Tetrahedron: *Asymmetry* 24 (2013) 362–373

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantioselective synthesis of orthogonally protected (2*R*,3*R*)-(−)-epicatechin derivatives, key intermediates in the de novo chemical synthesis of (−)-epicatechin glucuronides and sulfates

Mingbao Zhang [a,*], G. Erik Jagdmann Jr. [a], Michael Van Zandt [a], Paul Beckett [a], Hagen Schroeter [b]

[a] *The Institutes for Pharmaceutical Discovery, 23 Business Park Drive, Branford, CT 06405, USA*
[b] *MARS Symbioscience, 20425 Seneca Meadows Parkway, Germantown, MD 20876, USA*

ARTICLE INFO

Article history:
Received 25 December 2012
Accepted 28 February 2013

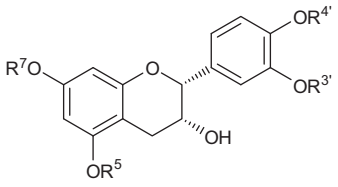
ABSTRACT

Ten orthogonally protected (−)-epicatechin and 3′- or 4′-*O*-methyl-(−)-epicatechin derivatives were prepared in a regiospecific and enantioselective manner. For each orthogonally protected (−)-epicatechin derivative, one specific phenolic hydroxyl was protected with a methoxymethyl (MOM) or *p*-methoxybenyzl (PMB) group and the remainder were protected as benzyl ethers. These uniquely protected (−)-epicatechin derivatives were designed to facilitate the regiospecific installation of a glucuronic acid or sulfate unit onto (−)-epicatechin after selective removal of the MOM or PMB protecting group to provide authentic standards of (−)-epicatechin glucuronides and sulfates.

1. Introduction

(−)-Epicatechin, its epimer (+)-catechin, and their oligomeric derivatives are believed to be the most abundant flavan-3-ols found in the plant kingdom.[1] Ingestion of flavanol-rich foods, such as red wines, green teas, apples, pears, and cocoa products has been correlated with health benefits including neuroprotection and reduced risk of cardiovascular disease.[2–9] In general, once ingested, these compounds undergo rapid and extensive metabolism to form the corresponding glucuronide, sulfate, and *O*-methyl ether products.[10–15] The methylated metabolites can undergo additional glucuronidation and sulfation to facilitate their excretion from the body.[10] Due to the polyphenolic structures of the (epi)-catechins, glucuronidation, sulfation, and methylation reactions can produce a wide variety of metabolites. Although the structures of several major metabolites have been tentatively assigned using LC/MS and various NMR techniques, the determination of the specific positional isomeric forms has generally been equivocal due to the lack of authentic standards.[10]

Recently, we have undertaken the task of gaining access to all possible mono-glucuronides and mono-sulfates (ten each[16]) of (−)-epicatechin, 3′-OMe and 4′-OMe-(−)-epicatechin via unambiguous chemical synthesis.[17,18] Key to our synthetic strategy is the availability of a set of orthogonally protected (−)-epicatechin intermediates **1a**–**1j** (Chart 1) prepared de novo. The key feature of these late stage intermediates is that one phenolic OH is protected as a methoxymethyl (MOM) or *p*-methoxybenzyl (PMB) ether while all remaining OHs are protected as benzyl ethers. Selective removal of the MOM or PMB group in the presence of the benzyl ethers permits the unmasking of a single phenolic OH group where glucuronidation or sulfation is desired. These orthogonally protected (−)-epicatechin derivatives are a unique



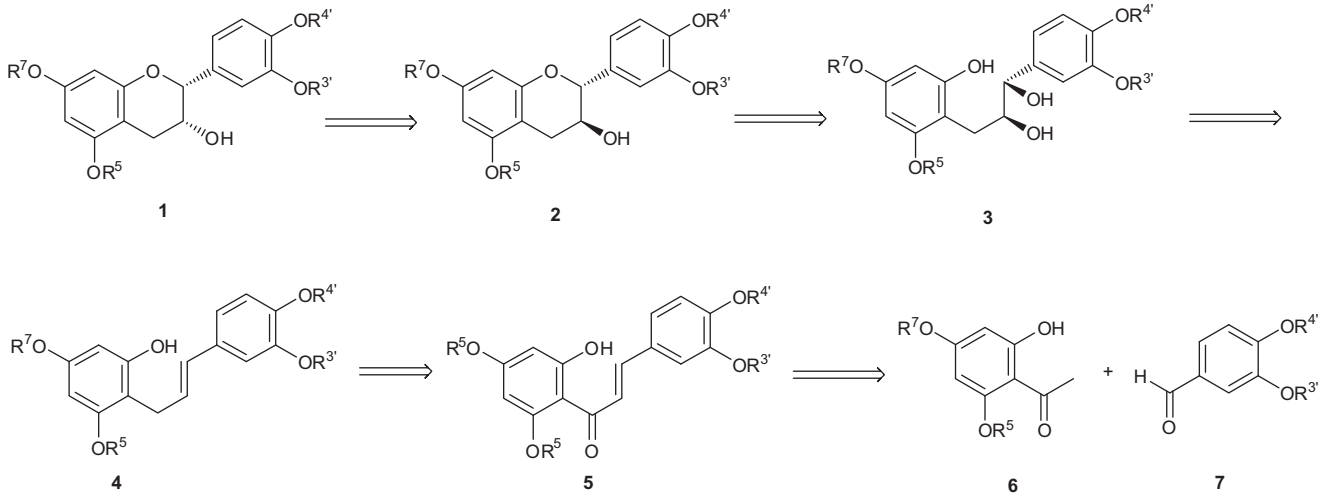
1

	$R^{3'}$	$R^{4'}$	R^5	R^7
1a	MOM	Bn	Bn	Bn
1b	Bn	PMB	Bn	Bn
1c	Bn	Bn	MOM	Bn
1d	Bn	Bn	Bn	MOM
1e	Me	MOM	Bn	Bn
1f	Me	Bn	MOM	Bn
1g	Me	Bn	Bn	MOM
1h	MOM	Me	Bn	Bn
1i	Bn	Me	MOM	Bn
1j	Bn	Me	Bn	MOM

Chart 1. Structures of the orthogonally protected (−)-epicatechin intermediates **1a**–**1j**.

* Corresponding author. Tel.: +1 203 570 8879; fax: +1 203 653 2803.
E-mail address: nengren@yahoo.com (M. Zhang).

0957-4166/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2013.02.012



Scheme 1. Retro-synthetic analysis of orthogonally protected (−)-epicatechins.

set of precursors, which enable the unambiguous chemical synthesis of (−)-epicatechin glucuronides and sulfates. Herein we report the regiospecific and enantioselective synthesis of **1a**–**1j**.

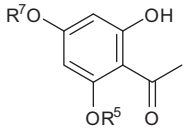
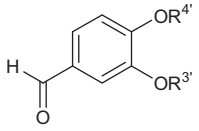
2. Results and discussion

2.1. Retro-synthetic analysis

The retro-synthetic analysis of **1** is shown in Scheme 1. The key step is the cyclization of optically active diol **3** to form the *trans*-isomer catechin **2**, from which **1** can be obtained after inversion of the 3-OH. Diol **3** can be obtained via the Sharpless asymmetric dihydroxylation[19] of the (*E*)-olefin intermediate **4**, which is accessible from the reduction of chalcone **5**. A similar approach has been applied to the synthesis of a non-orthogonally protected (−)-epicatechin analogue 5,7,3′,4′-*tetra*-*O*-benzyl epicatechin.[20,21] Herein, chalcone **5** is a key intermediate which provides the stage for setting the desired orthogonal protection patterns in the final compound **1**. The aldol condensation of the appropriately protected trihydroxy acetophenone derivatives **6** and 3,4-dihydroxy benzaldehyde derivatives **7** affords the chalcone **5** with the desired orthogonal protection patterns.

The selections of the protecting groups $R^{3'}$, $R^{4'}$, R^5, and R^7 are shown in Table 1. Their combinations provide the desired epicatechin derivatives **1** bearing the appropriate orthogonal protecting groups according to Scheme 2.

Table 1
Protecting group selections

		R^5	R^7
	**6a**	Bn	Bn
	6b	Bn	MOM
	6c	MOM	Bn
6			
		$R^{3'}$	$R^{4'}$
	**7a**	Bn	Bn
	7b	Bn	PMB
	7c	MOM	Bn
	7d	Me	Bn
	7e	Me	MOM
	7f	Bn	Me
7	**7g**	MOM	Me

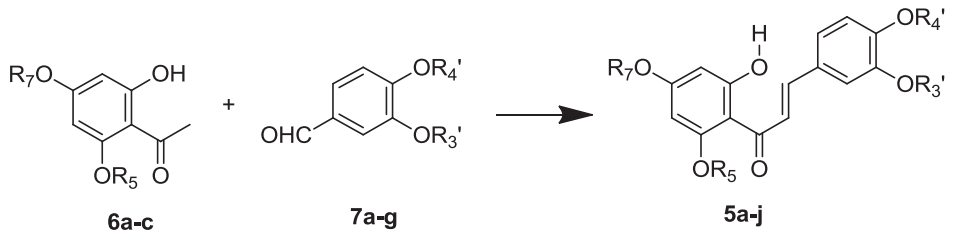
The successful development of this synthetic strategy required highly efficient and scalable syntheses of the various protected acetophenones **6a**–**c** and 3,4-dihydroxy benzaldehydes **7a**–**g**. These methods are described below.

2.2. Synthesis of acetophenones 6a–c

The synthetic scheme for making **6a**–**c** is shown in Scheme 3. Treatment of commercially available 2,4,6-trihydroxyacetophenone (phloroacetophenone) monohydrate **8** with benzyl chloride in the presence of potassium carbonate in DMF at 70 °C afforded 4,6-bisbenzyl ether **6a** in 46% yield. The structure of **6a** was unequivocally identified by its ^{1}H NMR spectrum in which the two aromatic protons H-3 and H-5 appeared as two weakly coupled doublets (J = 2.3 Hz) at δ 6.10 and 6.17 ppm, respectively. The ^{1}H NMR spectrum of **6a** also showed the presence of an intramolecularly H-bonded *ortho* OH group (δ 14.02). The regioselectivity of the benzylation likely results from the intramolecular hydrogen-bonding between the ketone carbonyl group and an adjacent phenolic OH. In the presence of a base, **6a** can behave like an enolate to react further, at the 3-position, with benzyl chloride via a nucleophilic substitution reaction to form the by-product
1-(3-benzyl-4,6-bis(benzyloxy)-2-hydroxyphenyl)ethanone.

