An efficient synthesis of the four mono methylated isomers of (+)-catechin including the major metabolites and of some dimethylated and trimethylated analogues through selective protection of the catechol ring

Cécile Cren-Olivé, Stéphane Lebrun and Christian Rolando *

Université des Sciences et Technologies de Lille, UPRESA 8009, Chimie Organique et Macromoléculaire, Equipe Polyphénols, 59655 Villeneuve d'Ascq, France. E-mail: Christian.Rolando@univ-lille1.fr; Fax: +333 20 33 61 36

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The four monomethylated isomers of (+)-catechin in positions 3′, 4′, 5 and 7, two dimethylated derivatives, the 5,7-dimethylcatechin and the 3′,4′-dimethylcatechin and two trimethylated isomers of (+)-catechin in positions 3′, 5, 7 and 4′, 5, 7 were synthesized by a new method based on successive and selective protections of the various phenol functions present on (+)-catechin. The key step was the selective protection of the catechol ring with dichlorodiphenylmethane and di-*tert*-butyldichlorosilane.

Introduction

Interest in food phenolics has recently increased greatly because of their protective effect against cancer,[1] cardiovascular[2] and neurodegenerative[3] diseases. Since these flavonoids are reported to exhibit a wide range of other biological effects, including antibacterial,[4] antiviral,[5] anti-inflammatory,[6] and antiallergic,[7] they are considered to be key compounds in the relationship between health and diet.[8] Indeed, flavan-3-ols are ubiquitously distributed in the plant kingdom and widely found in a number of foods.[7a,9] Recent studies[10] show the levels of flavan-3-ols, typically (+)-catechin, (−)-epicatechin, (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate and (−)-epigallocatechin range from 4.5 mg kg^{-1} in kiwi fruit to 610 mg kg^{-1} in black chocolate[10a] and for the beverages, from 27–96 mg per litre in red wine to 102–418 mg of total catechin per litre in tea infusions[10b] leading to an average consumption of 100 mg per day.

The protective effects have been mainly attributed to the antioxidative activities of flavan-3-ols and their ability to protect biomolecules from oxidative degradation by reactive oxygen species.[11] Therefore, the antioxidative properties of flavonoids have been extensively studied *in vivo* and *in vitro*,[12] but rather contradictory structure–activity relationships and kinetics have been derived.[12] Similar physical chemistry experiments have been limited by the lack of convenient model compounds giving access to the intrinsic reactivity of each ring (A, B, C)[13] and more precisely of each phenolic hydroxy. Until now, most biological studies have been mainly performed on polyphenols from either vegetal or commercially available sources. However polyphenols are mainly found circulating in blood as metabolites. For example, the most-studied flavan-3-ol, catechin, is present almost exclusively as methylated metabolites (3′-methylcatechin in majority) as well as sulfate and glucuronide conjugates in plasma.[14] These metabolites are not commercially available and are difficult to extract in the quantities required for biological or chemical studies from enzymatic synthesis.

This situation gives an impetus to the synthesis of the methylated metabolites of catechin and of selectively protected catechin analogues which, preserving the parent reactivity, allow the study of the intrinsic reactivity of each cycle or each catechin phenolic hydroxy. Total enantioselective syntheses of flavan-3-ols[15] appears to be difficult, long and expensive. Recently, two enantioselective syntheses[15a,15b] of epigallocatechin-3-gallate have been proposed but neither the choice of starting materials nor the yields of the epigallocatechin-3-gallate are satisfactory for access to catechin analogues and metabolites. On the other hand, the methylation of (+)-catechin **1**, under standard chemical conditions, is not selective and leads, with a very low yield, to a mixture of four monomethylated isomers.[16] So these two extreme routes do not constitute a suitable way to synthesize catechin metabolites for biological studies.

The syntheses of methylated derivatives of catechin is thus very quickly directed towards strategies of protection-deprotection of rings A and B. The only selective protections of catechin described previously are based on the use of cyclic borate[17a] or benzyl carbonate as protecting groups.[17b,c] Hathway and Seakins[17a] used the *in situ* borate protection to make 5,7-dimethylcatechin while Akimoto and Sugimoto[17b] and more recently Van Dyk *et al.*[17c] reported a synthetic sequence using both protecting groups leading to the 3′,4′-di-*O*-methyl and 5,7-di-*O*-methyl ethers. However, in our hands synthesis based on the use of selective protection of a B-ring by borate under mild basic conditions appeared difficult to reproduce. No traces of the desired compounds were detected during the analysis of the reaction mixture by HPLC-MS/MS. Moreover the use of benzyl carbonate, a protection which is not specific to the catechol moiety, led to a mixture of products since the difference of microscopic pK_a's between the different hydroxy functions was too small ($pK_{3'\text{-OH}} = 9.02$, $pK_{4'\text{-OH}} = 9.12$, $pK_{5\text{-OH}} = 9.43$, and $pK_{7\text{-OH}} = 9.58$ in water)[18] to obtain regiospecificity.[17c] So even if syntheses were proposed for these two compounds 5,7-dimethylcatechin and 3′,4′-dimethylcatechin, neither compound nor intermediate have been characterized. Moreover, none of these methods permits obtainment of trimethylated isomers of (+)-catechin and the four monomethylated derivatives of catechin, which are of capital importance for the comprehension of biological effects of flavan-3-ols on the human organism.

In this work we developed specific access to methylated flavan-3-ols starting from vegetal polyphenols available in pure

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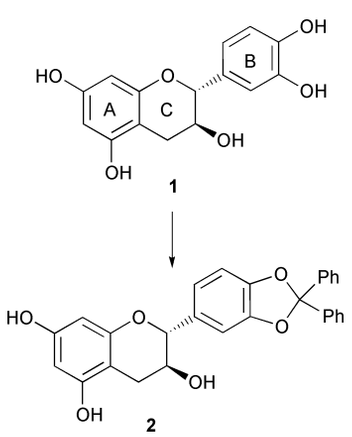
enantiomeric form. We applied this strategy to the syntheses of the four monomethylated isomers of (+)-catechin in positions 3′, 4′, 5 and 7 respectively, two dimethylated derivatives, the 5,7-dimethylcatechin and the 3′,4′-dimethylcatechin, and two trimethylated isomers of (+)-catechin in positions 3′, 5, 7 and 4′, 5, 7 respectively. The key step was the sequential protection of the catechol ring with dichlorodiphenylmethane and di-*tert*-butyldichlorosilane.

Results and discussion

We based our strategy for the selective protection of catechin on the differentiation between catechol and other phenols.[19] However the choice of the reagent is rather limited as catechin is known to undergo quite readily a base-catalyzed epimerization at C-2 to form *ent*-epicatechin through reversible opening of ring C *via* a B ring quinone methide intermediate which requires a free phenolic OH at the C4′ position.[20] This gave us another reason to modify the B ring to protect the reactive *o*-dihydroxyphenyl group. In the same way, it was shown by Sears *et al.*[20b] that catechin undergoes rearrangement to catechinic acid in hot alkaline solution. Thus it is imperative to exclude any protective groups requiring particularly drastic pH conditions during their introduction and removal to avoid epimerization and rearrangement. Even benzylation under mild conditions gave rather poor yields of only 20%.[21] We investigated various catechol-protecting groups: we recovered starting material upon exposure of catechin **1** to a mixture of P_2O_5 and anhydrous acetone at reflux. Treatment of catechin **1** with phosgene (pyridine, 5 °C) involved the irreversible destruction of the molecule. On the other hand, reaction of catechin with di-*tert*-butyldichlorosilane[22] and triethylamine in acetonitrile gave a reproducable 85% yield of the corresponding di-*tert*-butylsilylene derivative. Unfortunately, under basic conditions or during TLC separation on silica gel, the protection undergoes rapid hydrolysis to form hydroxysilyl mono ethers of the parent catechol, as already noticed by Corey and Hopkins for 1,2- and 1,4-diols.[23]

The protection of the *o*-dihydroxyphenyl group was then achieved with dichlorodiphenylmethane[24] which can be removed in the final step by a hydrogenolysis reaction that is usually clean and efficient (see Scheme 1). The reaction of



Scheme 1 *Reagents, conditions and yield*: Ph_2CCl_2 (1.1 eq.), Et_3N (5 eq.), CH_3CN, 0 °C to rt, 12 h (22%).

(+)-catechin **1** with 1.1 equivalents of dichlorodiphenylmethane and 5 equivalents of potassium carbonate in acetonitrile starting at 0 °C to room temperature (Table 1, entry 6) gave the target compound **2** with a yield of 15%. Variation of the quantity of dichlorodiphenylmethane or base led to comparable yields ranging from 10–15% (entries 7 and 8). A slight improvement of yield was gained using triethylamine as base, which afforded compound **2** in up to 22% (entries 1–3). Also, we noticed that the yield of the reaction did not change further with an increase in the temperature or reaction time (entries 4 and 5). However, the yield obtained here (22%) was comparable to other phenol protecting groups reported in the literature, *e.g.* benzyl protection as pointed out above.[21]

The protection of ring B with dichlorodiphenylmethane opened two methods of synthesis: the first one leading to the partial or total methylation of ring A (compounds **6**–**8**), the second one to the methylation of the same B ring (compound **14**) by the means of specific protection of ring A and deprotection of ring B.

