crude; (vi) PPh_3, Br_2, Et_3N, CH_2Cl_2, 0 °C to rt, R=H 85%, R=OBn 99%; (vii) DBU, PhMe, 110 °C, 16 h, R=H 57%, R=OBn 53%; (viii) AD-mix-β®, *t*-BuOH, H_2O, $MeSO_2NH_2$, 0 °C, 5 days, R=H 65% @75% ee, 48% @>99% ee, R=OBn 82% @75% ee, 46% @>99% ee; (ix) HCl, MeOH, Et_2O, reflux, 5 h, R=H 100% crude, R=OBn 100% crude; (x) HC (OMe)$_3$, PPTS cat., CH_2Cl_2, rt; w/up then AcBr, CH_2Cl_2, rt, R=H 88% crude, R=OBn 91% crude; (xi) K_2CO_3, acetone, rt, 5 h; w/up then K_2CO_3, MeOH rt, 16 h, R=H 61%, R=OBn 45%; (xii) DCC, tri-*O*Bn gallic acid, DMAP, CH_2Cl_2, rt, 16 h, R=H 64%, R=OBn 67%; (xiii) H_2, 10% Pd(OH)$_2$/C, EtOAc, rt, 12 h, R=H 94%, R=OH 37%.

Presumably similar cyclisations in the literature[17,27] have relied upon the ring B para-hydroxyl group activating the benzylic hydroxyl group toward cyclisation. Although, this meant we had to adopt an alternative and longer synthetic route to form ring C, this was again circumstantial evidence to support our hypothesis that ECg analogues **2** and **3** would be more stable toward possible epimerization (Scheme 1). Cyclisation to the 2,3-*cis* substituted C-ring followed Li and Chan's protocol[17] whereby the corresponding cyclic orthoformate of **14** was ring opened with acetyl bromide[28] to give benzylic bromide **15** as a single diastereoisomer by ^{1}H NMR. Immediate treatment with K_2CO_3 caused cyclisation and deformylation to give the *cis*-2,3 substituted C-ring compound **16**. Completion of the synthesis was achieved by DCC induced coupling with 3,4,5-tribenzyloxy benzoic acid (55%) and subsequent global debenzylation by hydrogenolysis with $Pd(OH)_2$ catalysis (48%) to give the enantiomerically pure 3-hydroxy B-ring analogue (−)-**2** of ECg. The stereochemical integrity of the 2,3-*cis* substitution was proven from the multiplicity of the ^{1}H NMR signal of C–1H (**2**, δ 5.27, s) that compares favourably with the analogous signal in (−)-EGCg (δ 5.36, d, $J=1.2$ Hz)[17] and 5,7,3′,4′-tetra-*O*-benzyl-(−)-epicatechin (δ 4.91, s).[29] Contrasting signals in similar molecules possessing the 2,3-*trans* relationship also support this; 5,7,3′,4′,5′-penta-*O*-benzyl-gallocatechin (δ 4.65, d, $J=8.1$ Hz)[17] and 5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (δ 4.63, d, $J=8.5$ Hz).[21] Absolute stereochemistry was assumed from the Sharpless mnemonic for AD-mix-β®[19] and the fact that the final compound exhibits the same sense of optical rotation as naturally occurring (−)-ECg.

Repetition of this synthesis starting with 3,5-dibenzyloxy-acetophenone **17** led to the enantiomerically pure 3,5-dihydroxy B-ring analogue (−)-**3** of ECg uneventfully in similar yield. The 2,3-*cis* stereochemical relationship was again verified from the multiplicity of the ^{1}H NMR signal of C–1H (**3**, δ 4.99, s) that compares favourably with the above data.

3. Microbiological evaluation

With the B-ring modified analogues **2** and **3** in hand, their efficacy as modulators for β-lactam resistance in *S. aureus* was evaluated by determining their capacity to reduce the minimum inhibitory concentration (MIC) of oxacillin against MRSA strains BB 568, EMRSA-15 and EMRSA-16 (Table 1). The monohydroxylated B-ring analogue **2** possessed little or no intrinsic antibacterial activity against the three MRSA strains and in this respect was comparable to ECg (Table 1). Interestingly, the 3,5-dihydroxy B-ring analogue **3** showed weak to moderate anti-staphylococcal activity that was significantly higher than that shown by ECg and analogue **2**, suggesting that the position of hydroxyl groups on the B-ring may influence the intrinsic antibacterial activity of ECg analogues. Sub-inhibitory concentrations (6.25, 12.5 and 25 mg/L) of both compounds were effective in reducing the MIC of all three strains examined. At a concentration of 25 mg/L, ECg and the two analogues (**2** and **3**) fully sensitised each of the three MRSA strains to oxacillin, reducing the MICs to less than 0.5 mg/L, a figure well below the clinically-relevant breakpoint for

Table 1. Antibacterial activity of ECg, **2** and **3** and in combination with oxacillin against methicillin-resistant *S. aureus* (MRSA) strains

MRSA Strain	MIC (mg/L)[a]			Oxacillin MIC (mg/L)[a]								
	ECg	**2**	**3**	—	ECg[b]			**2**[b]			**3**[b]	
					6.25	12.5	25	6.25	12.5	25	6.25	12.5	25
BB 568	256	>128	128	256	1	≤0.5	≤0.5	16	2	≤0.5	16	1	≤0.5
EMRSA-15	256	>128	64	32	≤0.5	≤0.5	≤0.5	2	≤0.5	≤0.5	2	≤0.5	≤0.5
EMRSA-16	128	128	32	512	≤0.5	≤0.5	≤0.5	32	1	≤0.5	64	≤0.5	≤0.5

[a] MIC's were determined in Mueller-Hinton Broth +2% salt at 35 °C after 24 h incubation.
[b] Fixed concentrations of the compound were used (6.25, 12.5 and 25 mg/L).