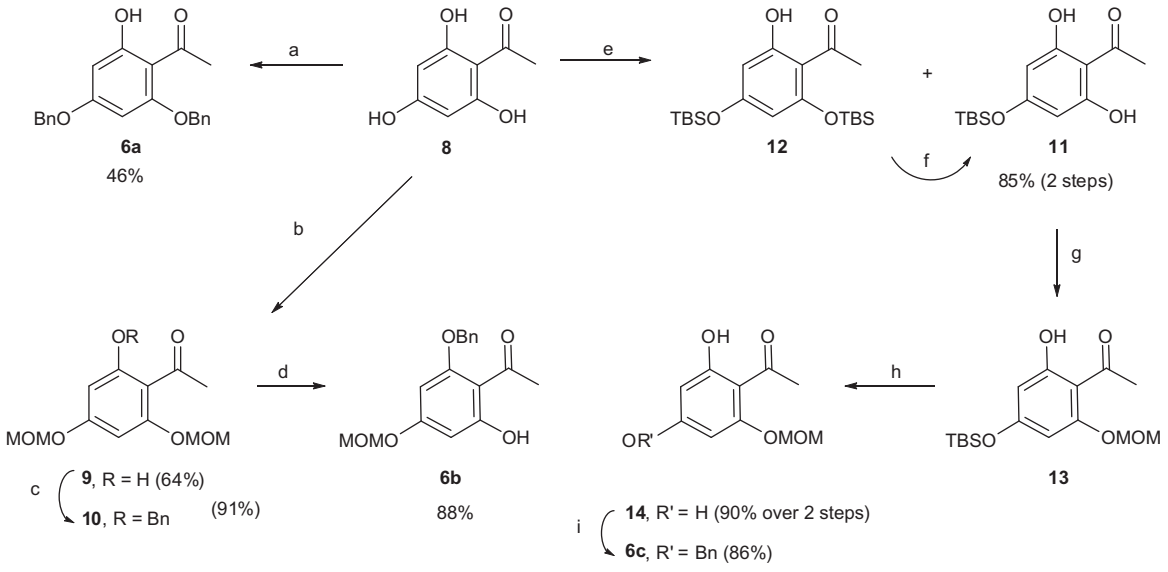
Treatment of **8** with bromomethyl methyl ether in the presence of Hunig's base in dichloromethane at 0 °C afforded the 4,6-bismethoxymethylether **9** in 64% yield. The ^{1}H NMR of **9** in which the two aromatic protons H-3 and H-5 appeared as an AB quartet at δ 6.25 (J_{AB} = 2.3 Hz) and the OH group was significantly downfield shifted (δ 13.70) is consistent with the 4,6-substitution pattern. Benzylation of the free phenolic OH group with benzyl chloride in DMF afforded the intermediate **10** in 91% yield. Treatment of **10** with Montmorillonite K-10[22] clay under refluxing conditions in acetone/water selectively removed the *ortho* MOM group to afford the desired orthogonally bis-protected 2-hydroxy acetophenone **6b** in 88% yield.

Treatment of **8** with TBDMS in DMF in the presence of imidazole afforded a readily separable mixture of the mono-silylated **11** (22%) and bis-silylated **12** (77%) products. When the bis-silylated product **12** was treated with 20 mol % pyridinum *p*-toluenesulfonate (PPTS)[23] under refluxing conditions in methanol for 4 h, the mono-silylated product **11** was isolated in 94% yield. Based on this



			$R^{3'}$	$R^{4'}$	R^5	R^7
6a + 7c	⟶	**5a**	MOM	Bn	Bn	Bn
6a + 7b	⟶	**5b**	Bn	PMB	Bn	Bn
6c + 7a	⟶	**5c**	Bn	Bn	MOM	Bn
6b + 7a	⟶	**5d**	Bn	Bn	Bn	MOM
6a + 7e	⟶	**5e**	Me	MOM	Bn	Bn
6c+ 7d	⟶	**5f**	Me	Bn	MOM	Bn
6b + 7d	⟶	**5g**	Me	Bn	Bn	MOM
6a + 7g	⟶	**5h**	MOM	Me	Bn	Bn
6c + 7f	⟶	**5i**	Bn	Me	MOM	Bn
6b + 7f	⟶	**5j**	Bn	Me	Bn	MOM

Scheme 2. Synthesis of the orthogonally protected chalcones **5a**–**j**.

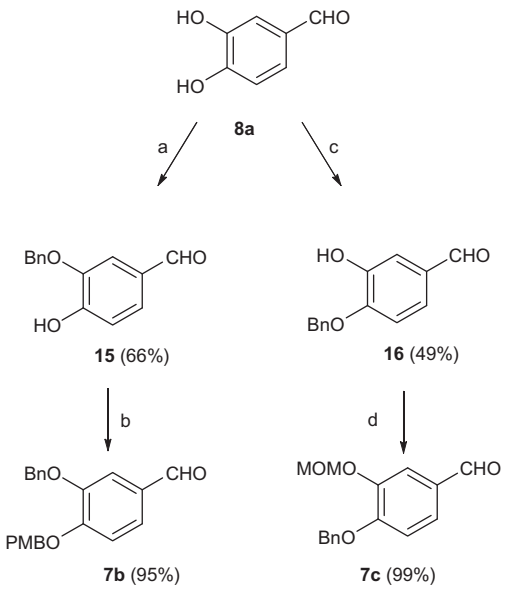


Scheme 3. Synthesis of orthogonally protected 2,4,6-trihydroxyacetophenone **6a**–**c**. Reagents and conditions: (a) BnCl (2.2 equiv), K_2CO_3 (2.2 equiv), DMF, 70 °C, 3 h; (b) $EtN(iPr)_2$ (5 equiv), $BrCH_2OCH_3$ (2.1 equiv), CH_2Cl_2, 0 °C, 3 h; (c) BnCl (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 90 °C, 20 h; (d) Montmorillonite K-10 clay, acetone/water (9:1), reflux, 4 h; (e) imidazole (3 equiv), TBDMSCl (2.2 equiv), DMF, rt, 1 h; (f) PPTS (0.2 equiv), MeOH, reflux, 3 h; (g) $EtN(iPr)_2$ (1.5 equiv), $BrCH_2OCH_3$ (1.1 equiv), CH_2Cl_2, 0 °C, 30 min; (h) TBAF (1.2 equiv), AcOH (1.2 equiv), THF, 0 °C, (i) BnCl (1.1 equiv), K_2CO_3 (1.3 equiv), DMF, 75 °C, 3 h.

observation, in a subsequent experiment, the mixture of **11** and **12** was not separated prior to treatment with PPTS to afford the desired product **11** in 85% yield. Treatment of **11** with bromomethyl methyl ether followed by de-silylation with TBAF afforded 2-MOM protected phloroacetophenone **14** in 90% yield over two steps. Regioselective benzylation of **14** with benzyl chloride gave orthogonally bis-protected phloroacetophenone **6c** in 86% yield. The structure of **6c** was confirmed by the presence of an intramolecularly H-bonded *ortho* OH group with a large downfield shift (δ 13.86 ppm) by ^{1}H NMR. This synthesis is better than that reported in the literature where either expensive starting materials or low yielding steps were involved.[14,24,25]

2.3. Synthesis of benzaldehydes 7a–g

The di-benzylated benzaldehyde **7a** was commercially available. The orthogonally protected 3,4-dihydroxybenzaldehydes **7b** and **7c** were synthesized according to Scheme 4. Treatment of the commercially available 3,4-dihydroxybenzaldehyde **8a** with 2 equiv of sodium hydride followed by 1.25 equiv of benzyl chloride in DMF afforded the 3-*O*-benzyl intermediate **15** which was readily converted into **7b** (*p*-anisyl chloride/NaH, DMF). It is noteworthy that treatment of **8a** with only 1.1 equiv of sodium hydride followed by 1.1 equiv of benzyl bromide led to the formation of 4-*O*-benzyl intermediate **16**. The structures of **15** and **16** were as-



Scheme 4. Synthesis of orthogonally protected 3,4-dihydroxybenzaldehydes **7b** and **7c**. Reagents and conditions: (a) NaH (2.0 equiv), BnCl (1.25 equiv), DMF; (b) NaH, DMF, *p*-anisyl chloride (1.2 equiv); (c) NaH (1.1 equiv), BnBr (1.1 equiv), DMF; (d) $EtN(iPr)_2$ (2 equiv), $BrCH_2OCH_3$ (1.1 equiv), CH_2Cl_2.

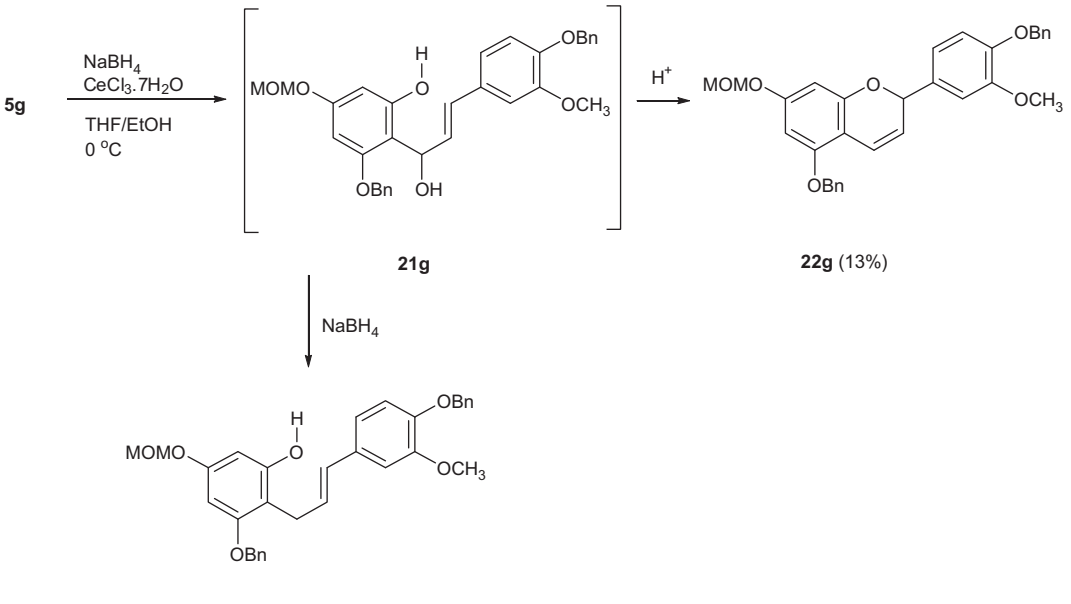
signed based on their ^{1}H NMR spectra. The chemical shift of the aromatic proton H-2 was larger for **15** (δ 6.32 ppm) than **16** (δ 5.92 ppm) due to the benzylation of the adjacent OH group. The regioselectivity observed can be explained by relative stability of the 4-phenoxy anion versus 3-phenoxy anion. With 1 equiv of NaH, the more stable 4-phenoxy anion (*para* to the CHO group) is formed; the 3-phenoxy anion is formed with the second equivalent base and is more reactive toward alkylation because it is not stabilized by the *para* aldehyde group. The intermediate **16** was converted into **7c** via treatment with bromomethyl methyl ether in the presence of the Hünig's base in dichloromethane. The protected methoxyl benzaldehydes **7d**–**7g** were prepared according to known procedures by the reaction of commercially available 3-methoxy-4-hydroxy-or 4-methoxy-3-hydroxybenzadehyde with benzyl bromide or methoxymethyl bromide.[14]