Synthesis of methylated catechin derivatives on ring A

Under partial methylating conditions of compound **2** with dimethyl sulfate (1 equivalent, 1.1 equivalents of potassium carbonate at room temperature for 3 days), a mixture of two monomethyl ethers **3**,**4** with a 9 : 1 ratio (determined from ^{1}H NMR of the crude product) was obtained and could be separated by column chromatography using ethyl acetate–hexane (30 : 70) as eluent (see Scheme 2).

The position of the methyl groups in both compounds were unambiguously assigned from ^{1}H NMR spectra and further confirmed by one-dimensional (1D)-nuclear Overhauser effect (NOE) spectroscopy which was conducted using two experiments: the first one with irradiation of the resonance frequency of the methyl peak and the second one with irradiation off-resonance. NOESY and ROESY experiments have also been done to ascertain the results. Fig. 1 shows the spectra (region

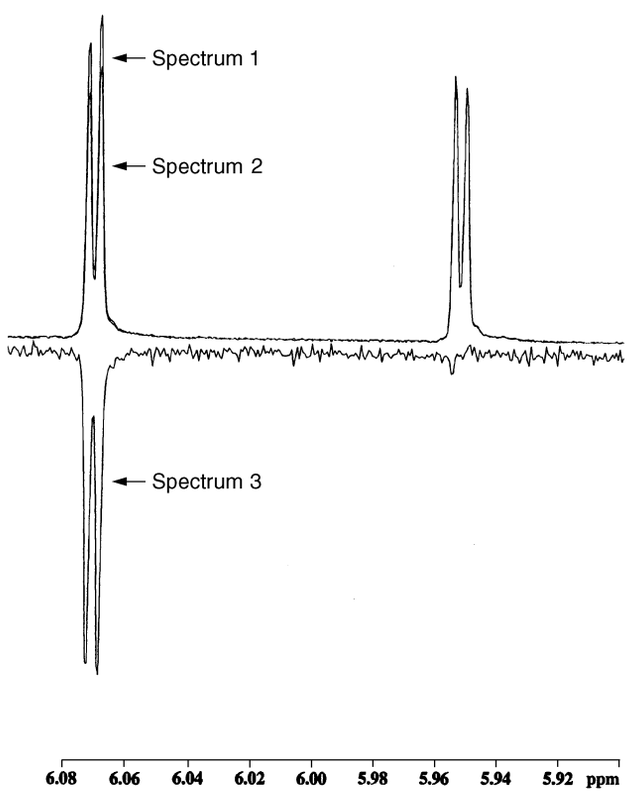


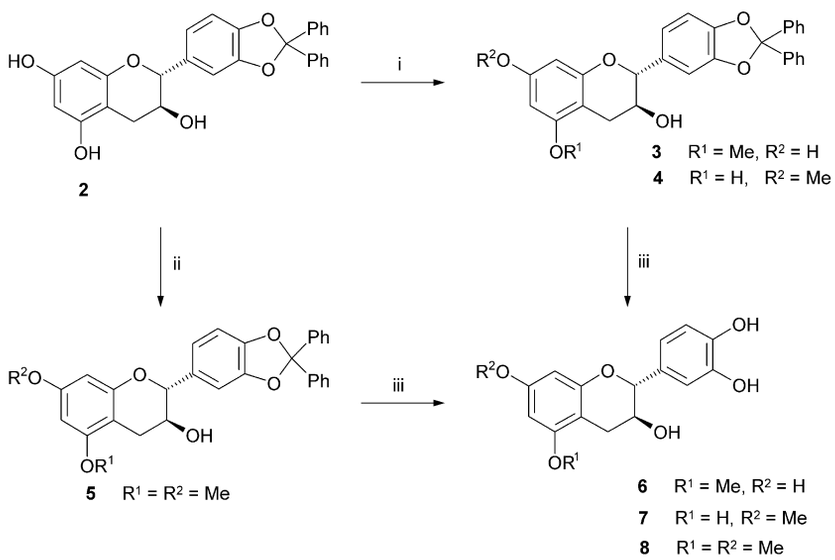
Fig. 1 Region of H_6 at δ = 6.07 ppm and H_8 at δ = 5.96 ppm obtained by one-dimensional nuclear Overhauser effect spectroscopy on the major compound **3**: spectrum 1 with sustained off-resonance irradiation, spectrum 2 with irradiation of the resonance frequency of the methyl peak, and curve 3 (displayed on a magnified scale) exhibits the difference of the first two spectra.

of H6 at δ = 6.07 ppm and H8 at δ = 5.96 ppm) obtained by one-dimensional nuclear Overhauser effect spectroscopy on the major compound **3**: spectrum 1 with sustained off-resonance irradiation, spectrum 2 with irradiation of the resonance frequency of the methyl peak (δ = 3.75), and curve 3 exhibits the

Table 1 Reaction of (+)-catechin **1** with dichlorodiphenylmethane (Ph_2CCl_2) [a]

Entry	Base (equiv.)	Ph_2CCl_2/equiv.	Time/h	T/°C [b]	Yield (%)
1	Et_3N (5)	1.1	12	20	22
2	Et_3N (2)	1.1	12	20	15
3	Et_3N (5)	3	12	20	18
4	Et_3N (5)	1.1	12	80	20
5	Et_3N (5)	1.1	24	20	22
6	K_2CO_3 (5)	1.1	12	20	15
7	K_2CO_3 (2)	1.1	12	20	10
8	K_2CO_3 (5)	3	12	20	15

[a] Reactions were performed using (+)-catechin **1** (1.72 mmol) and dichlorodiphenylmethane (Ph_2CCl_2) in 30 mL of acetonitrile. [b] All reactions were started at 0 °C.



Scheme 2 *Reagents, conditions and yields*: (i) Me_2SO_4 (1 eq.), K_2CO_3 (1.1 eq.), rt, 3 d (**3** 63%, **4** 7%); (ii) Me_2SO_4 (3 eq.), K_2CO_3 (3 eq.), reflux, 5 h (**5** 90%); (iii) H_2, atmospheric pressure, $Pd(OH)_2$, THF–Et_2O, rt, (**6** 92%, **7** 86%, **8** 90%).

difference of the two first spectra. So we can note that the intensity of the H6 signal was decreased by irradiation of the resonance frequency of the methyl peak while the intensity of the H8 peak was not affected, indicating that the methyl group is located at the 5 position. For the minor compound, both protons were affected by the irradiation of the methyl peak confirming that methylation occurred at the 7 position.

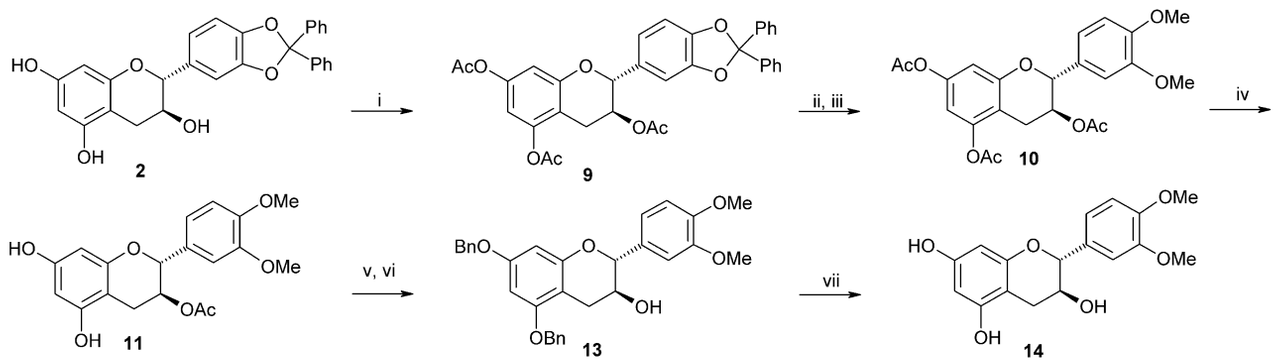
These experiments suggest that the major isomer is compound **3**. Moreover, an exhaustive methylation (3 equivalents of dimethyl sulfate, 3 equivalents of potassium carbonate, reflux for 5 h) of compound **2** led to the dimethylated compound **5** with a high yield (90%). Final deprotection of the catechol group by hydrogenolysis on palladium hydroxide in EtOH–THF (1 : 2) at room temperature delivered millimolar quantities of pure compounds **6**–**8** with very acceptable yields. In a preliminary communication [13] we reported antioxidant properties of compounds **6**, **7**, and **8** but no experimental details of their syntheses were given. Yet, to the best of our knowledge 5-methylcatechin has not been described previously. ^1H and ^{13}C spectra are in agreement with the previously described 7-methylcatechin.[25] The melting point of compound **8** is in agreement with those previously reported.[17a,b,26] The observed optical rotatory powers for compounds **7** and **8** (+ 6.0°, + 9° respectively) are quite different from the values previously described (+15° and −2° respectively) for natural products.[17a,b,25,26] However in the flavan-3-ol series the optical rotatory power is very sensitive to the substitution pattern; catechin and epicatechin which differ only by the configuration of the C3 carbon have optical rotatory powers of opposite signs (+16° and −51° respectively). So the optical rotatory power is very sensitive to traces of similar compounds, which are difficult to purify in the case of a complex mixture of natural products. Furthermore, catechin exists in the solid form either as the pure compound or as an hydrate with very different melting points (175–177 °C and 93–96 °C respectively). So, the optical rotation power and melting points reported here may be affected by the presence of impurities or water of crystallisation ascertained by some poor elemental microanalysis of the synthesized compounds after the final deprotection step.