β-lactam antibiotics. At 6.25 mg/L of catechin gallate, the lowest concentration used in this study, both the mono-hydroxylated B-ring analogue and the 3,5-dihydroxy B-ring analogue were less potent than the natural compound (Table 1).

4. Conclusion

A flexible asymmetric synthesis of two B-ring modified ECg analogues has been developed that originates from an aldol dehydration/reduction protocol to form a key A,B-ring styrene precursor. We believe this strategy could be used to synthesise other B and A ring modified ECg analogues for biological evaluation. The control of absolute stereochemistry by the Sharpless asymmetric dihydroxylation, and subsequent stereoselective cyclisation to form the C-ring is an analogous strategy to that reported by Li and Chan[17] in their synthesis of EGCg. As demonstrated by them this route can provide either enantiomer of the desired analogues. Biological evaluation showed that at concentrations of 12.5 and 25 mg/L, ECg and the two B-ring analogues (**2** and **3**) fully sensitised each of the three MRSA strains to oxacillin, reducing the MICs to less than 0.5 mg/L. Results at lower concentration of catechin suggests that not only the degree, but the relative position of hydroxylation of the B-ring is important for optimal interaction with biological membranes in MRSA. We are currently investigating the intrinsic stability of ECg, **2** and **3**, and their capacity to intercalate into staphylococcal membranes, the results of which will be reported in due course.

5. Experimental

5.1. General

Our general experimental details have been reported.[30]

5.1.1. 4,6-Dibenzyloxy-2-*O*-methoxymethylbenzaldehyde (8). To a stirred solution of aldehyde **7** (5.0 g, 35 mmol) in DMF (50 mL) was added K_2CO_3 (9.7 g, 70 mmol) followed by BnBr (8.4 mL, 70 mmol) and the mixture was stirred at rt overnight. The mixture was then diluted with Et_2O (100 mL) and washed with H_2O (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to yield a yellow solid, which was recrystallised from Et_2O to furnish the 4,6-dibenzyl protected aldehyde as a pale yellow semi-solid (8.1 g, 69%); IR ν_{max} 2922, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 2H, OCH_2Ph), 5.06 (s, 2H, OCH_2Ph), 6.14 (d, 1H, J=2.1 Hz, Ar*H*), 6.17 (d, 1H, J=2.1 Hz, Ar*H*), 7.37–7.50 (m, 10H, Ar*H*), 10.24 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9, 80.1, 92.8, 94.6, 106.8, 127.5, 127.9, 128.0, 128.1, 128.8, 128.9, 129.0, 129.2, 129.3, 136.1, 163.1, 166.6, 166.8, 192.4; MS (ES, *m*/*z*) 334 (M^+, 20%), 91 (Bn^+, 100%); HRMS (ES, *m*/*z*) found 334.1215, $C_{21}H_{18}O_4$ requires 334.1205.

To a stirred solution of NaH (2.6 g, 66 mmol) in THF (100 mL) at 0 °C was added the 4,6-dibenzyl protected aldehyde (11 g, 33 mmol), in THF (30 mL). After 5 min MOMCl (5.0 mL, 33 mmol) was added and the mixture allowed to warm to rt. Brine (5.0 mL) was then added and the reaction partitioned between Et_2O (100 mL) and H_2O (100 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield aldehyde **8** as a brown oil (11 g, 88%); IR ν_{max} 3063, 3031, 2875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H, OCH_2OCH_3), 5.09 (s, 2H, OCH_2Ph), 5.15 (s, 2H, OCH_2Ph), 5.27 (s, 2H, OCH_2OCH$_3$), 6.30 (d, 1H, J=2.1 Hz, Ar*H*), 6.48 (d, 1H, J=2.1 Hz, Ar*H*), 7.35–7.48 (m, 10H, Ar*H*), 10.49 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 70.8, 71.0, 94.5, 95.1, 95.4, 110.5, 127.4, 127.5, 128.1, 128.4, 128.8, 128.9, 129.0, 129.1, 129.2, 136.2, 136.5, 161.8, 163.3, 165.3, 188.0; MS (ES, *m*/*z*) 378 (M^+, 10%), 91 (Bn^+, 100%); HRMS (ES, *m*/*z*) found 378.1456, $C_{23}H_{22}O_5$ requires 378.1467.

5.1.2. 3′,4,6-Tribenzyloxy-2-*O*-methoxymethyl-*E*-*retro*-chalcone (10). To a solution of acetophenone **9** (6.9 g, 32 mmol) in EtOH (100 mL) was added aq. KOH solution (10 mL of 50% m/v) and the mixture stirred at rt for 20 min. A solution of benzaldehyde **8** (11 g, 29 mmol) in THF (50 mL) was then added, and the mixture stirred overnight. The precipitate, which had formed was then filtered and washed with Et_2O to yield chalcone **10** (12 g, 69%), as a fine yellow powder; mp 108–110 °C; IR ν_{max} 3064, 3032, 2933, 1601, 1566, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (s, 3H, OCH_2OCH_3), 5.16 (s, 2H, OCH_2Ph), 5.17 (s, 2H, OCH_2Ph), 5.19 (s, 2H, OCH_2Ph), 5.35 (s, 2H, OCH_2OCH$_3$), 6.46 (d, 1H, J=2.2 Hz, Ar*H*), 6.62 (d, 1H, J=2.2 Hz, Ar*H*), 7.19–7.21 (m, 1H, Ar*H*), 7.28–7.30 (m, 2H, Ar*H*), 7.42–7.57 (m, 15H, Ar*H*), 7.66 (d, 1H, Ar*H*), 7.99 (d, 1H, J=16 Hz, ArC*H*=CHCO), 8.41 (d, 1H, J=16 Hz, ArCH=C*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 70.5, 70.7, 71.4, 94.5, 94.9, 95.3, 108.2, 114.0, 119.9, 121.7, 122.5, 128.1, 128.5, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 129.8, 136.2, 136.5, 136.7, 137.2, 140.9, 159.4, 159.9, 161.3, 162.5, 191.5; MS (ES, *m*/*z*) 586 (M^+, 7%), 91 (Bn^+, 100%); HRMS (ES, *m*/*z*) found 586.2340, $C_{38}H_{34}O_6$ requires 586.2355.