2.4. Synthesis of chalcones 5a–j

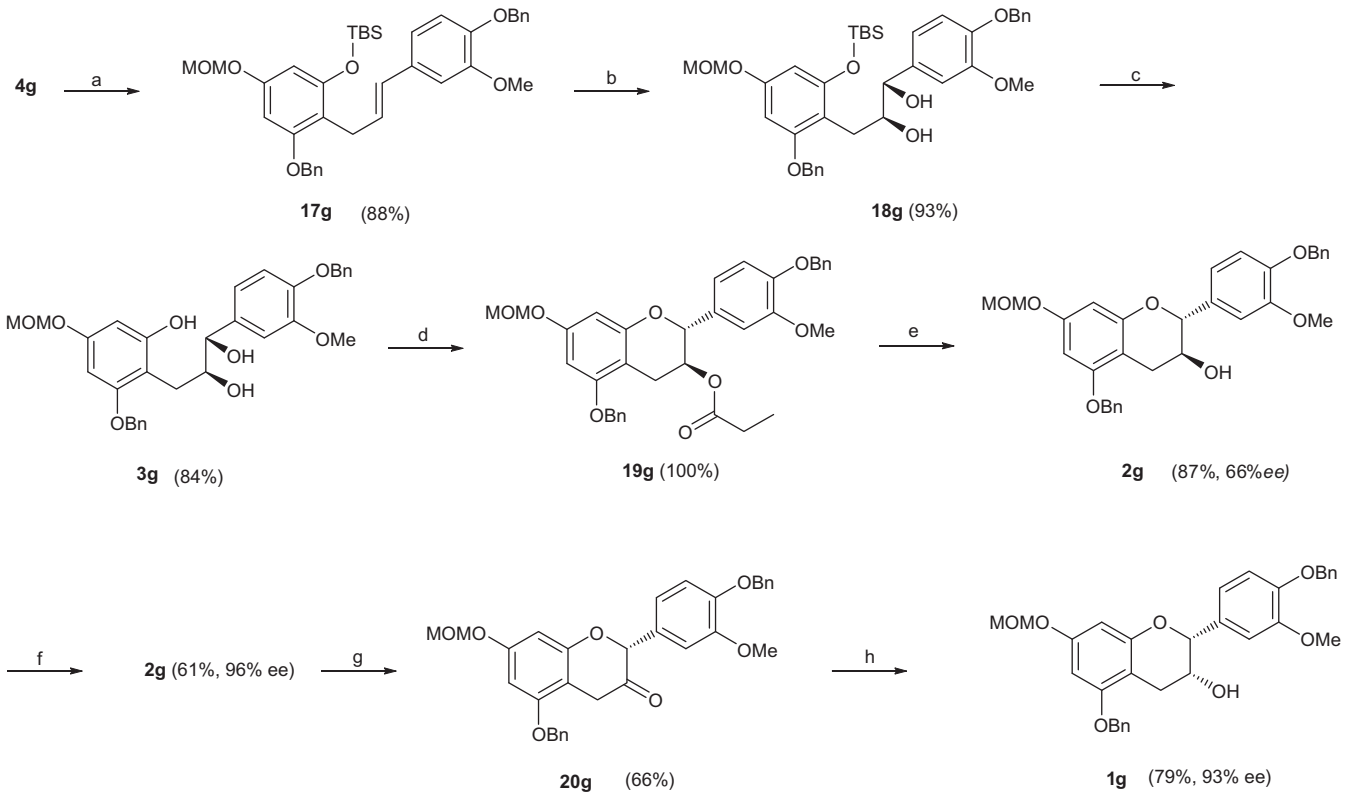
With the appropriately protected acetophenones **6a**–**c** and benzaldehydes **7a**–**g** in hand, the orthogonally protected chalcones **5a**–**j** were prepared by condensing acetophenone **6a**–**c** and benzaldehyde **7a**–**j** according to Scheme 2 with sodium hydride in DMF at room temperature. Upon pouring the reaction in ice water and acidification to pH 3–4, a crystalline suspension was obtained in all cases, which thus allowed the convenient isolation of the analytically pure chalcone **5a**–**j** by simple filtration in near quantitative yields.

2.5. Synthesis of the protected (−) epicatechins 1a–j

With the orthogonally protected chalcones **5a**–**j** in hand, we were ready to synthesize the (−)-epicatechin derivatives bearing the desired orthogonal protecting groups **1a**–**j**. For clarity, the synthesis is illustrated by the preparation of 3′-*O*-methyl-4′,5-di-*O*-benzyl-7-*O*-methoxymethoxy-(−)-epicatechin **1g**. Chalcone **5g** was converted into the olefin intermediate **4g** via reduction by $NaBH_4$ in the presence of cerium chloride in a mixture of THF and ethanol at a low temperature (0 °C).[18] Both visual observation (yellow color fading away) and TLC analysis indicated the rapid disappearance of the chalcone **5g** (<1 h) under the reaction conditions. However, quenching the reaction with 5% citric acid shortly after the total consumption of **5g** resulted in low yields of the desired product **4g** and the by-product **22g** was isolated as the major product (Scheme 5). Apparently, the reduction of the carbonyl group with $NaBH_4/CeCl_3$[26,27] occurred in two steps: the rapid first step to the alcohol intermediate **21g**, which was followed by a much slower de-oxygenation step to form the desired product **4g**. The position and the *E*-configuration of the double bond in **4g** were determined based on ^{1}H NMR. The coupling constant between the two olefin protons was large (J = 16.0 Hz), which is characteristic of the *E*-configuration. When the reaction was quenched prematurely with an acid, the alcohol intermediate **21g** underwent an acid-catalyzed intra-molecular cyclization to form the by-prod-



Scheme 5. Reduction of chalcone **5g**.



Scheme 6. Synthesis of orthogonally protected (−)-epicatechin derivative **1g**. Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) AD-mix-α, $MeSO_2NH_2/K_2CO_3$, *t*-BuOH/water/THF, 0 °C; (c) TBAF, AcOH, THF, 0 °C; (d) $EtC(OEt)_3$, PPTS, CH_2Cl_2, 65 °C; (e) K_2CO_3, MeOH; (f) Mosher's acid (0.2 equiv), DCC (0.2 equiv), DMAP (3.3 mol %), CH_2Cl_2, 0 °C, 30 min; (g) Dess–Martin periodinane, CH_2Cl_2, rt; (h) $Al(O\text{-}iPr)_3$, 2-propanol/toluene, reflux.

uct **22g**. Prolonged stirring (overnight to 24 h) after disappearance of the chalcone was thus required to minimize the formation of the by-product **22g** (<15%).

The Sharpless asymmetric dihydroxylation of olefin intermediate **17g** after the phenolic OH was protected as a silyl ether (TBDMSCl, imidazole in DMF) afforded the optically active 2,3-*cis* diol **18g** in 93% yield (Scheme 6).[19] The ee of diol **18g** was assessed by ^{1}H NMR using (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol) as a chiral shift reagent.[28] In the presence of 68 equiv of Pirkle's alcohol, the aromatic OCH_3 protons of the racemic diol **18g** appeared as baseline-resolved doublets in $CDCl_3$ (δ 3.701, 3.724 ppm). The enantiomeric purity of the optically active **18g** was determined to be 67% ee. Removal of the TBS group followed by cyclization, effected by triethyl orthopropionate in the presence of catalytic amount of PPTS,[18,29] afforded the catechin intermediates **19g** with the 3-OH protected as a propionate (84% yield over two steps). Saponification of **19g** (K_2CO_3, MeOH) resulted in the formation of the (+)-catechin intermediate **2g** in 87% yield with 66% ee as determined by chiral HPLC.

The enantioselectivity of the asymmetric dihydroxylation reactions of the olefin intermediate **17a–j** was variable and generally lower than expected, except for **18i**, based on ee assessments of the selected diols **18e**, **18g**, **18h**, and **18i** using Pirkle's alcohol (8–68 equiv). The enantiomeric excess values of the corresponding catechin intermediates **2** correlate very closely to those of the diol precursors (Table 2), thus suggesting minimal loss of enantiomeric purity during these transformations.

The enantiomeric excess values of catechin intermediates **2e**, **2g**, **2h**, and **2i** were further enhanced by treatment with 0.2–0.5 equiv of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid) in the presence of DCC and DMAP in CH_2Cl_2

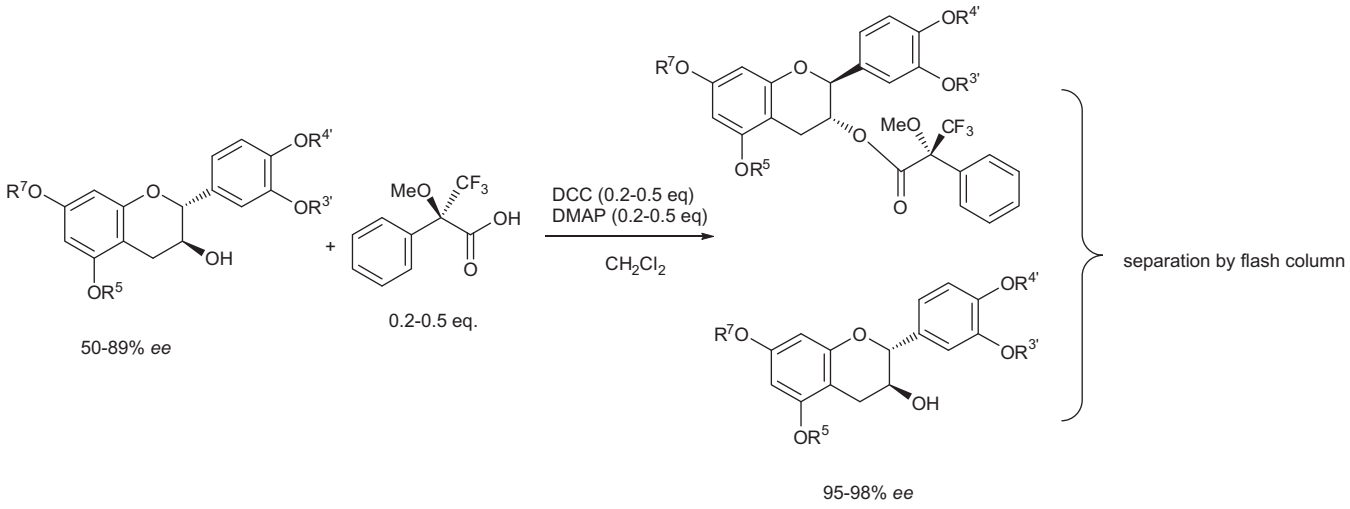
Table 2
Enantiomeric excess values of some selected diols and the corresponding catechins

Diol precursor[a] (ee %)	Catechin[b] (ee %)
18e (60%)	**2e** (59%)
18g (67%)	**2g** (66%)
18h (50%)	**2h** (50%)
18i (90%)	**2i** (89%)

[a] Estimated based on ^{1}H NMR integration values in the presence of Pirkle's alcohol in $CDCl_3$.
[b] Determined by chiral HPLC.

(Scheme 7). Under these conditions, the minor enantiomer of the catechin intermediate **2** undergoes a faster (3–7 fold) esterification reaction with the (*R*)-Mosher's acid. The unreacted catechin starting materials were conveniently recovered by flash chromatography on silica gel with 95–98% ee. The catechin intermediates **2a–2d**, **2f**, and **2j** were not treated with the (*R*)-Mosher's acid because they had already been converted into the final epicatechin targets before this procedure was discovered. It is noteworthy that the two enantiomers of the corresponding epicatechins reacted at a similar rate with Mosher's acid under the reaction conditions, thus no ee enhancement was observed for the epicatechin compounds.

The Mitsunobu reaction failed to effect the required inversion of the stereochemistry of the 3-ol.[30] The best method reported to date is an oxidation/stereoselective reduction sequence, converting the 3-OH into the 3-one via Dess–Martin periodinane oxidation followed by Meerwein–Ponndorf–Verley reduction with aluminum isopropoxide/propanol in refluxing toluene.[31] Thus, the enatiomerically enriched catechin intermediate **2g** (96% ee) was converted into the 3-one **20g** in 66% yield by the treatment of the Dess–Mar-



Scheme 7. Enantiomeric excess enhancement of the catechin intermediate **2** via kinetic resolution with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid.

tin periodinane in CH_2Cl_2 at room temperature. Reduction of **20g** with aluminum isopropoxide/propanol in refluxing toluene afforded the final target **1g** in 79% yield with 93% ee by Chiral HPLC (Table 3). The data suggest that there was a slight loss of enantiomeric purity after the conversion.