Synthesis of dimethylated catechin derivative on ring B

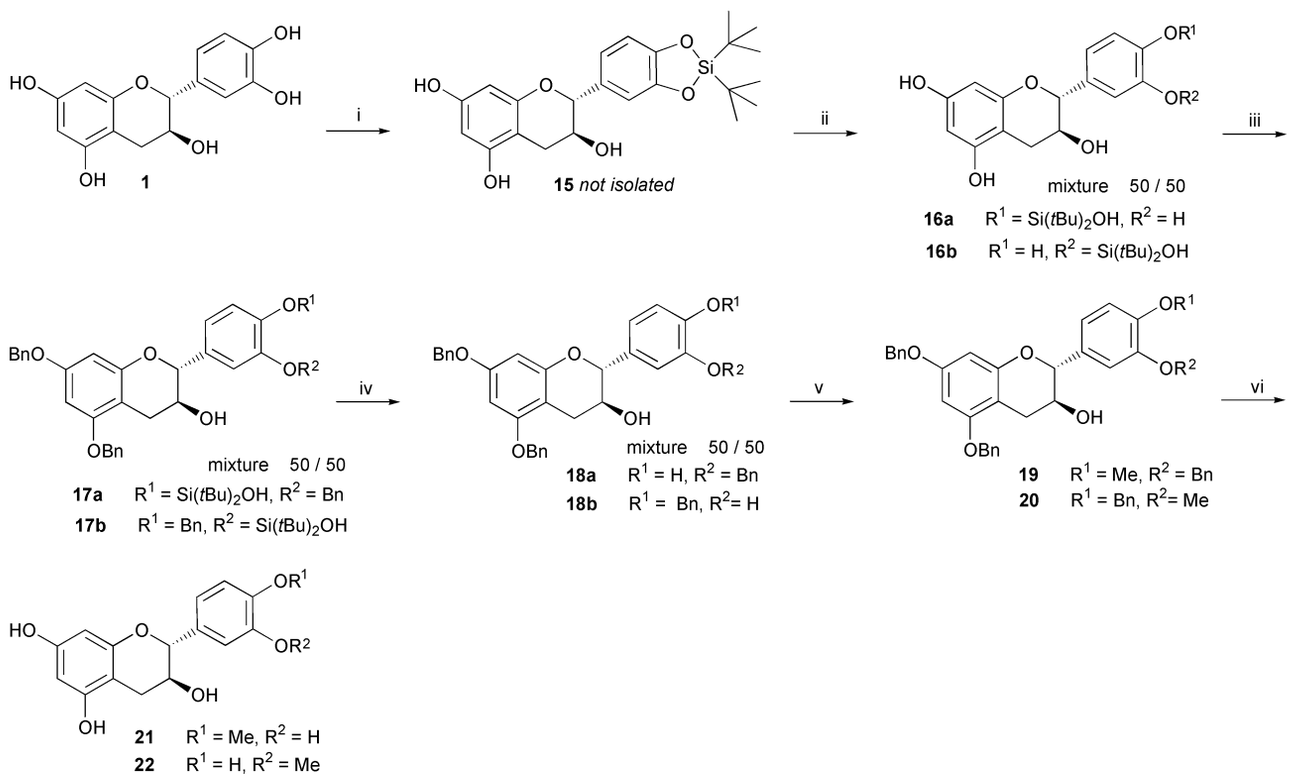
The crucial step in the synthesis of compounds methylated on the B ring consists of the selective and successive protection of rings B and A . Indeed, after protecting the B ring catechol moiety selectively, we had to find a protection of ring A whose deprotection conditions were different from those of the B ring protection, to allow selective deprotection of the B ring and so selective methylation on ring B.

Unlike A ring methylated derivatives **6**–**8**, the dimethylated compound and the two monomethylated compounds were synthesized by two different methods: while the 3′,4′-(diphenylmethylenedioxy)catechin **2** initiated the synthesis of 3′,4′-dimethylcatechin (Scheme 3) the two hydroxysilyl mono ethers **16a**,**b** led to the two isomeric monomethylcatechins (Scheme 4).

Scheme 3 shows the synthesis of 3′,4′-dimethylcatechin, which involved as a key step the formation of the 3,5,7-triacetate derivative of catechin **9** readily obtained after acetylation of 3′,4′-(diphenylmethylenedioxy)catechin **2** by action of acetic anhydride in the presence of pyridine in very good yield (90%). Hydrogenolysis of this product by treatment with palladium hydroxide in THF followed by the action of dimethyl sulfate and potassium carbonate in acetone allowed



Scheme 3 *Reagents, conditions and yields*: (i) Ac_2O, pyridine, rt, 10 h (90%); (ii) H_2, atmospheric pressure, $Pd(OH)_2$, THF–Et_2O, rt; (iii) Me_2SO_4 (3 eq.), K_2CO_3 (3 eq.), reflux, 5 h (88%); (iv) Na_2SO_3, MeOH, rt, 3 h (90%); (v) BnBr, K_2CO_3, DMF (85%); (vi) MeONa, MeOH, rt, 30 min (92%); (vii) H_2, Pd–C, THF, rt, 10 h (96%).



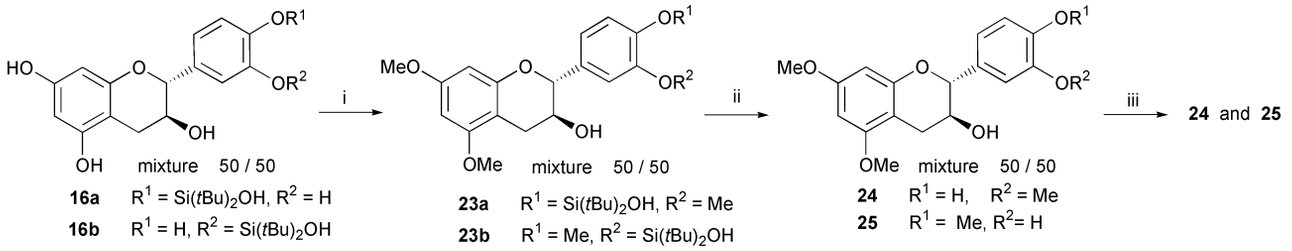
Scheme 4 *Reagents, conditions and yields*: (i) $Cl_2Si(t\text{-}Bu)_2$, CH_3CN, 0 °C to rt, 12 h; (ii) chromatography on silica gel, acetone–petroleum ether 60:40 (**16a** + **16b** 75%); (iii) BnBr, K_2CO_3, DMF (**17a** + **17b** 70%); (iv) Bu_4NF, THF, rt, 30 min (**18a** + **18b** 93%); (v) Me_2SO_4 (3 eq.), K_2CO_3 (3 eq.), reflux, 4 h (**19** 35%, **20** 30%); (vi) H_2, atmospheric pressure, Pd–C, THF, rt, 10 h (**21** 85%, **22** 87%).

the methylation of the free hydroxys in position 3′ and 4′ and delivered the triacetate compound **10** in a quantitative way.

The usual deprotection of phenyl acetates in slightly basic medium led to the formation of a complex mixture of tars in the case of compound **10**. In order to deprotect the phenol acetate we thought that a reagent both nucleophilic and reductive would give the desired deprotected products. Indeed, sodium borohydride gave a better result giving diol **11** in 60% yield. Gratifyingly, the rarely employed method using sodium sulfite[27] in methanol led to the removal of acetyl protecting groups on ring A and gave straightforward access to compound **11** with an excellent yield (90%). Unfortunately all attempts to deacetylate the C ring by this protocol were unrewarding. So, a reprotection step was a prerequisite to the deacetylation of the hydroxy group at the 3 position. Treatment of compound **11** with benzyl bromide followed by the action of sodium methoxide afforded the expected product **13** in 78% yield. Final removal of the benzyl protecting group delivered the 3′,4′-dimethylcatechin **14** with quite a good yield (53% over the last seven steps). The melting point of 3′,4′-dimethylcatechin **14** (247–248 °C) is in agreement with the only value previously described (246–247 °C).[17b]

Synthesis of monomethylated catechin derivatives of ring B

For the synthesis of the two monomethylated isomers of the (+)-catechin in position 3′ or 4′ **21** and **22**, we decided to adopt an alternative strategy which is depicted in Scheme 4, based on the use of di-*tert*-butyldichlorosilane instead of dichlorodiphenylmethane during the protection of the B ring hydroxy. Indeed during the screening for protection of the catechol ring of cycle B in catechin we observed the cleavage of the O–Si bond and the formation of two hydroxysilyl ethers, **16a**,**b**, of **1** (with a ratio 1 : 1) during purification by chromatography on silica gel. The instability of this protecting group opened new and expeditious syntheses of monomethylated derivatives of (+)-catechin in position 3′ or 4′. This protocol proceeded in four steps (see Scheme 4) from the two hydroxysilyl ethers. The first one consisted of a benzylation of the phenolic hydroxys of triols **16a**,**b** under standard conditions (BnBr, K_2CO_3 in DMF