5.1.3. 1-(3′-Benzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propan-1-ol (11). Catechol borane (1 M solution in THF, 10 mL, 10 mmol) was added dropwise to a stirred solution of chalcone **10** (5.0 g, 8.5 mmol) in THF (80 mL) at −78 °C. The mixture was allowed to warm to rt and stirred for a further 1 h before acetone (10 mL) and sat. aq. NH_4Cl (10 mL) were added. The mixture was extracted into Et_2O (2×50 mL), the combined organic layers washed with 2 M NaOH (50 mL) and brine (50 mL), then dried ($MgSO_4$) filtered, and concentrated in vacuo to afford the corresponding ketone (4.3 g, 86%). The crude ketone was immediately dissolved in methanol (30 mL) and $NaBH_4$ (310 mg, 8.0 mmol) was added at rt. The mixture was stirred for 1 h before all volatile material was removed in vacuo, H_2O (50 mL) added and the mixture extracted into Et_2O (3×30 mL). The combined organic layers were dried ($MgSO_4$) filtered, and concentrated in vacuo to give alcohol **11** (5.0 g, 99%) as a pale yellow solid; mp 120–122 °C; IR ν_{max} 3500, 2931, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95–2.08 (m, 2H, ArCH$_2$CH_2CHOH), 2.90–2.92 (m, 2H, ArCH_2CH$_2$-CHBr), 3.52 (s, 3H, OCH_2OCH_3), 4.61 (dd, 1H, J=8.8, 4.3 Hz, ArCH$_2$CH$_2$C*H*OH), 5.07 (s, 2H, OCH_2Ph), 5.08 (s, 2H, OCH_2Ph), 5.09 (s, 2H, OCH_2Ph), 5.23 (s, 2H,

OCH_2OCH_3), 6.41 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.55 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.90 (ddd, 1H, $J=8.2$, 2.6, 0.8 Hz, Ar*H*), 6.93 (d, 1H, $J=8.2$ Hz, Ar*H*), 7.06 (apt, 1H, $J=2.6$ Hz, Ar*H*), 7.26 (t, 1H, $J=8.2$ Hz, Ar*H*), 7.35–7.50 (m, 15H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 39.3, 56.7, 70.3, 70.7, 70.9, 73.4, 94.8, 95.0, 95.3, 112.1, 112.8, 113.9, 118.9, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5, 129.0, 129.1, 129.7, 137.3, 137.6, 146.9, 156.9, 158.3, 158.9, 159.3; MS (ES, *m/z*) 613 ($M^+ + Na$, 80%), 523 ($M^+ - 67$, 100%); HRMS (ES, *m/z*) found 613.2578, $C_{38}H_{38}O_6Na$ requires 613.2566.

5.1.4. (*E*)-1-(3′-Benzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propene (12). To a stirred solution of PPh_3 (1.4 g, 5.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Br_2 (0.30 mL, 5.4 mmol) dropwise and after 5 min, Et_3N (0.90 mL, 9.7 mmol) was added and the mixture stirred for a further 5 min. A solution of the alcohol **11** (2.1 g, 3.6 mmol) in CH_2Cl_2 (10 mL) was then added dropwise and the mixture allowed to warm to rt. After 2 h the mixture was concentrated in vacuo and purified by flash chromatography (neutral alumina, 50% Et_2O/hexanes) to afford the bromide as a yellow oil (2.0 g, 85%); IR ν_{max} 2931, 1594, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50–2.58 (m, 2H, ArCH_2CH$_2$CHBr), 2.74–2.76 (m, 1H, ArCH$_2$CH_2CHBr), 2.89–2.93 (m, 1H, ArCH$_2$CH_2-CHBr), 3.52 (s, 3H, OCH_2OCH_3), 5.05–5.09 (m, 7H, 3× OCH_2Ph and ArCH$_2$CH$_2$C*H*Br), 5.21 (dd, 2H, $J=8.0$, 6.7 Hz, OCH_2OCH_3), 6.37 (d, 1H, $J=2.3$ Hz, Ar*H*), 6.53 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.89 (ddd, 1H, $J=8.2$, 2.5, 0.8 Hz, Ar*H*), 7.00 (d, 1H, $J=7.8$ Hz, Ar*H*), 7.07 (t, 1H, $J=2.2$ Hz, Ar*H*), 7.20–7.23 (m, 1H, Ar*H*), 7.33–7.47 (m, 15H, 15× Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 39.8, 56.0, 56.5, 56.6, 70.5, 70.6, 70.7, 94.6, 94.9, 95.1, 111.8, 114.7, 120.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.5, 129.0, 130.0, 137.3, 137.4, 137.6, 144.3, 157.0, 158.3, 159.0, 159.3; MS (FAB, *m/z*) 654 (M^+, 100%); HRMS (FAB, *m/z*) found 654.1809, $C_{38}H_{37}O_5Br$ requires 654.1804.

A solution of bromide (3.3 g, 5.0 mmol) in DBU and toluene (25 mL, 4:1), was heated to reflux overnight. The mixture was then allowed to cool and extracted into Et_2O (3×25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (Silica, 20% Et_2O/hexanes) gave styrene **12** (1.68 g, 57%) as a colourless oil; IR ν_{max} 3031, 2929, 1592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H, OCH_2OCH_3), 3.63–3.64 (m, 2H, ArCH_2CH=CH), 5.08–5.10 (m, 6H, 3×OCH_2Ph), 5.24 (s, 2H, OCH_2OCH_3), 6.38–6.41 (m, 3H, ArCH$_2$C*H*=C*H* and Ar*H*), 6.55 (d, 1H, $J=2.3$ Hz, Ar*H*), 6.95–7.00 (m, 1H, Ar*H*), 7.24 (t, 1H, $J=4.3$ Hz, Ar*H*), 7.33–7.50 (m, 16H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 56.5, 70.3, 70.4, 70.7, 94.7, 95.0, 95.1, 110.9, 112.7, 113.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 129.0, 129.7, 129.8, 130.2, 137.4, 137.6, 140.1, 156.8, 158.3, 159.1, 159.4; MS (ES, *m/z*) 573 (MH^+, 100%); HRMS (ES, *m/z*) found 573.2556, $C_{38}H_{37}O_5$ requires 573.2641.