Table 3
Summary data of orthogonally protected epicatechin intermediates **1a**–**1j**[a]

Entry	Yield[b] (%)	Mp (°C)	ee[d] (%)	$[\alpha]_D^{20}$
1a	67	129–130	57[c]	−10.3 (*c* 6.69)
1b	61	131–132	70[c]	−9.8 (*c* 7.06)
1c	63	106–108	86 (90)[c]	−22.4 (*c* 4.93)
1d	30	102–103	81 (84)[c]	−15.4 (*c* 5.30)
1e	22	94–95	96 (98)	−18.2 (*c* 4.95)
1f	57	150–152	75 [c]	−19.5 (*c* 6.08)
1g	12	110–111	93 (97)	−15.8 (*c* 5.10)
1h	26	74–75	93 (95)	−17.7 (*c* 5.60)
1i	26	130–132	94 (96)	−24.4 (*c* 4.44)
1j	35	114–115	74 (76)[c]	−14.8 (*c* 5.33)

[a] All compounds were fully characterized by ^1H and ^{13}C NMR, LC/MS and gave satisfactory combustion analysis.
[b] Overall yield from chalcone.
[c] The corresponding (+)-catechin intermediates **2** were not treated with Mosher's acid to enhance the ee.
[d] The ee values were determined by chiral HPLC (Chiralpak® AD-RH 5 μ particle size 4.6 × 150 mm with acetonitrile/water 60:40 as the mobile phase at 60 °C). Numbers in parenthesis are the ee values of the corresponding catechin precursors.

The rest of the orthogonally protected (−)-epicatechin derivatives were prepared in a manner similar to **1g**. The overall yields, melting points, enantiomeric excess values, and specific rotations are summarized in Table 3.

Racemic versions of the catechin intermediates **2a**–**j** and epicatechin final targets **1a**–**j** required for Chiral HPLC analyses were prepared according to Scheme 8. For the sake of clarity, the synthesis is illustrated by the preparation of racemic **2g** and **1g**. The cyclic olefin intermediate **22g** obtained as a by-product from the $NaBH_4/CeCl_3$ reduction of the chalcone **5g** (vide supra) was dihydroxylated using a non asymmetric dihydroxylation protocol reported in the literature[32] to afford the racemic diol **23g**. Reduction of **23g** with sodium cyanoborohydride in acetic acid at 50 °C afforded a 9:1 mixture of the racemic catechin **2g** and racemic epicatechin **1g** as determined by ^1H NMR in 57% overall yield. Both the racemic **2g** and **1g** were baseline resolved by chiral HPLC using a Chiralpack AD-RH column.

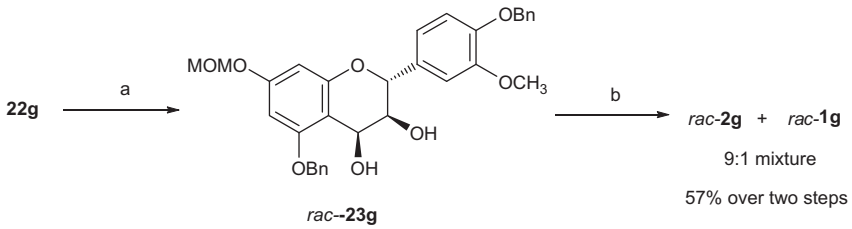
3. Conclusion

In conclusion, we have developed an enantioselective synthesis of orthogonally protected (−)-epicatechins and 3′/4′-*O*-methyl epicatechins in which one phenolic hydroxyl group is protected with a MOM or PMB protecting group and the remaining phenolic hydroxyl groups are protected as benzyl ethers. These orthogonally protected (−)-epicatechins are useful precursors to the unambiguous chemical synthesis of (−)-epicatechin sulfates and glucuronides, important metabolites of (−)-epicatechin in vivo. The syntheses and characterization of these metabolites will be reported separately.[18]

4. Experimental

4.1. General

Reagents and solvents were obtained from commercial sources and used without further purification. All reactions were run under a nitrogen atmosphere at room temperature unless specified otherwise. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz



Scheme 8. Synthesis of the racemates of the catechin intermediate **2g** and (−)-epicatechin final target **1g**. Reagents and conditions: (a) $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.1 equiv), $OsCl_3.H_2O$ (2.2 mol %), quinuclidine (7.2 mol %), methane sulfonamide (1.1 equiv), *t*-butanol/H_2O/THF (1:1:2), rt, 18 h; (b) $NaBH_3CN$ (2.4 equiv), HOAc, 50 °C, 2 h.

spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts are expressed in ppm relative to TMS. Coupling constants are expressed in Hz. LC/MS was obtained on a LC/MS system equipped with an autosampler and LC pump. Chiral analytical HPLC runs were performed on a Chiralpack AD-RH column (150 × 4.6 mm, 5 μ particle size). Mobile phase was an isocratic binary system consisting of 60/40 acetonitrile and water at a flow rate of 1 ml/min. The UV detection wavelength was 230 nm. The column temperature was 60 °C. Optical rotations were measured at 589 nm at room temperature (20 °C) in chloroform.

4.2. Preparation of 2,4-dibenzyloxy-6-hydroxyacetophenone 6a

A 1 L 3-neck flask was charged with *N*,*N*-dimethylformamide (180 mL) under nitrogen, heated to 35 °C, then phloroglycinol hydrate (37.23 g, 0.20 mol) was added in one portion, followed by more DMF (120 mL). Potassium carbonate (60.8 g, 0.44 mol) was added and the mixture was heated to 65 °C. Benzyl chloride (50.6 mL, 0.44 mol) was introduced in one portion, and the mixture was heated to 70 °C for 3 h, cooled to room temperature, and filtered. The filter cake was then rinsed with methylene chloride. The combined filtrates were concentrated in vacuo and the residual orange oil was taken up in dichloromethane (400 mL), stirred for a few minutes, filtered, and the filtrate added to a pad of silica gel and eluted with dichloromethane. The filtrate volume was reduced to 150 mL, after which heptane (200 mL) was added, and the mixture was stirred for 20 min. The resultant white crystalline solid was collected by filtration, washed with heptane and air dried. The filtrate solution was loaded directly onto a silica gel column (700 mL) and eluted with 1:1 dichloromethane/heptane, then with 2:1 dichloromethane/heptane to yield additional product. The two batches were combined to afford 32.22 g (46%) of 2,4-dibenzyloxy-6-hydroxyacetophenone **6a** as a white crystalline solid: mp 103.5–105.5 °C (lit.[33] 103 °C); LC/MS *m*/*z* 349 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 5.07 (m, 4H), 6.10 (d, J = 2.3, 1H), 6.17 (d, J = 2.3, 1H), 7.31–7.45 (m, 10H), 14.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.4, 70.4, 71.3, 92.5, 95.0, 106.6, 127.8, 128.1, 128.5, 128.6, 128.86, 128.9, 135.8, 136.1, 162.2, 165.3, 167.7, 203.3. Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.88; H, 5.79.

4.3. Preparation of 2,4-di(methoxymethoxy)-6-hydroxyacetophenone 9

To a stirred suspension of phloroglycinol hydrate (13.97 g, 75 mmol) in dichloromethane (300 mL) under nitrogen was added *N*,*N*-diisopropylethylamine (65.3 mL, 375 mmol), while cooling in an ice bath (3 °C). Bromomethyl methyl ether (14.3 mL, 158 mmol corrected for 90% purity) was added dropwise at a rate to keep the reaction temperature below 8 °C. The mixture was stirred at 3 °C for 3 h, then quenched with saturated aqueous sodium bicarbonate (250 mL). The mixture was stirred at room temperature for a few minutes, after which the phases were separated, and the aqueous solution extracted with dichloromethane (2 × 75 mL). The combined organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in the minimal amount of dichloromethane and then added to a silica gel column. Elution with dichloromethane and then with 1.5% ethyl acetate/dichloromethane afforded 2,4-di(methoxymethoxy)-6-hydroxyacetophenone **9** (14.32 g, 74.5%) as a white solid after evaporation: mp 49–50 °C (lit.[34] 49–52 °C); LC/MS *m*/*z* 257 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 3.47 (s, 3H), 3.51 (s, 3H), 5.16 (s, 2H), 5.25 (s, 2H), 6.25 (ABq, J_{AB} = 2.3, $\Delta\nu_{AB}$ = 8.3, 2H), 13.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.1, 56.6, 56.8, 94.2, 94.7, 97.4, 107.2, 160.5, 163.6, 167.0, 203.3. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.38; H, 6.23.

4.4. Preparation of 6-benzyloxy-2,4-di(methoxymethoxy)acetophenone 10

A stirred solution of 2,4-di(methoxymethoxy)-6-hydroxyacetophenone (14.09 g, 55 mmol) in *N*,*N*-dimethylformamide (115 mL) was treated with solid potassium carbonate (11.4 g, 82.5 mmol) and benzyl chloride (7.95 mL, 69 mmol). The mixture was heated to 75 °C for 16 h, cooled to room temperature, diluted with water (500 mL), and stirred for an hour during which time a precipitate formed. The suspension was cooled in an ice bath, and filtered. The solid was rinsed with water and partially air dried, before dissolving in dichloromethane (150 mL). The solution was dried (Na_2SO_4), added directly to a silica gel column, eluted with dichloromethane, then with 5% ethyl acetate/dichloromethane to afford a pale yellow solid. Trituration with petroleum ethers afforded 6-benzyloxy-2,4-di(methoxymethoxy)acetophenone **10** (17.81 g, 94%) as a white solid: mp 66–67 °C (lit.[35] 64–65 °C); LC/MS *m*/*z* 347 [M+1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 3H), 3.46 (s, 6H), 5.05 (s, 2H), 5.13 (s, 2H), 5.14 (s, 2H), 6.38 (d, J = 1.9, 1H), 6.47 (d, J = 1.9, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.7, 56.3, 56.5, 70.7, 94.7, 95.0, 95.6, 96.7, 116.7, 127.4, 128.1, 128.7, 136.5, 155.5, 157.0, 159.8, 201.5. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.69; H, 6.46.

4.5. Preparation of 2-benzyloxy-4-(methoxymethoxy)-6-hydroxyacetophenone 6b

A stirred solution of 6-benzyloxy-2,4-di(methoxymethoxy)acetophenone (17.32 g, 50 mmol) in 9:1 acetone/water (180 mL) was treated with Montmorillonite K-10 clay (50 g), heated at reflux for 5 h, cooled to room temperature, and filtered through Celite®. The filter pad was rinsed with dichloromethane and acetone, and the combined filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane (125 mL), dried (Na_2SO_4), added directly to a silica gel column, and eluted with dichloromethane to afford 2-benzyloxy-4-(methoxymethoxy)-6-hydroxyacetophenone **6b** as a very pale yellow solid (13.15 g, 87%): mp 97–99 °C; LC/MS *m*/*z* 303 [M+1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 3.47 (s, 3H), 5.09 (s, 2H), 5.17 (s, 2H), 6.14 (d, J = 2.2, 1H), 6.24 (d, J = 2.2, 1H), 7.33–7.45 (m, 5H), 13.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.5, 56.5, 71.3, 92.6, 94.2, 96.8, 107.0, 128.2, 128.6, 128.9, 135.8, 162.2, 163.7, 167.3, 203.5. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.27; H, 5.89.

4.6. Preparation of 2,6-dihydroxy-4-(*t*-butyldimethylsilyloxy)-acetophenone 11

A stirred solution of phloroglucinol hydrate (13.96 g, 75 mmol) and imidazole (15.32 g, 225 mmol) in anhydrous DMF (175 mL) was treated in portions with *t*-butyldimethylsilyl chloride (24.87 g, 165 mmol), then stirred at room temperature for 1 h and diluted with water (700 mL). The mixture was extracted with ethyl acetate (500 mL, then 2 × 100 mL), and the combined organic extracts were washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in a minimal volume of dichloromethane and loaded onto a silica gel column and eluted with dichloromethane to afford a mixture of mono-**11** and disilylated **12** products after evaporation. This mixture was dissolved in methanol (250 mL) under nitrogen, treated with pyridinium *p*-toluene sulfonate (3.77 g, 15 mmol), and refluxed for 4 h, then concentrated in vacuo. The residue was dissolved in a minimal volume of dichloromethane and loaded onto a silica gel column and eluted with dichloromethane to afford 2,6-dihydroxy-4-(*t*-butyldimethylsilyloxy)-acetophenone **11** (21.01 g, 99%) as a pale yellow solid: mp 97–98.5 °C; LC/MS *m*/*z* 283

[M+1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.22 (s, 6H), 0.95 (s, 9H), 2.69 (s, 3H), 5.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.2, 17.3, 24.7, 31.9, 99.4, 104.9, 162.0, 162.4, 202.9. Anal. Calcd for $C_{14}H_{22}O_4Si$: C, 59.54; H, 7.85. Found: C, 59.70; H, 7.99.