Scheme 5 *Reagents, conditions and yields*: (i) CH_3I (4 eq.), K_2CO_3 (4 eq.), rt, 12 h (**23a** + **23b** 83%); (ii) Bu_4NF, THF, rt, 30 min; (iii) HPLC RP C_{18} (**24** 35% + **25** 40%).

at room temperature for 10 h). Compounds **17a**,**b** were subsequently subjected to a fluoride ion source to induce desilylation. The reaction proceeded smoothly at room temperature (using tetrabutylammonium fluoride as initiator) and gave the expected desilylated products **18a**,**b** in high yield (93%). These compounds were then easily methylated by treatment with dimethyl sulfate and potassium carbonate in acetone to afford a mixture of derivatives **19** and **20**. Subsequent separation of this mixture by flash column chromatography and successive recrystallizations from petroleum ether–AcOEt followed by final removal of the benzyl protecting groups completed the synthesis of the target compounds **21** and **22**. The position of the methyl groups in both compounds were assigned from LC-ESI-MS/MS experiments[16a] and confirmed by one-dimensional NOE experiments. Compound **21** with a methyl group at the 4′ position showed a strong enhancement of the intensity of the doublet at 6.91 ppm upon irradiation of the resonance frequency of the methyl group (3.83 ppm) whereas the 3′-methyl ether of (+)-catechin (compound **22**) gave a strong enhancement of the intensity of the doublet at 7.02 ppm by irradiation of the resonance frequency of the methyl peak (3.84 ppm). 3′-Methylcatechin has been reported many times in the literature[28] but has never been chemically characterized, so our physical data cannot be compared with literature values. The reported melting point for 4′-methylcatechin varies in a wide range (152 °C–228 °C)[16b,29] and the value for compound **22** (186–187 °C) lies between these two extremes. The observed optical rotatory power is in rough agreement with the value previously reported (+4.0° and +6.7° respectively).[29]

Synthesis of trimethylated isomers of (+)-catechin

The syntheses of the two trimethylated isomers of (+)-catechin in positions 3′, 5, 7 and 4′, 5, 7 respectively was ensured according to the same synthetic approach described for the two monomethylated compounds **21** and **22** (Scheme 5).

Starting from a mixture of compounds **16a**,**b** we envisioned the methylation of the three free phenolic functions. Reaction of compounds **16a**,**b** with dimethyl sulfate and potassium carbonate in acetone at reflux led to the partial removal of the hydroxysilyl function and furnished the tetramethylated isomer of catechin. However, treatment of compounds **16a**,**b** with methyl iodide (4 equivalents), potassium carbonate (4 equivalents) in DMF at room temperature during one night gave access to a 50 : 50 mixture of trimethylated catechin derivatives **23a**,**b**. Final deprotection with tetrabutylammonium fluoride, delivered compounds **24** and **25** in a 1 : 1 ratio. The separation of these compounds was accomplished by preparative HPLC (Scheme 5). The position of the methyl groups in both compounds **24** and **25** were determined from ^{1}H NMR spectra and confirmed by a ROESY experiment. To the best of our knowledge 3′,5,7-trimethylcatechin has not been described previously, 4′,5,7-trimethylcatechin has been isolated from *Cinnamomun cassia*. The melting point of compound **25** is higher than those previously reported (154–155 °C *versus* 125 °C) but exhibits a similar rotatory power.[30]

Conclusion

This work describes the first chemical syntheses of 3′- and 4′-methylcatechin, the major metabolites of catechin in humans and rats respectively. These metabolites are not available from natural sources but deserved biological studies as they are more abundant than the parent flavan-3-ol in plasma. Furthermore the two other monomethylated isomers of (+)-catechin in positions 5 and 7, two dimethylated derivatives: 5,7-dimethylcatechin and 3′,4′-dimethylcatechin and two trimethylated isomers of (+)-catechin in positions 3′, 5, 7 and 4′, 5, 7 respectively were also obtained. These trimethylated and dimethyl analogues bearing only one or two free phenolic groups are key model compounds for establishing reliable structure–activity relationships in biological tests and for the determination of thermodynamic constants.[18] The key step of this synthesis is the differentiation of the catechol B ring of catechin from the resorcinol-like A ring by the formation of permanent or transient dioxolanes. Until now acetylation has been limited mainly to increase the solubility of polyphenols as no efficient deprotection was available. We have shown that the use of a nucleophilic reducing reagent like sodium sulfite allows the quantitative deprotection of the acetylated phenolic hydroxys in catechin. The efficiency of the methodology and the biological need deserves further work to expand the scope of these reactions to other flavan-3-ols. The syntheses of more polar catechin metabolites such as sulfated and glucuronidated compounds are currently under investigation in our laboratory.

Experimental

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under Ar before use and NEt_3 was distilled from CaH_2. For flash chromatography, Merck silica-gel 60 (230–400 mesh ASTM) was used. The melting points were taken on a Reichert-Thermopan apparatus and are not corrected. NMR: Bruker AM 300 (300 and 75 MHz, for ^{1}H and ^{13}C NMR, respectively) and AM 600 (600 MHz for ^{1}H) for NOE, NOESY and ROESY experiments. For ^{1}H and ^{13}C NMR, $CDCl_3$, [D_6]acetone, [D_4]MeOH, and [D_6]DMSO were used as solvents, TMS as an internal standard. *J* values are given in Hz. MS experiments (Electronic Ionization, Chemical Ionization) were carried out on a JEOL mass Station 700 spectrometer. Microanalyses were performed by the CNRS "Service central d'analyse" (Vernaison, France); for each sample carbon, hydrogen and oxygen contents were determined.

(2*R*,3*S*)-2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)chroman-3,5,7-triol (2)

To a stirred solution of (+)-catechin **1** (500 mg, 1.72 mmol) in acetonitrile (30 mL) was added triethylamine (1.2 mL, 8.6 mmol) and dichlorodiphenylmethane (0.36 mL, 1.9 mmol) over 30 min at 0 °C and under Ar. When addition was complete, the reaction mixture was stirred at room temperature for 12 h. The resulting mixture was washed with water (30 mL). The aqueous layer was extracted twice with AcOEt (2 × 50 mL). The organic layer was then dried over $MgSO_4$. The dried extract was

concentrated *in vacuo* to afford a brown oil. The crude product was separated by flash column chromatography using AcOEt–hexane (75 : 25) as eluent and finally recrystallized from acetone, yielding protected catechin **2** (172 mg, 22%) as a pale yellow solid which is an hydrate according to the elemental analysis data, mp 121–122 °C (Found: C, 68.79; H, 5.68%; $C_{28}H_{22}O_6 \cdot 2H_2O$ requires C, 68.56; H, 5.34%; $[\alpha]_D^{20}$ +20.4° (*c* 0.9 in acetone); λ_{max} (CH_3CN)/nm 217 (ε/dm^3 mol^{-1} cm^{-1} 5600), 286 (1980); δ_H (300 MHz, CD_3OD) 2.48 (1 H, dd, *J* 16.0 and 8.8, 4a-H), 2.90 (1 H, dd, *J* 16.0 and 5.4, 4b-H), 3.93 (1 H, m, 3-H), 4.55 (1 H, d, *J* 8.0, 2-H), 5.84 (1 H, d, *J* 2.0, 8-H), 5.93 (1 H, d, *J* 2.0, 6-H), 6.88–6.91 (2 H, m, 6′-H and 5′-H), 6.97 (1 H, s, 2′-H), 7.33–7.41 (6 H, m, Ph), 7.52–7.60 (4 H, m, Ph); δ_C (75 MHz, CD_3OD) 30.7, 68.2, 82.7, 95.3, 96.2, 100.6, 108.5, 108.6, 122.5, 127.3, 129.3, 130.2, 134.7, 141.4, 147.8, 156.7, 157.1, 157.7; *m*/*z* (EI, 70 eV) 454 (M^+, 64%), 316 (100), 287 (28), 239 (52), 165 (27), 105 (18); *m*/*z* (CI, NH_3) 455 (100%), 216 (10); HR *m*/*z* (EI) 454.1412 ± 1 ppm $C_{28}H_{22}O_6$.