5.1.5. (1*R*,2*R*)-1-(3′Benzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propane-1,2-diol (13). To a solution of AD-mix-β® (5.0 g) in *t*-BuOH (30 mL) and H_2O (30 mL) at 0 °C was added methane sulfonamide (270 mg, 2.9 mmol) followed by styrene **12** (1.5 g, 2.6 mmol) in THF (30 mL) and the mixture stirred at 0 °C for 5 days. Solid sodium sulfite (5 g) was added and the product was extracted into EtOAc (3×30 mL), the combined organics dried ($MgSO_4$), filtered and concentrated in vacuo to yield the crude product, which was purified by flash chromatography (Silica, 80% Et_2O/hexanes) to yield the desired product **13** as a white solid (1.0 g, 65%, 75% ee by HPLC[26]) that was then recrystallised (80% Et_2O/EtOAc) to give enantiomerically pure **13** (740 mg, 48%); mp 114–116 °C; IR ν_{max} 3405, 2964, 2923, 2851, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (br s, 1H, O*H*), 2.97 (dd, 1H, $J=14$, 5.8 Hz, ArCH_2CH(OH)CH(OH)), 3.03 (dd, 1H, $J=14$, 8.1 Hz, ArCH_2CH(OH)CH(OH)), 3.36 (br s, 1H, O*H*), 3.53 (s, 3H, OCH_2OCH_3), 4.02–4.05 (m, 1H, ArCH$_2$-C*H*(OH)CH(OH)), 4.60 (d, 1H, $J=4.8$ Hz, ArCH$_2$-CH(OH)C*H*(OH)), 5.11–5.13 (m, 6H, 3×OCH_2Ph), 5.22 (dd, 2H, $J=11$, 6.7 Hz, OCH_2OCH_3), 6.47 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.58 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.98 (dd, 1H, $J=8.2$, 2.0 Hz, Ar*H*), 7.03 (d, 1H, $J=8.2$ Hz, Ar*H*), 7.15 (apt, 1H, $J=2.0$ Hz, Ar*H*), 7.32 (t, 1H, $J=8.2$ Hz, Ar*H*), 7.40–7.53 (m, 15H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 56.7, 70.4, 70.7, 71.0, 76.1, 76.7, 94.9, 95.1, 95.2, 108.7, 113.8, 114.3, 119.8, 127.7, 128.0, 128.1, 128.4, 128.5, 128.6, 129.0, 129.2, 129.7, 137.2, 137.5, 143.4, 157.2, 158.5, 159.3, 159.4; MS (ES, *m/z*) 629 ($M^+ + Na$, 100%); HRMS (ES, *m/z*) found 629.2629, $C_{38}H_{38}O_7Na$ requires 629.2515; $[\alpha]_D$ +9.9 (*c* 0.1, CH_2Cl_2, at 21 °C).

5.1.6. (1*R*,2*R*)-1-(3′Benzyloxyphenyl)-3-(2″hydroxy-4″,6″-dibenzyloxyphenyl)propane-1,2-diol (14). To a solution of diol **13** (740 mg, 1.2 mmol) in MeOH (10 mL) and Et_2O (10 mL) was added conc. HCl (5 drops) and the mixture heated at reflux for 5 h. The mixture was then concentrated in vacuo, diluted with EtOAc and washed with H_2O, the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the product **14** as a white solid (730 mg, 100%); mp 120–122 °C; IR ν_{max} 3436, 2923, 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (dd, 1H, $J=15$, 8.5 Hz, ArCH_2CH(OH)CH(OH)), 2.97 (dd, 1H, $J=15$, 3.8 Hz, ArCH_2CH(OH)CH(OH)), 4.00–4.04 (m, 1H, ArCH$_2$C*H*(OH)CH(OH)), 4.50 (d, 1H, $J=6.3$ Hz, ArCH$_2$-CH(OH)C*H*(OH)), 4.90 (dd, 2H, $J=14$, 12 Hz, OCH_2Ph), 4.99–5.01 (m, 4H, 2×OCH_2Ph), 6.26 (d, 1H, $J=2.3$ Hz, Ar*H*), 6.31 (d, 1H, $J=2.3$ Hz, Ar*H*), 6.88–6.92 (m, 1H, Ar*H*), 6.99–7.00 (m, 1H, Ar*H*), 7.17–7.20 (m, 2H, Ar*H*), 7.33–7.47 (m, 15H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 70.4, 70.5, 77.2, 77.3, 93.9, 96.3, 106.7, 119.8, 127.2, 127.3, 128.0, 128.1, 128.4, 128.9, 129.0, 130.1, 137.3, 137.4, 142.6, 157.7, 158.3, 159.3, 159.5; MS (ES, *m/z*) 585 ($M^+ + Na$, 40%), 563 (MH^+, 100%); HRMS (ES, *m/z*) found 563.2358, $C_{36}H_{35}O_6$ requires 563.2434; $[\alpha]_D$ −15.6 (*c* 3.7, CH_2Cl_2, at 24 °C).