4.7. Preparation of 4-(*t*-butyldimethylsilyloxy)-6-hydroxy-2-(methoxymethoxy)acetophenone 13

To an ice cooled, stirred solution of 2,6-dihydroxy-4-(*t*-butyldimethylsilyloxy) acetophenone (20.9 g, 74 mmol) and *N*,*N*-diisopropylethylamine (19.3 mL, 111 mmol) in anhydrous dichloromethane (250 mL), under a nitrogen atmosphere, was added dropwise bromomethyl methyl ether (7.7 mL, 85 mmol corrected for 90% purity). The reaction was stirred at 3 °C for 30 min, then quenched with saturated aqueous sodium bicarbonate (150 mL) and stirred at room temperature for 15 min. The layers were separated, the aqueous solution extracted with dichloromethane (100 mL), and the combined organic solution was washed with water (200 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimum volume of dichloromethane and loaded onto a silica gel column and eluted with dichloromethane to afford 4-(*t*-butyldimethylsilyloxy)-6-hydroxy-2-(methoxymethoxy)acetophenone (23.20 g, 96%) as a pale yellow solid: mp 45–47 °C; LC/MS *m*/*z* 327 [M+1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.25 (s, 6H), 0.97 (s, 9H), 2.64 (s, 3H), 3.51 (s, 3H), 5.23 (s, 2H), 6.05 (d, *J* = 2.2, 1H), 6.10 (d, *J* = 2.2, 1H), 13.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.2, 18.4, 25.7, 33.1, 56.7, 94.6, 97.9, 102.0, 107.1, 160.7, 163.0, 166.8, 203.3. Anal. Calcd for $C_{16}H_{26}O_5Si$: C, 58.87; H, 8.03. Found: C, 58.93; H, 8.04.

4.8. Preparation of 4,6-dihydroxy-2-(methoxymethoxy)acetophenone 14

An ice cooled stirred solution of 4-(*t*-butyldimethylsilyloxy)-6-hydroxy-2-(methoxymethoxy-oxy)acetophenone (23.05 g, 70.6 mmol) in anhydrous THF (300 mL) under nitrogen was treated with glacial acetic acid (4.9 mL, 85 mmol), then dropwise with 1 M tetra-*n*-butylammonium fluoride/THF (85 mL, 85 mmol), and stirred for 1 h at 3 °C. Aqueous acetic acid (1 M, 150 mL) was then added, and stirring continued for a few minutes, before diluting with ethyl acetate (700 mL). The layers were separated, and the aqueous solution extracted with ethyl acetate (2 × 100 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in a minimum volume of dichloromethane and loaded onto a silica gel column and eluted with 9:1 dichloromethane/ethyl acetate to afford 4,6-dihydroxy-2-(methoxymethoxy)acetophenone (13.78 g, 92%) as a white solid: mp 130–132 °C (lit.[36] 117–119 °C, EtOAc/hexane); LC/MS *m*/*z* 213 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 3.52 (s, 3H), 5.24 (s, 2H), 6.04 (d, *J* = 2.2, 1H), 6.13 (d, *J* = 2.2, 1H), 6.27 (s, broad, 1H), 13.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.0, 56.8, 93.7, 94.6, 97.6, 106.6, 161.2, 162.9, 167.1, 203.4. Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.72; H, 5.65.

4.9. Preparation of 4-benzyloxy-6-hydroxy-2-(methoxymethoxy)acetophenone 6c

A stirred solution of 4,6-dihydroxy-2-(methoxymethoxy)acetophenone (15.28 g, 72 mmol) in anhydrous DMF (200 mL) under nitrogen, was treated with anhydrous potassium carbonate (12.44 g, 90 mmol), then benzyl chloride (9.2 mL, 80 mmol) was added via syringe. The mixture was heated to 75 °C for 4 h and cooled to room temperature and combined with water (750 mL). The aqueous suspension was stirred for 15 min, filtered, and the solid rinsed with water, partially air dried, dissolved in dichloromethane (200 mL), dried (Na_2SO_4), and concentrated to a 100 mL volume. The solution was then added to a silica gel column and eluted with dichloromethane to afford 4-benzyloxy-6-hydroxy-2-(methoxymethoxy)acetophenone (18.98 g, 87%) as a pale yellow solid: mp 82–83 °C; LC/MS *m*/*z* 303 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 3.51 (s, 3H), 5.06 (s, 2H), 5.23 (s, 2H), 6.18 (d, *J* = 2.4, 1H), 6.24 (d, *J* = 2.4, 1H), 7.31–7.45 (m, 5H), 13.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.0, 56.8, 70.4, 94.0, 94.6, 95.7, 106.6, 127.7, 128.4, 128.8, 136.0, 160.5, 165.2, 167.3, 203.2. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.82; H, 5.96.

4.10. Preparation of 3-benzyloxy-4-hydroxybenzaldehyde 15

An ice cooled stirred suspension of 60% sodium hydride/oil (4.16 g, 104 mmol) in anhydrous DMF (100 mL) under nitrogen was treated dropwise with a solution of 3,4-di-hydroxybenzaldehyde (6.91 g, 50 mmol) in anhydrous DMF (50 mL) and the mixture was stirred at room temperature for 1 h and re-cooled on an ice bath. Benzyl chloride (6.62 mL, 57.5 mmol) was added via syringe and the mixture allowed to reach room temperature and stirred overnight (18 h). The mixture was concentrated in vacuo to remove most of the DMF, and ice water (300 mL) was added. The aqueous solution was extracted with diethyl ether (3 × 100 mL), acidified with concentrated hydrochloric acid (~10 mL), and stirred for 30 min, during which time a solid precipitated. The solid was filtered, rinsed with water, partially air dried, and dissolved in dichloromethane (125 mL) and dried (Na_2SO_4). The solution was added directly to a silica gel column and eluted with dichloromethane to afford 3-benzyloxy-4-hydroxybenzaldehyde (7.52 g, 66%) as a white solid: mp 117–118 °C (lit.[37] 113–114 °C); LC/MS *m*/*z* 229 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.17 (s, 2H), 6.32 (s, 1H), 7.06 (d, *J* = 8.1, 1H)), 7.35–7.46 (m, 6H), 7.51 (d, *J* = 1.6, 1H), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.5, 110.5, 114.8, 127.7, 128.2, 128.9, 129.0, 130.1, 135.6, 146.5, 152.0, 190.9. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.93; H, 5.27.

4.11. Preparation of 3-benzyloxy-4-(4-methoxybenzyl)benzaldehyde 7b

An ice cooled stirred suspension of 60% sodium hydride/oil (88 mg, 2.2 mmol) in anhydrous DMF (2 mL) under nitrogen was treated with a solution of 3-benzyloxy-4-hydroxybenzaldehyde (0.456 g, 2.0 mmol) in anhydrous DMF (2.0 mL) and the mixture was stirred at room temperature for 30 min and re-cooled on an ice bath. A solution of 4-methoxybenzyl chloride (0.376 g, 2.4 mmol) in anhydrous DMF (1.0 mL) was added and the mixture was allowed to reach room temperature and stirred overnight (18 h). Water (50 mL) was added and after 30 min, a precipitate formed. This was filtered, rinsed with water, partially air dried, dissolved in dichloromethane (40 mL), and dried (Na_2SO_4). The solution was added directly to a column of silica gel and eluted with dichloromethane to afford 3-benzyloxy-4-(4-methoxybenzyl)-benzaldehyde (0.665 g, 95%) as a white solid: mp 79–81 °C; LC/MS *m*/*z* 349 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81(s, 3H), 5.18 (s, 2H), 5.20 (s, 2H), 6.91 (d, *J* = 8.6, 2H), 7.04 (d, *J* = 8.2, 1H), 7.28–7.53 (m, 9H), 9.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4, 71.0, 71.2, 112.9, 113.5, 114.2, 126.7, 127.5, 128.1, 128.4, 128.7, 129.0, 130.5, 136.8, 149.5, 154.6, 159.7, 190.9. Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.59; H, 5.78.

4.12. Preparation of 4-benzyloxy-3-hydroxybenzaldehyde 16

An ice cooled, stirred suspension of 60% sodium hydride/oil (1.76 g, 44 mmol) in anhydrous DMF (40 mL) under nitrogen was treated dropwise with a solution of 3,4-di-hydroxybenzaldehyde (5.525 g, 40 mmol) in anhydrous DMF (40 mL) and the mixture was stirred at room temperature for 30 min and recooled on an

ice bath. Benzyl bromide (5.25 mL, 44 mmol) was then added via syringe and the mixture allowed to reach room temperature and stirred overnight (18 h). The mixture was combined with 1% aqueous sodium hydroxide (300 mL) and the cloudy solution was extracted with ether (2 × 75 mL) and acidified with concentrated hydrochloric acid. A precipitate soon formed, and the resulting suspension was stirred for a few minutes and filtered. The solid was rinsed with water, partially air dried, dissolved in dichloromethane (100 mL), and dried (Na_2SO_4). The solution was added directly to a column of silica gel and eluted with dichloromethane to yield a solid, which was triturated from petroleum ethers to afford 4-benzyloxy-3-hydroxybenzaldehyde (4.46 g, 49%) as a white solid: mp 122–123 °C (lit.[38] 121–122 °C); LC/MS *m*/*z* 229 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.20 (s, 2H), 5.92 (s, 1H), 7.03 (d, *J* = 8.3, 1H), 7.35–7.44 (m, 6H), 7.46 (d, *J* = 1.9, 1H), 9.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.5, 111.7, 114.6, 124.4, 128.0, 128.9, 129.0, 131.0, 135.4, 146.5, 151.1, 191.1. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.91; H, 5.19.

4.13. Preparation of 4-benzyloxy-3-methoxymethoxybenzaldehyde 7c

An ice cooled stirred solution of 4-benzyloxy-3-hydroxybenzaldehyde (6.85 g, 30 mmol) and *N*,*N*-diisopropylethylamine (10.5 mL, 60 mmol) in anhydrous methylene chloride (200 mL) under nitrogen was treated dropwise with bromomethyl methyl ether (3.0 mL, 33 mmol corrected for 90%) and stirred on an ice bath for 1 h. Aqueous sodium hydroxide (1 M, 75 mL) was added and the mixture stirred a few minutes and separated. The aqueous solution was extracted with dichloromethane (75 mL) and the combined organic solution washed with water and brine (100 mL each), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in minimum dichloromethane and loaded onto a silica gel column and eluted with 2:1 heptane/ethyl acetate to afford 4-benzyloxy-3-methoxymethoxybenzaldehyde (8.09 g, 99%) as a colorless viscous oil: LC/MS *m*/*z* 273 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.53 (s, 3H), 5.24 (s, 2H), 5.28 (s, 2H), 7.02 (d, *J* = 8.3, 1H), 7.30–7.46 (m, 5H), 7.48 (dd, *J* = 8.3, 1.9, 1H), 7.66 (d, *J* = 1.9, 1H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.5, 71.0, 95.8, 113.4, 116.7, 126.8, 127.3, 128.4, 128.9, 130.6, 136.2, 147.5, 154.6, 190.8. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.51; H, 6.01.