(2*R*,3*S*)-2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-5,7-dimethoxychroman-3-ol (5)

A solution of compound **2** (500 mg, 1 mmol), potassium carbonate (420 mg, 3 mmol) and dimethyl sulfate (0.3 mL, 3 mmol) in acetone (50 mL) was refluxed for 5 h. Acetone was removed under vacuum and the resulting mixture was washed with water (30 mL). The aqueous layer was extracted with AcOEt (3 × 50 mL). The solvent was removed under vacuum and the residue was purified by flash column chromatography with AcOEt–hexane (50 : 50) as eluent. Recrystallization from acetone afforded the dimethylcatechin derivative **5** (480 mg, 90%) as a colourless oil; $[\alpha]_D^{20}$ 3.0° (*c* 1.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.51 (1 H, dd, *J* 16.3 and 8.8, 4a-H), 2.93 (1 H, dd, *J* 16.3 and 5.6, 4b-H), 3.72 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.01–4.08 (1 H, m, 3-H), 4.15 (1 H, d, *J* 5.0, OH), 4.62 (1 H, d, *J* 8.1, 2-H), 6.03 (1 H, d, *J* 2.2, 8-H), 6.12 (1 H, d, *J* 2.2, 6-H), 6.93–6.98 (2 H, m, 6′-H and 5′-H), 7.04 (1 H, s, 2′-H), 7.37–7.44 (6 H, m, aromatic H), 7.56–7.63 (4 H, m, aromatic H); δ_C (75 MHz, $CDCl_3$) 27.5, 55.3, 55.5, 68.1, 81.8, 91.9, 92.9, 101.6, 107.3, 108.5, 121.4, 126.3, 128.3, 129.2, 131.6, 140.1, 147.6, 148.8, 155.2, 158.7, 159.7; *m*/*z* (EI, 70 eV) 482 (M^+, 78%) 316 (51), 239 (42), 167 (100), 105 (22); *m*/*z* (CI, NH_3) 483 (100%); HR *m*/*z* (EI) 482.1727 ± 0.6 ppm $C_{30}H_{26}O_6$.

General procedure for the synthesis of the two monomethyl catechin isomers 3, 4

A solution of compound **2** (300 mg, 0.6 mmol), potassium carbonate (105 mg, 0.66 mmol) and dimethyl sulfate (0.13 mL, 0.66 mmol) in acetone (30 mL) was stirred at room temperature under Ar for 3 days. Acetone was removed under vacuum and water (30 mL) was added to the reaction mixture. The aqueous layer was extracted with AcOEt (3 × 30 mL). The organic layer was dried ($MgSO_4$) and the residue obtained after removal of the solvent was purified by flash column chromatography using AcOEt–hexane (30 : 70) as eluent to afford the two monomethyl ethers **3** and **4** in a ratio 9 : 1 (70% yield) and a trace of dimethylated compound **5**.

(2*R*,3*S*)-2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-5-methoxychroman-3,7-diol (3). Yield 63%; mp 179–180 °C; $[\alpha]_D^{20}$ +4.7° (*c* 1.3, acetone); λ_{max} (CH_3CN)/nm 208 (ε/dm^3 mol^{-1} cm^{-1} 2250), 284 (250); δ_H (300 MHz, [D_6]acetone) 2.48 (1 H, dd, *J* 16.3 and 8.7, 4a-H), 2.90 (1 H, dd, *J* 16.3 and 5.6, 4b-H), 3.75 (3 H, s, OMe), 3.96–4.03 (1 H, m, 3-H), 4.08 (1 H, d, *J* 5.0, OH), 4.60 (1 H, d, *J* 8.1, 2-H), 5.96 (1 H, d, *J* 2.2, 8-H), 6.07 (1 H, d, *J* 2.2, 6-H), 6.92 (1 H, d, *J* 8.1, 6′-H), 6.95 (1 H, d, *J* 8.1, 5′-H), 7.04 (1 H, s, 2′-H), 7.40–7.46 (6 H, m, aromatic H), 7.59–7.63 (4 H, m, aromatic H); δ_C (75 MHz, [D_6]acetone) 29.3, 55.6, 68.0, 82.7, 92.5, 96.1, 101.7, 108.5, 108.7, 122.4, 126.8, 129.2, 130.2, 134.6, 141.5, 147.8, 151.3, 156.5, 158.3; *m*/*z* (EI, 70 eV) 468 (M^+, 35%), 316 (100), 287 (74), 239 (68), 153 (53), 105 (38), 77 (21); *m*/*z* (CI, NH_3) 469 (100%), 317 (27%); HR *m*/*z* (EI) 468.1570 ± 0.5 ppm $C_{29}H_{24}O_6$.

(2*R*,3*S*)-2-(2,2-Diphenylbenzo[1,3]dioxol-5-yl)-7-methoxychroman-3,5-diol (4). Yield 7%; mp 111–112 °C; $[\alpha]_D^{20}$ +17.0° (*c* 0.57, acetone); λ_{max} (CH_3CN)/nm 209 (ε/dm^3 mol^{-1} cm^{-1} 2250), 284 (350); δ_H (300 MHz, [D_6]acetone) 2.54 (1 H, dd, *J* 16.2 and 8.8, 4a-H), 2.96 (1 H, dd, *J* 16.2 and 5.6, 4b-H), 3.67 (3 H, s, OMe), 3.97–4.05 (2 H, m, 3-H and OH), 4.62 (1 H, d, *J* 8.1, 2-H), 5.95 (1 H, d, *J* 2.2, 8-H), 6.07 (1 H, d, *J* 2.2, 6-H), 6.88 (1 H, d, *J* 8.1, 6′-H), 6.90 (1 H, d, *J* 8.1, 5′-H), 6.98 (1 H, s, 2′-H), 7.34–7.39 (6 H, m, Ph), 7.52–7.56 (4 H, m, Ph); δ_C (75 MHz, [D_6]acetone) 29.0, 55.3, 68.1, 82.8, 93.4, 95.3, 101.8, 108.5, 108.7, 122.5, 126.9, 129.2, 130.0, 134.6, 141.4, 147.8, 148.6, 156.7, 157.1, 158.0; *m*/*z* (EI, 70 eV) 468 (M^+, 54%), 316 (100), 287 (26), 239 (51), 165 (35), 153 (33), 105 (27); *m*/*z* (CI, NH_3) 469 (100%); HR *m*/*z* (EI) 468.1572 ± 0.1 ppm $C_{29}H_{24}O_6$.

General procedure for the deprotection of ring B (access to products 6–8)

10% Palladium hydroxide on carbon (0.018 mmol) was added to a stirring solution of flavanol **3**, **4** or **5** (0.18 mmol) in EtOH–THF (1 : 2, 20 mL) under an atmosphere of hydrogen. The suspension was stirred overnight and then the solution was filtered through a plug of Celite eluting with EtOH (20 mL) and CH_2Cl_2 (20 mL). The filtrate was concentrated under vacuum and the resulting solid recrystallized from EtOH to give the flavanol **6**, **7** or **8**.

(2*R*,3*S*)-2-(3′,4′-Dihydroxyphenyl)-5-methoxychroman-3,7-diol (6). Yield 92%; mp 222–223 °C (Found: C, 63.23; H, 5.88%; $C_{16}H_{16}O_6$ requires C, 63.15; H, 5.30%; $C_{16}H_{16}O_6 \cdot H_2O$ requires C, 59.62; H, 5.63%; $[\alpha]_D^{20}$ −1.2° (*c* 0.85, acetone); λ_{max} (CH_3CN)/nm 210 (ε/dm^3 mol^{-1} cm^{-1} 3990), 282 (600); δ_H (300 MHz, [D_6]acetone) 2.49 (1 H, dd, *J* 16.2 and 8.0, 4a-H), 2.85 (1 H, dd, *J* 16.2 and 5.2, 4b-H), 3.75 (3 H, s, OMe), 3.95–3.99 (2 H, m, 3-H and OH), 4.56 (1 H, d, *J* 7.3, 2-H), 5.95 (1 H, d, *J* 2.2, 8-H), 6.04 (1 H, d, *J* 2.2, 6-H), 6.73–6.89 (3 H, m, 6′-H, 5′-H, 2′-H), 7.86 (1 H, s, OH), 7.90 (1 H, s, OH), 8.17 (1 H, s, OH); δ_C (75 MHz, [D_6]acetone) 28.6, 55.6, 68.1, 82.6, 92.4, 96.0, 101.4, 115.1, 115.6, 119.9, 132.0, 145.5, 145.6, 156.4, 157.9, 159.6; *m*/*z* (EI, 70 eV) 304 (M^+, 34%), 167 (18), 153 (100), 123 (33); *m*/*z* (CI, NH_3) 305 (100), 219 (5); HR *m*/*z* (EI) 304.0951 ± 1.3 ppm $C_{16}H_{16}O_6$.

(2*R*,3*S*)-2-(3',4'-Dihydroxyphenyl)-7-methoxychroman-3,5-diol (7).[25] Yield 86%; mp 205–206 °C; $[\alpha]_D^{20}$ +6.0° (*c* 0.48, acetone); λ_{max} (CH_3CN)/nm 208 (ε/dm^3 mol^{-1} cm^{-1} 3850), 284 (460); δ_H (300 MHz, [D_6]acetone) 2.50 (1 H, dd, *J* 16.2 and 8.1, 4a-H), 2.87 (1 H, dd, *J* 16.2 and 5.3, 4b-H), 3.77 (3 H, s, OMe), 3.92–3.96 (2 H, m, 3-H and OH), 4.59 (1 H, d, *J* 7.3, 2-H), 5.98 (1 H, d, *J* 2.2, 8-H), 6.06 (1 H, d, *J* 2.2, 6-H), 6.70–6.85 (3 H, m, 6′-H and 5′-H and 2′-H), 7.85 (1 H, s, OH), 7.90 (1 H, s, OH), 8.15 (1 H, s, OH); δ_C (75 MHz, [D_6]acetone) 28.5, 55.6, 68.0, 82.9, 92.7, 94.8, 101.6, 115.2, 115.7, 119.8, 131.9, 145.5, 145.7, 156.5, 157.8, 159.5.