5.1.7. (1*S*,2*R*)-1-Bromo-2-formate (15). To a solution of triol **14** (730 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) was added trimethyl orthoformate (1.4 mL, 13 mmol) followed by PPTS (5.0 mg) and the mixture stirred at rt for 10 min. The mixture was then washed with satd. aq. $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered and concentrated to in vacuo. The crude cyclic orthoformate was then redissolved in CH_2Cl_2 (15 mL), treated with AcBr (0.14 mL, 1.9 mmol) and stirred

for 10 min at rt. The mixture was then washed with satd. aq. $NaHCO_3$ (10 mL) and concentrated in vacuo to afford bromo formate **15** as a brown foam (750 mg, 88%). This compound was used immediately without purification or characterisation.

5.1.8. (2*R*,3*R*)-3′-Benzyloxy-4″,6″-dibenzyloxyflavan (16). Crude bromo formate **15** (750 mg, 1.1 mmol) was treated with K_2CO_3 (170 mg, 1.1 mmol) in acetone (10 mL) and stirred at rt over 5 h. The mixture was diluted with H_2O (5.0 mL), extracted into EtOAc (3×10 mL), the combined organics dried with ($MgSO_4$), filtered and concentrated to dryness. The resulting compound was then redissolved in MeOH (10 mL), treated with K_2CO_3 (170 mg, 1.1 mmol) and the mixture stirred at rt overnight. The mixture was then concentrated in vacuo, extracted into EtOAc (3×15 mL), the combined organics dried ($MgSO_4$), filtered, concentrated to dryness and the product purified by flash chromatography (Silica, 50% Et_2O/hexanes) to give **16** as a colourless oil (310 mg, 61%); IR ν_{max} 3439, 3031, 2924, 1619, 1592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.06 (dd, 1H, J=17, 4.4 Hz, ArCH_2CHCHO), 3.11 (dd, 1H, J=9.8, 2.1 Hz, ArCH_2CHCHO), 4.39 (br s, 1H, ArCH$_2$C*H*CHO), 5.10–5.15 (m, 5H, ArCH$_2$CHC*H*O, and 2×OCH_2Ph), 5.19 (s, 2H, OCH_2Ph), 6.38 (d, 1H, J=2.3 Hz, Ar*H*), 6.40 (d, 1H, J=2.3 Hz, Ar*H*), 7.06 (dd, 1H, J=8.2, 2.5 Hz, Ar*H*), 7.18 (dd, 1H, J=8.2, 0.6 Hz, Ar*H*), 7.29 (s, 1H, Ar*H*), 7.41–7.56 (m, 16H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 66.5, 69.9, 70.1, 70.2, 78.6, 94.2, 94.7, 101.0, 113.0, 114.4, 118.8, 127.2, 127.3, 127.7, 128.0, 128.1, 128.6, 128.7, 129.8, 136.9, 137.1, 139.9, 155.2, 158.4, 158.8, 159.1; MS (ES, *m/z*) 567 (M^++Na, 20%), 545 (MH^+, 100%); HRMS (ES, *m/z*) found 567.2111, $C_{36}H_{32}O_5Na$ requires 567.2147; $[\alpha]_D$ −25.7 (*c* 3.4, CH_2Cl_2, at 23 °C).

5.1.9. (−)-3-Hydroxy B-ring modified (−)-ECg (2). To a solution of tri-*O*-benzyl gallic acid (54 mg, 0.12 mmol) in CH_2Cl_2 (5.0 mL) was added DCC (25 mg, 0.12 mmol) and the mixture was stirred at rt for 5 min. Alcohol **16** (42 mg, 0.081 mmol) was then added in CH_2Cl_2 (5.0 mL) followed by DMAP (5.0 mg) and the mixture was stirred at rt overnight. The mixture was then filtered, concentrated in vacuo and purified by flash chromatography (Silica, 10% Et_2O/hexanes) to yield the globally protected gallate ester as a colourless oil (49 mg, 64%); IR ν_{max} 2923, 2851, 1707, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (d, 2H, J=3.4 Hz, ArCH_2CHCHO), 4.82 (d, 1H, J=11 Hz, OCH_2Ph), 4.91 (d, 1H, J=11 Hz, OCH_2Ph), 5.08–5.10 (m, 11H, ArCH$_2$C*H*CHO, and 5×OCH_2Ph), 5.70–5.71 (m, 1H, ArCH$_2$CHC*H*O), 6.39 (d, 1H, J=2.3 Hz, Ar*H*), 6.47 (d, 1H, J=2.3 Hz, Ar*H*), 6.93 (dd, 1H, J=7.9, 2.2 Hz, Ar*H*), 7.06 (d, 1H, J=7.9 Hz, Ar*H*), 7.20–7.21 (m, 1H, Ar*H*), 7.33–7.52 (m, 33H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 69.2, 70.4, 70.6, 71.4, 71.9, 75.0, 78.1, 94.4, 95.2, 101.4, 109.5, 110.6, 113.7, 114.9, 119.6, 127.7, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 129.9, 137.0, 137.3, 137.9, 139.9, 142.9, 152.8, 156.0, 158.5, 159.3, 165.6; MS (ES, *m/z*) 967 (M^+, 5%), 647 (MH^+−318, 100%); HRMS (ES, *m/z*) found 967.3859, $C_{64}H_{55}O_9$ requires 967.3846; $[\alpha]_D$ −31.4 (*c* 3.3, CH_2Cl_2, at 23 °C).