4.14. Preparation of 3-methoxy-4-methoxymethoxybenzaldehyde 7e

An ice cooled stirred solution of 3-methoxy-4-hydroxybenzaldehyde (9.13 g, 60 mmol) and *N*,*N*-diisopropylethylamine (21 mL, 120 mmol) in anhydrous methylene chloride (400 mL) under nitrogen was treated dropwise with bromomethyl methyl ether (6.0 mL, 66 mmol corrected for 90%) and stirred on an ice bath for 45 min. Aqueous sodium hydroxide (1 M, 150 mL) was added and the mixture stirred for a few minutes and separated. The aqueous solution was extracted with dichloromethane (100 mL) and the combined organic solution washed with water (200 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in minimum dichloromethane and loaded onto a silica gel column and eluted with 1.5% ethyl acetate/dichloromethane to afford 3-methoxy-4-methoxymethoxybenzaldehyde (11.56 g, 98%) as a colorless oil: LC/MS *m*/*z* 197 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (s, 3H), 3.95 (s, 3H), 5.32 (s, 2H), 7.27 (d, *J* = 8.2, 1H), 7.41–7.45 (m, 2H), 9.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.2, 56.6, 95.2, 109.8, 115.0, 126.4, 131.3, 150.3, 152.2, 191.0. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.94; H, 6.23.

4.15. Preparation of 4-methoxy-3-methoxymethoxybenzaldehyde 7g

An ice cooled stirred solution of 4-methoxy-3-hydroxybenzaldehyde (6.85 g, 45 mmol) and *N*,*N*-diisopropylethylamine (15.75 mL, 90 mmol) in anhydrous dichloromethane (200 mL) under nitrogen was treated dropwise with bromomethyl methyl ether (5.0 mL, 55 mmol corrected for 90%) and stirred on an ice bath for 1 h. Next, 1 M aqueous sodium hydroxide (125 mL) was added and the mixture stirred for a few minutes and separated. The aqueous solution was extracted with dichloromethane (50 mL) and the combined organic solution washed with water and brine (100 mL each), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in minimum dichloromethane and loaded onto a silica gel column and eluted with 1:1 ethyl acetate/heptane to afford 4-methoxy-3-methoxymethoxybenzaldehyde (8.74 g, 99%) as a pale yellow solid: mp 33–34 °C (lit.[39] 31–32 °C); LC/MS *m*/*z* 197 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.51 (s, 3H), 3.95 (s, 3H), 5.27 (s, 2H), 7.00 (d, *J* = 8.3, 1H), 7.53 (dd, *J* = 8.3, 1.9, 1H), 7.65 (d, *J* = 1.9, 1H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.3, 56.5, 95.6, 111.3, 115.6, 126.9, 130.3, 147.1, 155.3, 190.8. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.00; H, 6.07.

The experimental procedures for the preparation of the final targets **1a–j** are typified by those of (−)-3′-OMe-4′,5-di-*O*-benzyl-7-*O*-MOM-epicatechin **1g**.

4.16. Preparation of (*E*)-1-(2-benzyloxy-6-hydroxy-4-methoxymethoxy-phenyl)-3-(4-benzyloxy-3-methoxy-phenyl)-propenone 5g

A dried 250 mL 3-necked round-bottomed flask was charged with NaH (2.21 g, 55.31 mmol, 60% dispersion in mineral oil) under nitrogen. Heptane (5 ml) was then added and the mixture was stirred for 5 min. Next, DMF (60 mL) was added and the white suspension was cooled in an ice-water bath for 10 min. A solution of the acetophenone **6b** (7.60 g, 25.14 mmol) in DMF (30 mL) was added slowly via a syringe. The mixture was stirred for 30 min while cooling in an ice-water bath. A solution of the 3-*O*-methyl 4-*O*-benzyl benzaldehyde **7d** (6.39 g, 26.39 mmol) in DMF (30 mL) was added via syringe. The resultant orange mixture was stirred for an additional 10 min at 0 °C and at room temperature for 2 h. The reaction was then poured onto crushed ice (350 g). The mixture was stirred vigorously to obtain a yellow suspension. The solution pH was adjusted to neutral with 1 M HCl. The mixture was stirred until no sticky droplets were visible and a homogenous yellow suspension was obtained (ca 2 h). The yellow solid was collected by suction filtration, rinsed with water (2 × 30 mL), and suction dried to afford the title compound **5g** (13.44 g, 100% yield): mp 138–139 °C; LC/MS *m*/*z* 527 [M+H], ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (s, 3H), 3.69 (s, 3H), 5.11 (s, 2H), 5.02 (s, 4H), 6.22 (s, 1H), 6.32 (s, 1H), 6.66 (ABq, J_{AB} = 8.2, $\Delta\nu_{AB}$ = 25.7, 2H), 7.21–7.51 (m, 10H), 7.75 (ABq, J_{AB} = 15.7, $\Delta\nu_{AB}$ = 27.3, 2H), 14.32 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.0, 56.6, 71.0, 71.4, 92.8, 94.2, 97.1, 107.2, 112.0, 113.8, 121.9, 125.9, 127.2, 128.1, 128.5, 128.75, 128.79, 128.9, 135.7, 136.9, 143.0, 149.6, 150.1, 161.8, 163.6, 168.1, 192.8. Anal. Calcd for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74. Found: C, 72.88; H, 5.90.

4.17. Preparation of (*E*)-3-benzyloxy-2-[3-(3-benzyloxy-4-methoxy-phenyl)-allyl]-5-methoxymethoxy-phenol 4g

A jacketed 1 L round-bottomed flask was charged with cerium chloride heptahydrate (24.51 g, 65.8 mmol) and ethanol (92 mL). The mixture was stirred at room temperature under nitrogen to obtain a clear solution. Next, THF (224 mL) was added followed by the addition of the chalcone **5g** (13.30 g, 25.0 mmol). The reac-

tion was cooled to approximately 2 °C (internal temperature), after which sodium borohydride (2.49 g, 65.8 mmol) was added in portions. After completion of the addition, the reaction was stirred at approximately 2 °C for 65 h, after which it was quenched by the slow addition of 5 wt % citric acid solution. After vigorous gas release had subsided, the mixture was stirred for an additional 20 min, then extracted with ethyl acetate (300 mL). The solid material in the aqueous layer was dissolved by adding 1 M HCl (10 mL) and the aqueous phase was extracted with ethyl acetate (300 mL). The combined organic layers were washed with saturated sodium bicarbonate (200 mL × 3) and brine (200 mL). The pH of the final aqueous wash was ca 4–5. The organic layer was dried over anhydrous sodium sulfate. Removal of solvent in vacuo afforded the crude as an orange solid. This was dissolved in dichloromethane (30 mL) and purified by flash chromatography (silica gel, heptane/ethyl acetate 3:1, v/v). Two fractions were collected. The bottom fraction was concentrated in vacuo to obtain the desired compound as a white solid (9.30 g, 73% yield). An analytical sample was obtained by recrystallization from a mixture of heptane and ethyl acetate (3:1, v/v): mp 129–130 °C; LC/MS *m*/*z* 513 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ, 3.46 (s, 3H), 3.56 (d, J = 6.2, 2H), 3.85 (s, 3H), 5.04 (s, 2H), 5.11 (s, 2H), 5.12 (s, 2H), 5.26 (s, 1H), 6.11–6.22 (m, 1H), 6.25 (s, 1H), 6.32 (s, 1H), 6.38 (d, J = 15.8, 1H), 6.77 (m, 2H), 6.88 (s, 1H), 7.23–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 56.1, 70.5, 71.3, 94.7, 94.8, 97.1, 108.4, 109.6, 114.4, 119.2, 126.7, 127.4, 127.5, 127.9, 128.0, 128.6, 130.3, 131.4, 137.25, 137.33, 147.7, 149.9, 155.8, 157.3, 158.1. Anal. Calcd for $C_{32}H_{32}O_6$: C, 74.98; H, 6.29. Found: C, 74.89; H, 6.33.

The less polar top fraction contained mainly a cyclized by-product 5-benzyloxy-2-(4-benzyloxy-3-methoxy-phenyl)-7-methoxymethoxy-2*H*-chromene **22g** and a small amount of the desired product **4g**. This was further purified by flash column (silica gel, hepatane/ethyl acetate, 3:1, v/v) to obtain pure **22g** (1.66 g, 13%) as an orange oil: LC/MS *m*/*z* 511 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.45 (s, 3H), 3.89 (s, 3H), 5.06 (s, 2H), 5.10 (s, 2H), 5.16 (s, 2H), 5.62 (d, J = 9.9, 1H), 5.78 (s, 1H), 6.24 (d, J = 6.5, 2H), 6.83–6.97 (m, 3H), 7.05 (s, 1H), 7.27–7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.2, 70.5, 71.2, 94.6, 94.7, 97.3, 106.0, 111.4, 114.1, 119.2, 120.0, 120.6, 127.4, 127.5, 127.9, 128.1, 128.66, 128.67, 134.1, 137.0, 137.3, 148.5, 150.0, 155.0, 155.4, 158.9; HRMS (ESI): Calcd for $C_{32}H_{30}O_6$ ($[M+H]^+$): 511.2115. Found: 511.2105.

4.18. Preparation of (*E*)-{3-benzyloxy-2-[3-(4-benzyloxy-3-methoxy-phenyl)-allyl]-5-methoxymethoxy-phenoxy}-*tert*-butyl-dimethyl-silane 17g

A mixture of **4g** (9.18 g, 17.9 mmol), imidazole (3.66 g, 53.7 mmol), and TBDMSCl (5.40 g, 35.8 mmol) in DMF (70 mL) was stirred at room temperature under nitrogen overnight. Next, it was poured onto 250 g of crushed ice. The milky mixture was extracted with ethyl acetate (250 mL × 2). The combined organic layers were washed with water and brine (200 mL each) and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded the crude product as an oil, which was purified by flash chromatography (silica gel, heptane/ethyl acetate 3:1, v/v) to give **17g** (9.85 g, 88%) as a clear viscous oil: LC/MS, *m*/*z* 627 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.26 (s, 6H), 1.02 (s, 9H), 3.47 (s, 3H), 3.50 (d, J = 6.0, 2H), 3.86 (s, 3H), 5.04 (s, 2H), 5.11 (s, 2H), 5.13(s, 2H), 6.11–6.21 (m, 1H), 6.22–6.29 (m, 2H), 6.35 (s, 1H), 6.75 (ABq, J_{AB} = 8.2, $\Delta\nu_{AB}$ = 21.2, 1H), 6.85 (s, 1H), 7.27–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −3.9, 18.5, 26.0, 27.0, 56.0, 56.1, 70.3, 71.4, 94.9, 95.0, 100.3, 109.5, 113.5, 114.4, 119.0, 127.4, 127.5, 127.8, 127.86, 127.88, 128.58, 128.62, 129.4, 132.2, 137.47, 137.51, 147.4, 149.8, 154.9, 156.8, 158.4. Anal. Calcd for $C_{38}H_{46}O_6Si$: C, 72.81; H, 7.40. Found: C, 72.59; H, 7.51.