(2*R*,3*S*)-4-(3-Hydroxy-5,7-dimethoxychroman-2-yl)benzene-1,2-diol (8).[26,17a,17c] Yield 90%; mp 219–220 °C (Found: C, 61.43; H, 5.70%; $C_{17}H_{18}O_6 \cdot H_2O$ requires C, 60.71; H, 5.99%); $[\alpha]_D^{20}$ +9.0° (*c* 0.69, acetone); λ_{max} (CH_3CN)/nm 208 (ε/dm^3 mol^{-1} cm^{-1} 4390), 228 (1440), 280 (500); δ_H (300 MHz, [D_6]acetone) 2.50 (1 H, dd, *J* 16.3 and 8.3, 4a-H), 2.86 (1 H, dd, *J* 16.3 and 5.4, 4b-H), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.97–4.02 (1 H, m, 3-H), 4.59 (1 H, d, *J* 7.6, 2-H), 6.03 (1 H, d, *J* 2.2, 8-H), 6.11 (1 H, d, *J* 2.2, 6-H), 6.75 (1 H, dd, *J* 8.1 and 2.2, 6′-H), 6.79 (1 H, d, *J* 8.1, 5′-H), 6.88 (1 H, d, *J* 2.2, 2′-H); δ_C (75 MHz,

[D_6]acetone) 28.5, 55.4, 55.7, 68.0, 82.7, 91.9, 93.9, 102.6, 115.1, 115.7, 119.9, 131.9, 145.5, 145.6, 156.5, 159.5, 160.6; *m/z* (EI, 70 eV) 318 (M^+, 42%), 167 (100); *m/z* (CI, NH_3) 319 (100); HR *m/z* (EI) 318.1100 ± 1.0 ppm $C_{17}H_{18}O_6$.

Acetic acid 3,5-diacetoxy-2-(2,2-diphenylbenzo[1,3]dioxol-5-yl)chroman-7-yl ester (9)

A solution of compound **2** (850 mg, 1.72 mmol), pyridine (0.7 mL, 8.6 mmol) and acetic anhydride (2.43 mL, 25.8 mmol) was stirred at room temperature for 10 h. The excess of acetic anhydride and pyridine was removed *in vacuo* and the residue was purified by flash column chromatography with AcOEt–hexane (60 : 40) as eluent to afford compound **9** (977 mg, 90%) as a white crystalline material, mp 78–79 °C (Found: C, 69.52; H, 4.73%; $C_{34}H_{28}O_9 \cdot H_2O$ requires C, 68.22; H, 5.05%; $C_{34}H_{28}O_9$ requires C, 70.34; H, 4.86%; $[\alpha]_D^{20}$ +35.0° (*c* 0.57, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.94 (3 H, s, OAc), 2.25 (3 H, s, OAc), 2.26 (3 H, s, OAc), 2.62 (1 H, dd, *J* 16.7 and 6.3, 4a-H), 2.85 (1 H, dd, *J* 16.7 and 5.1, 4b-H), 5.04 (1 H, d, *J* 6.3, 2-H), 5.25 (1 H, m, 3-H), 6.57 (1H, d, *J* 2.2, 8-H), 6.62 (1 H, d, *J* 2.2, 6-H), 6.78–6.86 (3 H, m, 6′-H and 5′-H and 2′-H), 7.35–7.38 (6 H, m, Ph), 7.54–7.58 (4 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.7, 21.0, 21.1, 23.9, 68.4, 78.4, 106.8, 107.6, 108.5, 108.6, 110.3, 120.1, 126.2, 126.3, 128.3, 129.1, 131.1, 140.2, 147.3, 147.5, 149.4, 149.8, 154.7, 168.4, 169.0, 170.2; *m/z* (EI, 70 eV) 580 (M^+, 18%), 520 (32), 461 (100), 316 (53), 239 (39), 105 (28); *m/z* (CI, NH_3) 597 (100%); HR *m/z* (EI) 580.1727 ± 1.1 ppm $C_{34}H_{28}O_9$.

(2*R*,3*S*)-5,7-Diacetoxy-2-(3′,4′-dimethoxyphenyl)chroman-3-yl acetate (10)

A suspension of compound **9** (300 mg, 0.52 mmol) in THF (30 mL) was vigorously stirred with palladium hydroxide (10%) under an atmosphere of hydrogen. The reaction mixture was stirred for 12 h, filtered on Celite, and CH_2Cl_2 (20 mL) was added. The organic layer was dried over $MgSO_4$. Concentration *in vacuo* left an oily product which was used without any more purification.

A solution of this product (200 mg, 0.48 mmol), potassium carbonate (200 mg, 1.44 mmol) and dimethyl sulfate (0.14 mL, 1.44 mmol) in acetone (30 mL) was refluxed for 5 h. After removal of the solvent, water (30 mL) and AcOEt (40 mL) were added to the reaction mixture. The organic layer was dried ($MgSO_4$) and the product obtained was purified by flash column chromatography with AcOEt–hexane (40 : 60) as eluent and recrystallized from methanol to give compound **10** (202 mg, 88%) as a colourless oil (Found: C, 59.66; H, 5.67%; $C_{23}H_{24}O_9 \cdot H_2O$ requires C, 59.74; H, 5.67%; $[\alpha]_D^{20}$ −23.0° (*c* 0.15, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.90 (3 H, s, OAc), 2.26 (6 H, s, 2 OAc), 2.65 (1 H, dd, *J* 16.6 and 6.7, 4a-H), 2.85 (1 H, dd, *J* 16.6 and 5.2, 4b-H), 3.83 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.07 (1 H, d, *J* 5.2, 2-H), 5.30 (1 H, m, 3-H), 6.55 (1 H, d, *J* 2.2, 8-H), 6.64 (1 H, d, *J* 2.2 6-H), 6.82–6.89 (3 H, m, 6′-H and 5′-H and 2′-H); δ_C (75 MHz, $CDCl_3$) 20.8, 21.0, 21.2, 24.3, 55.9, 56.1, 68.5, 78.2, 106.7, 107.8, 109.4, 109.5, 110.7, 119.4, 130.3, 147.4, 148.1, 154.8, 157.7, 159.0, 168.6, 169.0, 170.3.

(2*R*,3*S*)-3′,4′-Dimethoxyphenyl-5,7-dihydroxychroman-3-yl acetate (11)

To a solution of 500 mg (1.12 mmol) of compound **10** in 10 mL of methanol was added a solution of 500 mg (3.97 mmol) of sodium sulfite in 10 mL of water. After stirring the reaction mixture for 3 h under nitrogen, the methanol was flash evaporated (45 °C) and the remaining aqueous layer extracted with diethyl ether (3 × 40 mL). Drying ($MgSO_4$) and evaporation of the ether gave a product which was purified by flash column chromatography with AcOEt–hexane (40 : 60) as eluent to afford compound **11** (365 mg, 90%) as a white solid, mp 90–91 °C (Found: C, 60.29; H, 5.87%; $C_{19}H_{20}O_7 \cdot H_2O$ requires C, 60.31; H, 5.86%; $[\alpha]_D^{20}$ +1.5° (*c* 0.49, acetone); δ_H (300 MHz, $CDCl_3$) 1.91 (3 H, s, OAc), 2.63 (1 H, dd, *J* 16.2 and 7.3, 4a-H), 2.88 (1 H, dd, *J* 16.2 and 5.2, 4b-H), 3.79 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.94 (1 H, d, *J* 7.3, 2-H), 5.27–5.31 (1 H, m, 3-H), 5.92 (1 H, d, *J* 2.2, 8-H), 6.04 (1 H, d, *J* 2.2, 6-H), 6.77–6.96 (3 H, m, 6′-H and 5′-H and 2′-H); δ_C (75 MHz, $CDCl_3$) 21.0, 24.0, 55.9, 69.4, 79.2, 95.6, 95.9, 99.4, 109.7, 110.9, 119.4, 130.2, 148.8, 155.2, 155.3, 155.8, 170.8; *m/z* (EI, 70 eV) 360 (M^+, 13%), 342 (14), 314 (55), 300 (91), 299 (40), 180 (100), 151 (36); *m/z* (CI, NH_3) 361 (100%); HR *m/z* (CI, NH_3) [M + H^+] 361.1290 ± 0.8 ppm $C_{19}H_{21}O_7$.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3′,4′-dimethoxyphenyl)chroman-3-yl acetate (12)