A solution of the globally protected gallate ester (170 mg, 0.18 mmol) and 10% Pd $(OH)_2$ (10 mg) in EtOAc (10 mL) was stirred under an atmosphere of H_2 (balloon) for 12 h. The mixture was then filtered through celite, concentrated in vacuo and purified by flash chromatography (Silica, Et_2O) to yield the product (−)-**2** (72 mg, 94%) as an off-white solid; mp >200 °C; IR ν_{max} 3329 (br), 2950, 1607 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 2.99 (dd, 1H, J=18, 2.0 Hz, ArCH_2CHCHO), 3.12 (dd, 1H, J=18, 4.6 Hz, ArCH_2CHCHO), 3.15 (br s, 1H, O*H*), 5.27 (s, 1H, ArCH$_2$CHC*H*O), 5.64–5.66 (m, 1H, ArCH$_2$C*H*CHO), 6.11 (d, 1H, J=2.3 Hz, Ar*H*), 6.12 (d, 1H, J=2.3 Hz, Ar*H*), 6.77 (ddd, 1H, J=8.0, 2.5, 0.9 Hz, Ar*H*), 7.07–7.20 (m, 5H, Ar*H*), 8.36 (br s, 5H, O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2O$) δ 13.5, 68.4, 77.2, 94.9, 95.7, 98.0, 109.0, 113.9, 114.6, 117.7, 120.8, 129.0, 138.0, 140.4, 145.1, 156.0, 156.6, 157.0, 157.2, 165.1; MS (ES, *m/z*) 449 (M^++Na, 65%), 257 (M^+−151, 100%); HRMS (ES, *m/z*) found 449.0818, $C_{22}H_{18}O_9Na$ requires 449.0846; $[\alpha]_D$ −130.8 (*c* 0.3, $(CH_3)_2CO$, at 23 °C).

5.1.10. 3′,4,5′,6-Tetrabenzyloxy-2-*O*-methoxymethyl-*E*-*retro*-chlacone (18). Acetophenone **17** (3.3 g, 13 mmol) and benzaldehyde **8** (4.2 g, 11 mmol) were condensed in an identical manner to the preparation of **10** to give **18** (6.5 g, 94%), as a fine yellow powder; mp 108–110 °C; IR ν_{max} 2933, 2872, 1650, 1585, 1568, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H, OCH$_2$OCH_3), 5.09 (s, 4H, 2×OCH_2Ph), 5.16 (s, 2H OCH_2Ph), 5.20 (s, 2H, OCH_2Ph), 5.34 (s, 2H, OCH_2OCH$_3$), 6.28 (d, 1H, J=2.2 Hz, Ar*H*), 6.60 (d, 1H, J=2.2 Hz, Ar*H*), 6.84, (t, 1H, J=2.3 Hz, Ar*H*), 7.23 (t, 1H J=2.3 Hz, Ar*H*), 7.35–7.53 (m, 21H, Ar*H*), 7.94 (d, 1H J=16 Hz, ArCH$_2$C*H*=CHCO), 8.41 (d, 1H J=16 Hz, ArCH$_2$CH=C*H*CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 70.1, 70.3, 70.9, 94.4, 94.5, 94.7, 95.0, 106.9, 107.4, 107.7, 122.3, 126.7, 127.3, 127.5, 127.6, 127.7, 127.8, 128.1, 128.3, 128.7, 128.9, 136.1, 139.7, 159.5, 159.6, 160.7, 162.1, 191.4; MS (ES, *m/z*) 693 (MH^+, 20%); HRMS (ES, *m/z*) found 693.2817, $C_{45}H_{41}O_7$ requires 693.2852.

5.1.11. 1-(3′,5′-Dibenzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propan-1-ol (19). In an identical manner to the preparation of **11** chalcone **18** (5.9 g, 9.5 mmol) was converted into crude ketone (4.7 g, 86%) and then alcohol **19** (4.7 g, 99%) as a pale yellow solid; mp 119–120 °C; IR ν_{max} 3575, 2946, 1594, 1497, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (m, 2H, ArCH$_2$CH_2-CHOH), 2.87 (m, 3H, ArCH_2CH$_2$CHOH and O*H*), 3.50 (s, 3H, OCH$_2$OCH_3), 4.53 (m, 1H, C*H*OH), 5.02 (s, 4H, 2×OCH_2Ph), 5.05 (s, 2H, OCH_2Ph), 5.07 (s, 2H, OCH_2Ph), 5.21 (s, 2H, OCH_2OCH$_3$), 6.37 (s, 1H, Ar*H*), 6.57 (s, 2H, Ar*H*), 6.68 (s, 2H, Ar*H*), 7.24–7.47 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.7, 39.2, 56.6, 70.5, 70.8, 73.5, 94.8, 95.0, 95.3, 101.1, 105.4, 112.0, 127.6, 128.0, 128.1, 128.3, 128.4, 128.5, 129.0, 129.1, 137.3, 147.8, 156.158.3, 160.3; MS (ES, *m/z*) 719 (M^++Na, 30%), 239 (M^+−480, 100%); HRMS (ES, *m/z*) found 719.2916 $C_{45}H_{44}O_7Na$ requires 719.2985.

5.1.12. (*E*)-1-(3′,5′-Dibenzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propene (20). In an identical manner to the preparation of **12**, alcohol **19** (2.5 g, 4.0 mmol) gave the corresponding bromide (2.8 g, 99%) as a white solid; mp 114–115 °C; IR ν_{max} 3062, 2932,

1595, 1497, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (m, 2H, $ArCH_2CH_2CHBr$), 2.78 (m, 1H, $ArCH_2CH_2$-CHBr), 2.93 (m, 1H, $ArCH_2CH_2CHBr$), 3.52 (s, 3H, OCH_2OCH_3), 5.06 (m, 9H, $4\times OCH_2Ph+CHBr$), 5.21 (s, 2H, OCH_2OCH_3), 6.36 (d, 1H, $J=2.2$ Hz, Ar*H*), 5.85 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.59 (t, 1H, $J=2.2$ Hz, Ar*H*), 6.75 (d, 2H, $J=2.2$ Hz, Ar*H*), 7.33–7.53 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 39.7, 56.1, 56.6, 70.6, 94.7, 94.9, 95.2, 102.1, 107.2, 111.8, 127.4, 127.7, 128.0, 128.1, 128.2, 128.4, 128.5, 129.0, 137.2, 137.6, 145.0, 157.0, 158.3, 159.0, 160.4; MS (ES, *m/z*) 760 (M^+, 10%), 723 (M^+-37, 100%); HRMS (ES, *m/z*) found 760.2229, $C_{45}H_{44}O_6Br$ requires 760.2222.