4.19. Preparation of (1*S*,2*S*)-3-[2-benzyloxy-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxymethoxy-phenyl]-1-(4-benzyloxy-3-methoxy-phenyl)-propane-1,2-diol 18g

To a cold mixture of ADMIX-α (56.7 g), *t*-butanol (150 mL), and water (150 mL) cooled by a circulating chiller was added a solution of **17g** (9.51 g, 15.17 mmol) in THF (173 mL). The mixture was cooled to −1 °C (internal temperature) followed by the addition of methanesulfonamide (1.88 g, 19.72 mmol). The reaction was stirred vigorously at −1 °C under nitrogen for 4 days, then quenched by carefully adding a 10 wt % solution of sodium bisulfite (170 mL). The cooling was turned off and the mixture was stirred at room temperature overnight. The greenish bi-phasic solution was transferred into a 1-L separatory funnel. The organic layer was concentrated in vacuo. The aqueous layer was extracted with ethyl acetate (250 ml × 2). The organic layers were combined with the above residue from the initial organic phase, then washed with water and brine (200 mL each) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded the crude product as a yellow oil. The crude product was then dissolved in 10 mL of dichloromethane and purified by flash column (silica gel, heptane/ethyl acetate 2:1, v/v) to obtain the desired product (9.28 g, 93%) as a clear oil: LC/MS *m*/*z* 627 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.20 (s, 6H), 0.94 (s, 9H), 2.60 (s, broad, 1H,OH), 2.82 (d, J = 7.1, 2H), 3.21 (s, broad, 1H, OH), 3.46 (s, 3H), 3.83 (s, 3H), 3.85 (m, partially overlaps with the aromatic OMe peak, 1H), 4.41 (d, J = 5.2, 1H), 5.00 (s, 2H), 5.10 (s, 2H), 5.12 (s, 2H), 6.28 (d, J = 2.1, 1H), 6.36 (d, J = 2.2, 1H), 6.77 (s, 2H), 6.93 (s, 1H), 7.27–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1, −3.9, 18.4, 25.9, 27.8, 56.0, 70.7, 71.3, 75.7, 77.1, 94.9, 95.1, 100.7, 110.6, 110.9, 114.0, 119.2, 127.4, 127.5, 127.9, 128.2, 128.6, 128.8, 134.5, 136.6, 137.5, 147.8, 149.8, 155.4, 157.2, 158.4. Anal. Calcd for $C_{38}H_{48}O_8Si$: C, 69.06; H, 7.36. Found: C, 69.24; H, 7.27. The ee was determined to be approximately 67% based on ^{1}H NMR in the presence of 68 equivalents of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol) in $CDCl_3$. Under these conditions, the OMe group on the aromatic ring exhibited baseline-resolved doublets with δ 3.70 [(*S*,*S*)-enantiomer] and 3.72 ppm [(*R*,*R*)-enantiomer], respectively.

4.20. Preparation of (1*S*,2*S*)-3-(2-benzyloxy-6-hydroxy-4-methoxymethoxy-phenyl)-1-(4-benzyloxy-3-methoxy-phenyl)-propane-1,2-diol 3g

To a solution of **18f** (9.12 g, 14.7 mmol) in THF (70 mL) cooled in an ice-water bath was added *n*-Bu_4NF (29.4 mL, 1 M solution in THF) containing acetic acid (1.77 g, 29.4 mmol) via an addition funnel. After completion of the addition, the reaction was stirred in the ice-water bath for 1 additional hour, then concentrated in vacuo to remove the THF. The residue was dissolved in dichloromethane (300 mL), washed with water (200 mL × 2), and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded the crude as a brown oil. The crude was dissolved in minimal volume of dichloromethane and purified by flash column (silica gel, heptane/EtOAc, 1:1, v/v) to obtain the desired product (6.73 g, 84%) as a white solid. An analytical sample was obtained by recrystallization from heptane/EtOAc (1:1, v/v): mp 136–138 °C; LC/MS *m*/*z* 547 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (dd, J = 14.6, 8.56, 1H), 2.93 (dd, J = 14.6, 3.4, 1H), 3.35 (s, 4H, OMe plus OH), 3.80 (s, 3H), 3.95–4.02 (m, 1H), 4.45 (d, J = 6.8, 1H), 4.87 (ABq, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 16.6, 2H), 5.05 (s, 2H), 5.11 (s, 4H), 6.24 (d, J = 2.3, 1H), 6.33 (d, J = 2.2, 1H), 6.73 (ABq, J_{AB} = 8.3, $\Delta\nu_{AB}$ = 17.1, 2H),[40] 6.86 (d, J = 1.7, 1H), 8.10 (s, broad, 1H, phenolic OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 56.09, 56.14, 70.2, 71.0, 76.9, 77.0, 94.2, 94.7, 98.1, 107.4, 110.6, 113.8, 119.4, 127.0, 127.4, 127.8, 128.0, 128.6, 128.7, 133.6, 137.0, 137.2, 148.3,

149.8, 157.5, 157.6, 157.9. HRMS (ESI): Calcd for $C_{32}H_{34}O_8$ ($[M+H]^+$): 547.2326. Found: 547.2321.

4.21. Preparation of 3′-*O*-methyl-4′,5-di-*O*-benzyl-7,-*O*-methoxymethoxy-(+)-catechin-3-*O*-propyl ester 19g

A mixture of **3g** (6.42 g, 11.75 mmol), triethyl orthopropionate (3.73 g, 21.14 mmol), and pyridinium *p*-toluenesulfonate (1.59 g, 6.35 mmol) in 1,2-dichloroethane (150 mL) was heated in an oil bath at 65 °C for 1 h, after which it was concentrated in vacuo. The oily residue was dissolved in dichloromethane (20 ml) and purified by flash chromatography (silica gel, heptane/ethyl acetate 4:1, v/v) to obtain the desired product **19g** (6.80 g, 100%) as a clear oil, which was solidified upon standing at room temperature. An analytical sample was obtained by recrystallization from heptane/EtOAc (4:1, v/v): mp 98–99 °C; LC/MS *m*/*z* 585 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, J = 7.6, 3H), 2.09–2.28 (m, 2H), 2.71 (dd, J = 16.8, 7.3, 1H), 3.00 (dd, J = 16.7, 5.6, 1H), 3.47 (s, 3H), 3.87 (s, 3H), 4.97 (d, J = 7.1, 1H), 5.02 (s, 2H), 5.13 (s, 2H), 5.15 (s, 2H), 5.36 (q, J = 6.4, 1H), 6.29 (d, J = 2.2, 1H), 6.35 (d, J = 2.2, 1H), 6.83 (s, 2H), 6.92 (s, 1H), 7.27–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.1, 24.8, 27.7, 56.2, 69.0, 70.2, 71.2, 78.7, 94.5, 94.8, 96.9, 102.7, 110.5, 114.0, 119.5, 127.4, 127.5, 128.0, 128.1, 128.67, 128.68, 131.0, 137.0, 137.2, 148.3, 149.8, 155.1, 157.4, 157.8, 173.6. $[\alpha]_D^{20} = +5.8$ (c 5.2, $CHCl_3$). Anal. Calcd for $C_{35}H_{36}O_8$: C, 71.90; H, 6.21. Found: C, 72.03; H, 6.27.

4.22. Preparation of 3′-*O*-methyl-4′,5-di-*O*-benzyl-7,-*O*-methoxymethoxy-(+)-catechin 2g

To a mixture of **19g** (6.70 g, 11.46 mmol) in methanol (210 mL) was added a solution of potassium carbonate (4.05 g, 29.34 mmol) in water (16 mL). The mixture was stirred at room temperature for 24 h which gave a white suspension. This was filtered by suction to obtain a wet cake. The filtrate was then concentrated in vacuo. The residue was combined with the wet cake in dichloromethane (500 mL). The dichloromethane solution was washed with water (200 mL), brine (200 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo afforded the crude as an off-white solid. The crude was stirred in methanol overnight, filtered, and dried to obtain 5.10 g of pure product. The mother liquor was concentrated and the residue was purified by flash chromatography (silica gel, heptane/EtOAc 2:1) to obtain 0.18 g of additional pure product. The two crops of product were combined (5.28 g, 87% yield). The enantiomeric excess was determined by chiral HPLC to be 66%.

The above enantiomerically enriched product (5.28 g, 10 mmol) and Mosher's acid (468 mg, 2.0 mmol) were dissolved in anhydrous dichloromethane (80 mL). The mixture was cooled in an ice-water bath followed by the addition of *N*,*N*′-dicyclohexylcarbodiimide (412 mg, 2 mol) and a catalytic amount of 4-dimethylaminopyridine (40 mg, 0.33 mmol). The reaction was then stirred at 0 °C. After 30 min, chiral HPLC indicated 75% ee of the unreacted catchin. After 60 min, additional Mosher's acid (468 mg, 2 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (412 mg, 2 mol) were added to the reaction. After 30 min, chiral HPLC showed 96% ee of the unreacted catechin. The reaction was concentrated to a volume of 20 mL. The residue (a suspension) was purified by flash chromatography (silica gel, heptane/EtOAc, 2:1, v/v) to obtain two fractions. Concentration of the bottom fraction afforded pure 3′-*O*-methyl-4′,5-di-*O*-benzyl-7-*O*-methoxymethyl-(+)-catechin **2g** (3.22 g, 61% yield, 96% ee) as a white solid: mp 137–138 °C; LC/MS *m*/*z* 529 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (dd, J = 16.4, 9.20, 1H), 3.18 (dd, J = 16.4, 5.76, 1H), 3.47 (s, 3H), 3.91 (s, 3H), 4.06 (m, 1H), 4.65 (d, J = 8.4, 1H), 5.06 (ABq, J_{AB} = 11.8, $\Delta\nu_{AB}$ = 8.1, 2H), 5.12 (t, J = 7.0, 2H), 5.18 (s, 2H), 6.33 (ABq, J_{AB} = 2.2, $\Delta\nu_{AB}$ = 10.7, 2H), 6.88–6.96 (m, 2H), 7.00 (d, J = 1.2, 1H), 7.28–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 56.1, 56.2, 68.4, 70.1, 71.2, 81.9, 94.6, 94.8, 96.9, 103.6, 110.8, 114.2, 120.0, 127.3, 127.4, 128.0, 128.66, 128.71, 130.9, 137.1, 137.2, 148.7, 150.2, 155.5, 157.3, 157.9. $[\alpha]_D^{20} = +7.1$ (c 5.4, $CHCl_3$). Anal. Calcd for $C_{32}H_{32}O_7$: C, 72.71; H, 6.10. Found: C, 72.79; H, 6.19.

Evaporation of the top fraction afforded an approximately 1:1 diastereomeric ester of the Mosher's acid by ^{1}H NMR as an oil which solidified upon standing (2.55 g, 86%).

4.23. Preparation of (2*R*)-5-benzyloxy-2-(4-benzyloxy-3-methoxy-phenyl)-7-methoxymethoxy-chroman-3-one 20g

A mixture of 3′-*O*-methyl-4′,5-di-*O*-benzyl-7-*O*-methoxymethyl-(+)-catechin **2g** (3.10 g, 5.86 mmol) and Dess–Martin periodinane (4.97 g, 11.71 mmol) in wet dichloromethane (60 mL) was stirred at room temperature until completion of the reaction (ca. 3 h). Saturated $NaHCO_3$ solution (60 mL) was then added and the mixture was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (150 mL × 2). The combined organic layers were washed with water (200 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent afforded the crude product as a light yellow oil, which was purified by flash chromatography (silica gel, heptane/EtOAc, 3:1, v/v) to obtain the desired product (2*R*)-5-benzyloxy-2-(4-benzyloxy-3-methoxy-phenyl)-7-methoxymethoxy-chroman-3-one **20g** (2.03 g, 66%) as a white solid: mp 120–121 °C; LC/MS *m*/*z* 527 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48 (s, 3H), 3.52 (d, J = 21.3, 1H), 3.66 (d, J = 21.3, 1H), 3.85 (s, 3H), 5.03 (s, 2H), 5.14 (s, 2H), 5.15 (s, 2H), 5.27 (s, 1H), 6.39 (d, J = 2.1, 1H), 6.50 (d, J = 2.1, 1H), 6.83 (m, 2H), 6.92 (s, 1H), 7.27–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 56.1, 56.2,70.3, 71.1, 83.3, 94.8, 95.9, 98.2, 103.3, 110.5, 114.0, 119.4, 127.3, 127.4, 128.0, 128.1, 128.2, 128.69, 128.73, 136.6, 137.1, 148.6, 149.9, 154.8, 157.2, 158.0, 205.2 (C=O). $[\alpha]_D^{20} = +59.9$ (c 5.0, $CHCl_3$). Anal. Calcd for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74. Found: C, 72.80; H, 5.76.