A solution of benzyl bromide (0.15 mL, 1.2 mmol) was added dropwise under Ar to a cooled (0 °C) solution of compound **11** (145 mg, 0.4 mmol) and potassium carbonate (165 mg, 1.2 mmol) in DMF (10 mL). Stirring was maintained for 2 hours at 0 °C and then allowed to come to room temperature over 10 hours. The reaction mixture was diluted in 50 mL of AcOEt, washed with 30 mL of water and 30 mL of brine and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using AcOEt–hexane (35 : 65) as eluent to give product **12** (185 mg, 85%) as a colourless oil, $[\alpha]_D^{20}$ +27.8° (*c* 0.65, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.95 (3 H, s, OAc), 2.71 (1 H, dd, *J* 16.8 and 6.8, 4a-H), 2.96 (1 H, dd, *J* 16.8 and 5.5, 4b-H), 3.82 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.02–5.04 (5 H, m, 2 OBn and 2-H), 5.36–5.42 (1 H, m, 3-H), 6.16 (1 H, d, *J* 2.2, 8-H), 6.28 (1 H, d, *J* 2.2, 6-H), 6.78–6.93 (3 H, m, 6′-H and 5′-H and 2′-H), 7.30–7.45 (10 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.1, 24.2, 55.9, 69.0, 70.0, 70.1, 78.3, 93.8, 94.4, 101.4, 109.5, 111.0, 119.2, 127.3, 127.6, 127.9, 128.0, 128.5, 128.6, 130.2, 136.8, 148.9, 154.9, 157.7, 158.9, 170.2.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3′,4′-dimethoxyphenyl)chroman-3-ol (13)

A solution of MeONa (15 mL prepared from sodium (1 g) and methanol (40 mL)) was added dropwise to a solution of compound **12** (340 mg, 0.63 mmol) in 15 mL of CH_2Cl_2 at room temperature with stirring under Ar. The reaction mixture was stirred for an additional 30 min and after removal of the solvent, washed with water (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude product was finally purified by flash column chromatography with AcOEt–hexane (40 : 60) as eluent and recrystallized from hexane–CH_2Cl_2 to afford compound **13** (290 mg, 92%) as a pale yellow solid, mp 115–116 °C (Found: C, 72.80; H, 6.29%; $C_{31}H_{30}O_6 \cdot H_2O$ requires C, 72.08; H, 6.24%; $[\alpha]_D^{20}$ −5.0° (*c* 0.79, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.66 (1 H, dd, *J* 16.3 and 9.2, 4a-H), 3.18 (1 H, dd, *J* 16.3 and 5.3, 4b-H), 3.89 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.09 (1 H, m, 3-H), 4.67 (1 H, d, *J* 9.2, 2-H), 4.99 (2 H, s, CH_2-Bn), 5.03 (2 H, s, CH_2-Bn), 6.23 (1 H, d, *J* 2.2, 8-H), 6.27 (1 H, d, *J* 2.2, 6-H), 6.89–7.01 (3 H, m, 6′-H and 5′-H and 2′-H), 7.31–7.46 (10 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 27.9, 55.8, 55.9, 68.2, 69.9, 70.1, 93.8, 94.4, 102.4, 109.9, 111.2, 120.0, 127.1, 127.5, 127.9, 128.0, 128.5, 128.6, 130.2, 136.9, 148.9, 149.3, 155.4, 157.8, 158.8; *m/z* (EI, 70 eV) 498 (M^+, 18%), 292 (61), 263 (94), 149 (49), 91 (100), 77 (58); *m/z* (CI, NH_3) 499, 423; HR *m/z* (CI, NH_3) [M + H^+] 499.2116 ± 0.9 ppm $C_{31}H_{31}O_6$.

(2*R*,3*S*)-2-(3′,4′-Dimethoxyphenyl)chroman-3,5,7-triol (14)[16b,17b,17c,30]

A suspension of compound **13** (200 mg, 0.4 mmol) in THF (15 mL) was stirred with activated Pd–C (10%, 10 mg) under an atmosphere of hydrogen for 10 h, filtered on Celite and eluted

with EtOH (30 mL) and CH_2Cl_2 (30 mL). The filtrate was concentrated under vacuum and the resulting product **14** was recrystallized from $CHCl_3$–MeOH to give a white solid (122 mg, 96%); mp 247–248 °C (Found: C, 63.10; H, 6.22%; $C_{17}H_{18}O_6 \cdot H_2O$ requires C, 60.71; H, 5.99%; $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.70%; $[\alpha]_D^{20}$ +6.0° (*c* 0.33, acetone); λ_{max} (CH_3CN)/nm 211 (ε/dm^3 mol^{-1} cm^{-1} 3600), 282 (550); δ_H (300 MHz, [D_6]DMSO) 2.36 (1 H, dd, *J* 16.0 and 8.6, 4a-H), 2.72 (1 H, dd, *J* 16.0 and 5.4, 4b-H), 3.73 (6 H, s, 2 OMe), 3.87–3.96 (1 H, m, 3-H), 4.55 (1 H, d, *J* 8.6, 2-H), 4.95 (1 H, br s, OH), 5.69 (1 H, d, *J* 2.2, 8-H), 5.90 (1 H, d, *J* 2.2, 6-H), 6.86–6.94 (3 H, m, 6′-H and 5′-H and 2′-H), 8.97 (1 H, br s, OH), 9.23 (1 H, br s, OH); δ_C (75 MHz, [D_6]DMSO) 31.5, 59.0, 71.4, 85.4, 98.0, 98.9, 103.4, 114.5, 115.2, 123.7, 135.9, 152.8, 159.4, 160.2, 160.4; *m*/*z* (EI, 70 eV) 318 (M^+, 65 %), 180 (100), 165 (30), 151 (42); *m*/*z* (CI, NH_3) 319 (100 %); HR *m*/*z* (EI) 318.1104 ± 0.1 ppm $C_{17}H_{18}O_6$.

(2*R*,3*S*)-2-[4′-(Di-*tert*-butylhydroxysilyloxy)-3′-hydroxyphenyl]chroman-3,5,7-triol and (2*R*,3*S*)-2-[3′-(di-*tert*-butylhydroxysilyloxy)-4′-hydroxyphenyl]chroman-3,5,7-triol (16a,b) (50 : 50 mixture)

To a stirred solution of (+)-catechin **1** (1 g, 3.45 mmol) in acetonitrile (50 mL) was added triethylamine (2.4 mL, 17.2 mmol) and di-*tert*-butyldichlorosilane (1.46 mL, 6.9 mmol) at 0 °C and under Ar. Upon completion of the addition, the reaction mixture was stirred at room temperature for 12 h and the resulting mixture washed with water (40 mL). The aqueous layer was extracted with AcOEt (3 × 40 mL). Drying ($MgSO_4$) and evaporation of the solvent gave an oily product. The crude product was analyzed by ^{1}H NMR and illustrated an effective protection of the catechol group (compound **15**). After purification by flash column chromatography with acetone–petroleum ether (60 : 40) as eluent, we observed the formation of a 50 : 50 mixture of two compounds **16a**,**b** (1.16 g, 75%) as a colourless oil which corresponds to the product of cleavage of the O–Si bond; δ_H (300 MHz, [D_6]acetone) 1.09 (36 H, br s, 4-*t*Bu), 2.50 (1 H, dd, *J* 16.0 and 7.9, 4a-H), 2.52 (1 H, dd, *J* 16.0 and 8.0, 4b-H), 2.89 (1 H, dd, *J* 16.0 and 5.1, 4a-H), 2.91 (1 H, dd, *J* 16.0 and 5.0, 4b-H), 3.96–4.03 (2 H, m, 3-H), 4.52 (1 H, d, *J* 7.0, 2-H), 4.54 (1 H, d, *J* 7.2, 2-H), 5.87 (1 H, d, *J* 2.3, 8-H), 5.88 (1 H, d, *J* 2.2, 8-H), 6.02 (1 H, d, *J* 2.3, 6-H), 6.03 (1 H, d, *J* 2.2, 6-H), 6.75–7.17 (6 H, m, 6′-H and 5′-H and 2′-H); δ_C (75 MHz, [D_6]acetone) 21.3, 26.3, 27.6, 27.7, 68.2, 68.3, 82.4, 82.7, 95.4, 96.0, 100.5, 116.1, 119.8, 120.4, 120.7, 121.2, 133.4, 134.2, 144.2, 147.6, 156.8, 157.1, 157.7; *m*/*z* (EI, 70 eV) 448 (M^+, 3%), 430 (50), 292 (100), 263 (30), 236 (17), 193 (19), 139 (22); *m*/*z* (CI, NH_3) 431 (100%); HR *m*/*z* (EI) 448.1949 ± 7.0 ppm $C_{23}H_{32}O_7Si$.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-[3′-benzyloxy-4′-(di-*tert*-butylhydroxysilyloxy)phenyl]chroman-3-ol and (2*R*,3*S*)-5,7-bis(benzyloxy)-2-[4′-benzyloxy-3′-(di-*tert*-butylhydroxysilyloxy)phenyl]chroman-3-ol (17a,b) (50 : 50 mixture)