The bromide (2.8 g, 4.0 mmol) gave styrene **20** (1.3 g, 53%) as a white solid; mp 103–104 °C; IR ν_{max} 3087, 2932, 1676, 1593, 1497, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H, OCH_2OCH_3), 3.65–3.66 (m, 2H, CH_2-CH=CH), 5.09 (s, 4H, $2\times OCH_2Ph$), 5.11 (s, 2H, OCH_2Ph), 5.14 (s, 2H, OCH_2Ph), 5.25 (s, 2H, OCH_2OCH_3), 6.37–6.38 (m, 2H, $ArCH_2CH=CH$), 6.42 (d, 1H, $J=$ 2.2 Hz, Ar*H*), 6.54 (t, 1H, $J=2.2$ Hz, Ar*H*), 6.57 (d, 1H, $J=$ 2.2 Hz, Ar*H*), 6.64 (s, 1H, Ar*H*), 6.65 (s, 1H, Ar*H*), 7.34–7.56 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 56.6, 70.4, 70.5, 70.6, 70.7, 94.7, 95.0, 95.1, 101.1, 105.8, 108.3, 110.9, 127.6, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5, 129.0, 129.1, 129.9, 130.5, 137.3, 137.4, 137.5, 137.7, 140.7, 156.9, 158.4, 159.1, 160.5; MS (ES, *m/z*) 679 (MH^+, 10%), 576 (M^+-103, 100%); HRMS (ES, *m/z*) found 679.3167 $C_{45}H_{43}O_6$ requires 679.3060.

5.1.13. (1*R*,2*R*)-1-(3′,5′-Dibenzyloxyphenyl)-3-(2″-*O*-methoxymethyl-4″,6″-dibenzyloxyphenyl)propane-1,2-diol (21). In an identical manner to the preparation of **13** styrene **20** (1.4 g, 2.3 mmol) gave **21** as a white solid (1.2 g, 82%, 75% *ee* by HPLC[15]) that was then recrystallised (80% Et_2O/EtOAc) to give enantiomerically pure **21** (670 mg, 46%); mp 84–86 °C; IR ν_{max} 3520, 2928, 1594, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.99–3.10 (m, 2H, $ArCH_2$-CH(OH)CH(OH)), 3.55 (s, 3H, OCH_2OCH_3), 4.06–4.09 (m, 1H, $ArCH_2CH(OH)CH(OH)$), 4.60 (d, 1H, $J=4.5$ Hz, $ArCH_2CH(OH)CH(OH)$), 5.11 (s, 4H, $2\times OCH_2Ph$), 5.13 (s, 2H, OCH_2Ph), 5.14 (s, 2H, OCH_2Ph), 5.25 (dd, 2H, $J=$ 13, 6.7 Hz, OCH_2OCH_3), 6.47 (d, 1H, $J=2.2$ Hz, Ar*H*), 6.58 (d, 1H, $J=2.2$ Hz, Ar*H*), 7.00 (t, 1H, $J=2.1$ Hz, Ar*H*), 7.05 (s, 1H, Ar*H*), 7.12 (s, 1H, Ar*H*), 7.40–7.53 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 56.4, 70.1, 70.3, 70.6, 75.7, 76.2, 94.5, 94.7, 94.9, 101.2, 105.9, 108.3, 127.3, 127.8, 128.1, 128.2, 128.7, 128.9, 136.6, 136.8, 137.0, 143.9, 156.9, 158.1, 159.0, 160.0; MS (ES, *m/z*) 735 (MH^+, 80%), 363 (M^+-372, 100%); HRMS (ES, *m/z*) found 735.2970, $C_{45}H_{45}O_8$ requires 735.2958; $[\alpha]_D$ +3.0 (*c* 0.1, CH_2Cl_2, at 24 °C).

5.1.14. (1*R*,2*R*)-1-(3′,5′-Dibenzyloxyphenyl)-3-(2″-hydroxy-4″,6″-dibenzyloxyphenyl)propane-1,2-diol (22). In an identical manner to the preparation of **14** diol **21** (670 mg, 1.0 mmol) gave triol **22** as a white solid (600 mg, 100%); mp 91–92 °C; IR ν_{max} 3384, 3031, 2910, 1595, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (dd, 1H, $J=15$, 12 Hz, $ArCH_2CH(OH)CH(OH)$), 3.01 (dd, 1H, $J=$ 15, 3.7 Hz, $ArCH_2CH(OH)CH(OH)$), 4.02–4.05 (m, 1H, $ArCH_2CH(OH)CH(OH)$), 4.50 (d, 1H, $J=5.9$ Hz, $ArCH_2CH(OH)CH(OH)$), 4.89–5.00 (m, 8H, $4\times OCH_2Ph$), 6.26 (d, 1H, $J=2.3$ Hz, Ar*H*), 6.31 (d, 1H, $J=$ 2.3 Hz, Ar*H*), 6.56 (t, 1H, $J=2.1$ Hz, Ar*H*), 6.63 (s, 1H, Ar*H*), 6.64 (s, 1H, Ar*H*), 7.18–7.48 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 70.4, 70.5, 77.1, 94.0, 96.3, 102.3, 106.4, 106.7, 127.1, 128.0, 128.1, 128.4, 128.5, 128.9, 129.0, 129.1, 137.2, 137.4, 143.5, 157.6, 158.3, 159.5, 160.4; MS (ES, *m/z*) 669 (MH^+, 100%); HRMS (ES, *m/z*) found 669.2855, $C_{43}H_{41}O_7$ requires 669.2852; $[\alpha]_D$ −7.5 (*c* 4.2, CH_2Cl_2, at 24 °C).

5.1.15. (1*S*,2*R*)-1-Bromo-2-formate (23). In an identical manner to the preparation of **15** triol **22** (550 mg, 0.93 mmol) gave bromo formate **23** as a brown foam (580 mg, 91%). This compound was used immediately without purification or characterisation.