4.24. Preparation of 3′-*O*-methyl-4′,5-di-*O*-benzyl-7-*O*-methoxymethoxy-(−)-epicatechin 1g

A mixture of (2*R*)-5-benzyloxy-2-(4-benzyloxy-3-methoxy-phenyl)-7-methoxymethoxy-chroman-3-one **20g** (1.90 g, 3.61 mmol) and aluminum isopropoxide (1.47 g, 7.22 mmol) in a mixed solvent of toluene (60 mL) and 2-propanol (18 mL) was heated at reflux under nitrogen. The distillate was collected via a Dean–Stark trap. After ca. 13 mL of the distillate was collected (ca. 1 h), heating was stopped, and the reaction was cooled to room temperature. The reaction mixture was then concentrated in vacuo. The residue was dissolved in dichloromethane (100 mL). The dichloromethane solution was washed with 1 M HCl (100 mL). The aqueous phase was back extracted with dichloromethane (100 mL). The combined dichloromethane layers were washed with saturated $NaHCO_3$ (200 mL) and water (200 mL × 2) and dried over anhydrous $MgSO_4$. Removal of the solvent afforded the crude product as a light yellow solid which was purified by flash chromatography (silica gel, hepatene/EtOAc, 3:1, v/v) to obtain the desired product 3′-*O*-methyl-4′,5-di-*O*-benzyl-7-*O*-methoxymethoxy-(−)-epicatechin **1g** (1.51 g, 79%) as a white solid: mp 110–111 °C; LC/MS *m*/*z* 529 [M+H]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.00 (ABq, J_{AB} = 17.4, $\Delta\nu_{AB}$ = 35.4, 2H)[41], 3.47 (s, 3H), 3.94 (s, 3H), 4.28 (s, br, 1H), 4.96 (s, 1H), 5.05 (s, 2H), 5.14 (s, 2H), 5.18 (s, 2H), 6.31 (d, J = 2.2, 1H), 6.40 (d, J = 2.2, 1H), 6.94 (ABq, J_{AB} = 8.3, $\Delta\nu_{AB}$ = 17.2, 2H, H-5′and H-6′),[42] 7.11 (d, J = 1.6, 1H, H-2′), 7.27–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 56.1, 56.3, 66.5, 70.2, 71.3, 78.6, 94.8, 94.9, 97.1, 102.2, 110.4, 114.3, 118.7, 127.4, 127.97, 128.02, 128.66, 128.68, 131.5, 137.1, 137.3, 148.2, 150.0, 155.4, 157.3, 158.4. $[\alpha]_D^{20} = -15.8$ (c 5.1, $CHCl_3$).

Anal. Calcd for $C_{32}H_{32}O_7$: C, 72.71; H, 6.10. Found: C, 72.73; H, 6.18. It is 93% ee by Chiral HPLC.

The experimental procedures for the preparation of the racemic chiral HPLC standards of the catechin **2a–j** and epicatechin **1a–j** are illustrated by those of (±)-3′-OMe-4′,5-di-*O*-benzyl-7-*O*-methoxymethoxy-catechin **2g** and the corresponding (±)-epicatechin **1g**.

To a mixture of $K_3Fe(CN)_6$ (840 mg, 2.55 mmol), potassium carbonate (366 mg, 2.65 mmol), osmium trichloride monohydrate (5.7 mg, 0.019 mmol), quinuclidine (6.9 mg, 0.062 mmol), and methane sulfonamide (93.5 mg, 0.98 mmol) in *t*-butanol/water (1:1, v/v, 12 mL) was added a solution of **22g** (440 g, 0.86 mmol) in tetrahydrofuran (12 mL). The resultant mixture was stirred at room temperature for 18 h, after which it was quenched by adding sodium bisulfite (1.2 g) and stirred for 1 h. The mixture was extracted with ethyl acetate (25 ml × 2). The combined organic layers were washed with water and brine (50 ml each), and dried over anhydrous magnesium sulfate. Removal of the solvent afforded an off-white solid (the crude product **23g**). This solid was suspended in acetic acid (20 mL) and treated with $NaBH_3CN$ (129 mg, 2.05 mmol) at 50 °C (oil bath) for 2 h. The light brown solution was poured into a cold 2 M NaOH solution (100 mL). This gave a white solid, which was collected by filtration, rinsed with water, suction dried, and purified by flash chromatography (silica gel, heptane/ethyl acetate 3:1, v/v) to obtain a 9:1 mixture of the desired racemic **2g** and racemic **1g** as a white solid (260 mg, 57% yield over two steps). The ratio of **2g**/**1g** was determined by both ^{1}H NMR and chiral HPLC. This mixture was used as a chiral HPLC standard without first separating the racemic catechin from the racemic epicatechin.

References

1. Porter, L. J. Flavans and Proanthocyanidins. In *The Flavonoids, Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman & Hall: London, 1994; pp 23–56.
2. Ellinger, S.; Reusch, A.; Stehle, P.; Helfrich, H. P. *Am. J. Clin. Nutr.* **2012**, *95*, 1365.
3. Hooper, L.; Kay, C.; Abdelhamid, A.; Kroon, P. A.; Cohn, J. S.; Rimm, E. B.; Cassidy, A. *Am. J. Clin. Nutr.* **2012**, *95*, 740.
4. Schroeter, H.; Heiss, C.; Spencer, J. P.; Keen, C. L.; Lupton, J. R.; Schmitz, H. H. *Mol. Aspects Med.* **2010**, *31*, 546.
5. Van Praag, H.; Lucero, M. J.; Yeo, G. W.; Stecker, K.; Heivand, N.; Zhao, C.; Yip, E.; Afanador, M.; Schroeter, H.; Hammerstone, J.; Gage, F. H. *J. Neurosci.* **2007**, *27*, 5869.
6. Heiss, C.; Jahn, S.; Taylor, M.; Real, W. M.; Angeli, F. S.; Wong, M. L.; Amabile, N.; Prasad, M.; Rassaf, T.; Ottaviani, J. I.; Mihardja, S.; Keen, C. L.; Springer, M. L.; Boyle, A.; Grossman, W.; Glantz, S. A.; Schroeter, H.; Yeghiazarians, Y. *J. Am. Coll. Cardiol.* **2010**, *56*, 218.
7. Curtis, P. J.; Sampson, M.; Potter, J.; Dhatariya, K.; Kroon, P. A.; Cassidy, A. *Diabetes Care* **2012**, *35*, 226.
8. Schroeter, H.; Heiss, C.; Balzer, J.; Kleinbongard, P.; Keen, C. L.; Hollenberg, N. K.; Sies, H.; Kwik-Uribe, C.; Schmitz, H. H.; Kelm, M. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 1024.
9. Mink, P. J.; Scrafford, C. G.; Barraj, L. M.; Harnack, L.; Hong, C. P.; Nettleton, J. A.; Jacobs, D. R., Jr. *Am. J. Clin. Nutr.* **2007**, *85*, 895.
10. Ottovani, J. I.; Momma, T. Y.; Kuhnle, G. K.; Keen, C. L.; Schroeter, H. *Free Radic. Biol. Med.* **2012**, *52*, 1403.
11. Ottaviani, J. I.; Kwik-Uribe, C.; Keen, C. L.; Schroeter, H. *Am. J. Clin. Nutr.* **2012**, *95*, 851.
12. Ottaviani, J. I.; Momma, T. Y.; Heiss, C.; Kwik-Uribe, C.; Schroeter, H.; Keen, C. L. *Free Radic. Biol. Med.* **2011**, *50*, 237.
13. Natsume, M.; Osakabe, N.; Oyama, M.; Sasaki, M.; Baba, S.; Nakamura, Y.; Osawa, T.; Terao, J. *Free Radic. Biol. Med.* **2003**, *34*, 840.
14. Auger, C.; Mullen, W.; Hara, Y.; Crozier, A. *J. Nutr.* **2008**, 1535S.
15. Mullen, W.; Borges, G.; Donovan, J. L.; Edwards, C. A.; Serafini, M.; Lean, M. E. J.; Crozier, A. *Am. J. Clin. Nutr.* **2009**, *89*, 1784.
16. See: (a) Kuhnle, G.; Spencer, J. P.; Schroeter, H.; Shenoy, B.; Debnam, E. S.; Srai, S. K.; Rice-Evans, C.; Hahn, U. *Biochem. Biophys. Res. Commun.* **2000**, *277*, 507; (b) Lu, H.; Meng, X.; Yang, C. S. *Drug Metab. Dispos.* **2003**, *31*, 572. The O-methylation of epicatechin and catechin primarily occurs at the 3′- and 4′-OH via the action of catechol-*O*-methyltransferase (COMT) and only one OH group is methylated, thus limiting the total number of the epicatechin glucuronides/sulfates that could be formed to ten each (4 non-methylated and 6 methylated forms). For references on the enzymology of methylation of epicatechin and catechin.
17. Mull, E. S.; Van Zandt, M.; Golebiowski, A.; Beckett, P.; Sharma, P. K.; Schroeter, H. *Tetrahedron Lett.* **2012**, *53*, 1501.
18. Zhang, M.; Jagdmann, Jr., G. E.; Van Zandt, M.; Sheeler, R.; Beckett, P.; Schroeter, H. *J. Nat. Prod.* Published on web on January 28, **2013**. http://dx.doi.org/10.1021/np300568m.
19. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z. *J. Org. Chem.* **1992**, *57*, 2768–2771. The absolute stereochemistry of the dihydroxylation products was assigned based on the Sharpless model and confirmed by the final product epicatechins, which show the expected negative specific rotation sign..
20. Romanczyk, L. J., Jr.; Sharma, P. K.; Gou, D.; Gou, Y. PCT Patent Application WO 2007/002877.
21. Sharma, P. K.; He, M.; Romanczyk, L. J., Jr.; Schroeter, H. *J. Label Compd. Radiopharm.* **2010**, *53*, 605.
22. Deville, J. P.; Behar, V. *J. Org. Chem.* **2001**, *66*, 4097.
23. Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19.
24. Cairns, H. *Tetrahedron* **1972**, *28*, 359.
25. Furuta, T.; Nakayama, M.; Suzuki, H.; Tajimi, H.; Inai, M.; Nukaya, H.; Wakimoto, T.; Kan, T. *Org. Lett.* **2009**, *11*, 2233.
26. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
27. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
28. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
29. Li, L.; Chan, T. H. *Org. Lett.* **2001**, *3*, 739.
30. Tuckmantel, W.; Kozikowski, A. P.; Romanczyk, L. J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073.
31. Sharma, P. K.; Kolchinski, A.; Shea, H. A.; Nair, J. J.; Gou, Y.; Romanczyk, L. J., Jr.; Schmitz, H. H. *Org. Process Res. Dev.* **2007**, *11*, 422.
32. Eames, J.; Mitchell, H. J.; Nelson, A.; ÓBrien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095–1103.
33. Kawamoto, H. *J. Wood Chem. Technol.* **1989**, *9*, 35.
34. Khupse, R. S. *J. Nat. Prod.* **2007**, *70*, 1507.
35. Kumazawa, T.; Minatogawa, T.; Matsuba, S.; Sato, S.; Onodera, J.-i. *Carbohydr. Res.* **2000**, *329*, 507.
36. Hossain, M. M.; Tokuoka, T.; Yamashita, K.; Kawamura, Y.; Tsukayama, M. *Synth. Commun.* **2006**, *36*, 1201.
37. Pearl, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 2630.
38. Hegedus, B. *Helv. Chim. Acta* **1963**, *46*, 2604.
39. Venturella, P. *Anal. Chim.* **1958**, *48*, 706.
40. The higher field doublets were further split by the third proton at δ 6.86 ppm with a J = 1.8 Hz.
41. Each H-4 proton was split by H-3 with J = 4.4, 1.7 Hz, respectively.
42. H-6′ was split by H-2′ (J = 1.7 Hz).