5.1.16. (2*R*,3*R*)-3′,5′-Dibenzyloxy-4″,6″-dibenzyloxyflavan (24). In an identical manner to the preparation of **16** crude bromo formate **23** (580 mg, 0.90 mmol) gave **24** as a colourless oil (222 mg, 45%); IR ν_{max} 3562, 3064, 3032, 2925, 1593, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, 1H, $J=5.2$ Hz, O*H*), 2.87 (dd, 1H, $J=18$, 4.4 Hz, $ArCH_2CHCHO$), 2.97 (dd, 1H, $J=18$, 2.0 Hz, $ArCH_2$-CHCHO), 4.19–4.23 (m, 1H, $ArCH_2CHCHO$), 4.86 (s, 1H, $ArCH_2CHCHO$), 4.88–5.02 (m, 8H, $4\times OCH_2Ph$), 6.21 (d, 1H, $J=2.4$ Hz, Ar*H*), 6.23 (d, 1H, $J=2.4$ Hz, Ar*H*), 6.53 (t, 1H, $J=2.4$ Hz, Ar*H*), 6.70 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 7.21–7.30 (m, 20H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 66.5, 70.0, 70.2, 77.2, 78.6, 94.1, 94.7, 101.0, 101.6, 105.4, 127.2, 127.6, 127.9, 128.1, 128.5, 128.6, 136.7, 136.9, 137.0, 140.7, 155.1, 158.3, 158.8, 160.2; MS (ES, *m/z*) 651 (MH^+, 80%), 225 ($M-426$, 100%); HRMS (ES, *m/z*) found 651.2741, $C_{43}H_{39}O_6$ requires 651.2747; $[\alpha]_D$ −17.2 (*c* 0.8, CH_2Cl_2, at 24 °C).

5.1.17. (−)-3,5-Dihydroxy B-ring modified (−)-ECg (3). In an identical manner to the preparation of **2**, alcohol **24** (100 mg, 0.17 mmol) was converted to the globally protected gallate ester (120 mg, 67%); IR ν_{max} 3063, 3031, 1714, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (d, 2H, $J=3.2$ Hz, $ArCH_2CHCHO$), 4.65 (d, 1H, $J=$ 12 Hz, OCH_2Ph), 4.73 (d, 1H, $J=12$ Hz, OCH_2Ph), 4.86–5.10 (m, 13H, $ArCH_2CHCHO$, and $6\times OCH_2Ph$), 5.56–5.57 (m, 1H, $ArCH_2CHCHO$), 6.23 (d, 1H, $J=2.4$ Hz, Ar*H*), 6.31 (d, 1H, $J=2.4$ Hz, Ar*H*), 6.42 (t, 1H, $J=2.0$ Hz, Ar*H*), 6.64 (s, 1H, Ar*H*), 6.65 (s, 1H, Ar*H*), 7.13–7.24 (m, 37H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 68.7, 70.0, 70.1, 70.2, 71.0, 75.1, 77.9, 94.0, 94.8, 101.0, 101.2, 106.0 109.1, 125.1, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.6, 136.6, 136.7, 136.9, 137.5, 138.1, 142.6, 152.4, 155.6, 158.0, 158.9, 160.0, 165.1; $[\alpha]_D$ −43.8 (*c* 2.4, CH_2Cl_2, at 24 °C).

A solution of the globally protected gallate ester (120 mg, 0.11 mmol) was hydrogenolysed to give (−)-**3** (18 mg, 37%) as an off-white solid; mp >200 °C; IR ν_{max} 3332, 1608, 1237 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 2.76–2.95 (m, 2H, $ArCH_2CHCHO$), 4.99 (s, 1H, $ArCH_2CHCHO$), 5.46–5.48 (m, 1H, $ArCH_2CHCHO$), 5.91–5.93 (m, 2H, Ar*H*), 6.11 (t, 1H, $J=2.4$ Hz, Ar*H*), 6.43–6.44 (m, 2H, Ar*H*), 6.88 (s, 2H, Ar*H*), 8.01 (br s, 7H, O*H*); ^{13}C NMR (100 MHz, $(CD_3)_2O$) δ 20.7, 26.6, 60.8, 66.6, 69.2, 78.1,

95.8, 96.6, 99.1, 102.8, 106.0, 110.0, 121.8, 138.8, 139.0, 141.0, 146.0, 156.9, 157.5, 157.8, 159.2, 166.1; MS (ES, *m/z*) 443 (MH^+, 80%), 273 ($M^+ - 169$, 100%); HRMS (ES, *m/z*) found 443.1017, $C_{22}H_{19}O_{10}$ requires 443.0978; $[\alpha]_D$ −55.0 (*c* 2.5, $(CH_3)_2O$, at 24 °C).

5.2. Microbiological evaluation of 2 and 3. *S. aureus* BB 568 was provided by Professor B. Berger-Bächi, University of Zürich, Switzerland. EMRSA-15 and EMRSA-16 were clinical isolates obtained from the Royal Free Hospital London. The capacity of the various compounds to modulate β-lactam resistance was evaluated by determination of the MIC at a fixed concentration in combination with oxacillin. Assays were performed in 96-well microtiter trays with a bacterial inoculum of about 10^4 colony-forming units in 100 µl of Mueller-Hinton broth (Oxoid, Basingstoke, UK) supplemented with 2% w/v NaCl. Doubling dilutions of oxacillin were employed. MIC values were recorded after incubation of the trays at 35 °C for 24 h. *S. aureus* ATCC 29213 was used as the standard. The intrinsic anti-staphylococcal activity of compounds was also evaluated using these methods.

Acknowledgements

This work was supported by MRC Strategic Grant G0000996. We thank S. Shah for undertaking the antibacterial assays, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra and Mr. T. J. Spencer for micro analytical data.

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