Compounds **17a**,**b** were prepared by benzylation of the parent phenol compounds **16a**,**b** (500 mg, 1.12 mmol) under standard conditions (BnBr 3.4 mmol, K_2CO_3 3.4 mmol, DMF, rt, 12 h). The crude product was purified by silica gel flash chromatography with AcOEt–hexane (40 : 60) as eluent affording a 50 : 50 mixture of products **17a**,**b** (561 mg, 70%) as a yellow solid, mp 58–63 °C (Found: C, 72.62; H, 7.11%, $C_{44}H_{50}O_7Si \cdot H_2O$ requires C, 71.71; H, 7.11%; δ_H (300 MHz; [D_6]-acetone) 1.10 (36 H, br s, 4-*t*Bu), 2.66 (1 H, dd, *J* 16.1 and 8.3, 4a-H), 2.67 (1 H, dd, *J* 16.2 and 8.1, 4a-H), 3.01 (1 H, dd, *J* 16.1 and 5.1, 4b-H), 3.04 (1 H, dd, *J* 16.2 and 5.1 Hz, 4b-H), 4.01–4.09 (2 H, m, 3-H), 4.67 (1 H, d, *J* 4.6, 2-H), 4.70 (1 H, d, *J* 4.6 Hz, 2-H), 5.05–5.11 (12 H, m, 6 CH_2-OBn), 6.20 (1 H, d, *J* 2.2, 8-H), 6.21 (1 H, d, *J* 2.2, 8-H), 6.36 (1 H, d, *J* 2.2, 6-H), 6.37 (1 H, d, *J* 2.2, 6-H), 6.86–7.18 (6 H, m, 2(6′-H, 5′-H, 2′-H)), 7.23–7.49 (30 H, m, Ph); δ_C (75 MHz, [D_6]acetone) 20.8, 27.3, 27.7, 68.2, 68.3, 69.9, 70.1, 71.4, 81.1, 81.7, 93.9, 94.4, 102.3, 102.4, 112.7, 114.1, 120.3, 120.4, 120.8, 121.7, 127.2, 127.5, 127.6, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7, 128.8, 131.1, 135.8, 136.0, 136.9, 137.0, 145.6, 145.7, 149.1, 155.3, 155.4, 157.8, 158.8; *m*/*z* (EI, 70 eV) 718 (M^+, 24%), 610 (36), 319 (100), 292 (64), 91 (100); *m*/*z* (CI, NH_3) 719 (M + H^+, 100%), 611 (20); HR *m*/*z* (EI) 718.3331 ± 0.8 ppm $C_{44}H_{50}O_7Si$.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3′-benzyloxy-4′-hydroxyphenyl)-chroman-3-ol and (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(4′-benzyloxy-3′-hydroxyphenyl)chroman-3-ol (18a,b) (50 : 50 mixture)

A solution of Bu_4NF (1 M in THF, 11.2 mL, 11.1 mmol) was added dropwise to a solution of the compounds **17a**,**b** (1.6 g, 2.3 mmol) in THF (30 mL) at room temperature with stirring under Ar. The yellow solution was stirred for an additional 30 min, washed with water (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was finally purified by flash column chromatography with AcOEt–hexane (40 : 60) as eluent to furnish a mixture of two products **18a**,**b** (1.16 g, 93%) as a pale yellow solid, mp 92–96 °C (Found: C, 74.95; H, 6.68%; $C_{36}H_{32}O_6 \cdot H_2O$ requires C, 74.72; H, 5.92%; δ_H (300 MHz, $CDCl_3$) 2.58–2.71 (2 H, m, 2 4a-H), 3.07–3.22 (2 H, m, 2 4b-H), 4.01–4.09 (2 H, m, 2 3-H), 4.64 (1 H, d, *J* 5.7, 2-H), 4.67 (1 H, d, *J* 6.0, 2-H), 4.98–5.13 (12 H, m, 6 CH_2-Bn), 6.21–6.32 (4 H, m, 2 8-H and 2 6-H), 6.91–7.09 (6 H, m, 2 (6′H, 5′-H, 2′-H)), 7.29–7.51 (30 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.3, 68.1, 68.3, 69.9, 70.1, 71.2, 81.5, 81.8, 93.8, 94.4, 102.2, 102.4, 111.0, 112.2, 113.5, 114.9, 119.2, 121.0, 127.1, 127.5, 127.6, 127.8, 128.0, 128.1, 128.5, 128.6, 128.8, 129.6, 135.9, 136.1, 136.9, 146.1, 146.2, 146.3, 155.3, 157.8, 158.8; *m*/*z* (EI, 70 eV) 560 (M^+, 14%), 409 (7), 332 (7), 319 (37), 181 (12), 91 (100); *m*/*z* (CI, NH_3) 561 (100%); HR *m*/*z* (EI) 560.2198 ± 0.1 ppm $C_{36}H_{32}O_6$.

General procedure for the preparation of compounds 19 and 20

Compounds **19**, **20** were prepared by methylation of the parent phenolic compounds **18a**,**b** (1 eq.) under standard conditions [dimethyl sulfate (5 eq.), potassium carbonate (5 eq.), acetone, reflux 4 h]. The separation of the two isomeric compounds **19** and **20** was effected by flash column chromatography with AcOEt–hexane (30 : 70) and successive recrystallizations from petroleum ether–AcOEt.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3′-benzyloxy-4′-methoxyphenyl)chroman-3-ol (19). Yield 30%; mp 131–132 °C (Found: C, 76.11; H, 6.01%; $C_{37}H_{34}O_6 \cdot H_2O$ requires C, 74.98; H, 6.12%; $C_{37}H_{34}O_6$ requires C, 77.33; H, 5.96%; $[\alpha]_D^{20}$ +3.0° (*c* 0.21, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.66 (1 H, dd, *J* 16.3 and 8.0, 4a-H), 3.17 (1 H, dd, *J* 16.3 and 5.6, 4b-H), 3.90 (3H, s, OMe), 4.02–4.10 (1 H, m, 3-H), 4.64 (1 H, d, *J* 8.4, 2-H), 4.98 (2 H, s, 2 CH_2-Bn), 5.03 (2 H, s, 2 CH_2-Bn), 5.18 (2 H, s, 2 CH_2-Bn), 6.22 (1 H, d, *J* 1.9, 8-H), 6.27 (1 H, d, *J* 1.9, 6-H), 6.88–7.02 (3 H, m, 6′-H and 5′-H and 2′-H), 7.29–7.48 (15 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 27.8, 56.0, 68.2, 69.9, 70.1, 71.0, 81.8, 93.8, 94.3, 102.4, 110.5, 113.9, 119.9, 127.1, 127.5, 127.9, 128.5, 128.6, 130.6, 136.9, 148.5, 150.0, 155.3, 157.7, 158.8; *m*/*z* (EI, 70 eV) 574 (54), 319 (100), 256 (62), 91 (75); *m*/*z* (CI, NH_3) 575 (M + H^+, 100%); HR *m*/*z* (EI) 574.2354 ± 0.3 ppm $C_{37}H_{34}O_6$.

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(4′-benzyloxy-3′-methoxyphenyl)chroman-3-ol (20). Yield 35%; mp 168–169 °C (Found: C, 76.55; H, 6.31%; $C_{37}H_{34}O_6 \cdot H_2O$ requires C, 74.98; H, 6.12%; $C_{37}H_{34}O_6$ requires C, 77.33; H, 5.96%; $[\alpha]_D^{20}$ +3.5° (*c* 0.88, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.64 (1 H, dd, *J* 16.3 and 8.9, 4a-H), 3.10 (1 H, dd, *J* 16.3 and 5.6, 4b-H), 3.89 (3H, s,

OMe), 3.95–4.02 (1 H, m, 3-H), 4.63 (1 H, d, *J* 8.2, 2-H), 4.99 (2 H, s, CH_2-Bn), 5.02 (2 H, s, CH_2-Bn), 5.15 (2 H, s, CH_2-Bn), 6.21 (1 H, d, *J* 2.2, 8-H), 6.27 (1 H, d, *J* 2.2, 6-H), 6.91 (1 H, d, *J* 7.9, 5′-H), 6.95 (1 H, dd, *J* 7.9 and 1.8, 6′-H), 7.02 (1 H, d, *J* 1.8, 2′-H), 7.27–7.43 (15 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 27.6, 56.1, 68.2, 69.9, 70.1, 71.0, 81.6, 93.8, 94.3, 102.3, 111.8, 112.8, 120.5, 127.1, 127.5, 127.9, 128.5, 128.6, 130.0, 136.8, 148.9, 150.1, 155.3, 157.8, 158.8; *m*/*z* (EI, 70 eV) 574 (M^+, 60%), 319 (100), 165 (43), 91 (95); *m*/*z* (CI, NH_3) 575 (100%), 485 (26), 274 (47); HR *m*/*z* (EI) 574.2347 ± 1.4 ppm $C_{37}H_{34}O_6$.

Synthesis of 4′-methylcatechin 21 and 3′-methylcatechin 22

The final deprotection of compounds **19** and **20** was carried out as described previously for 3′,4′-dimethylcatechin **14**.

(2*R*,3*S*)-2-(4′-Hydroxy-3′-methoxyphenyl)chroman-3,5,7-triol (21).[14a,16b,29c,30] Yield 85%; mp 186–187 °C; $[\alpha]_D^{20}$ +4.0° (*c* 0.28, acetone); δ_H (300 MHz, [D_6]acetone) 2.52 (1 H, dd, *J* 16.0 and 8.8, 4a-H), 2.97 (1 H, dd, *J* 16.0 and 5.5, 4b-H), 3.84 (3H, s, OMe), 3.94–4.05 (1 H, m, 3-H), 4.56 (1 H, d, *J* 8.1, 2-H), 5.87 (1 H, d, *J* 2.1, 8-H), 6.03 (1 H, d, *J* 2.1, 6-H), 6.80 (1 H, d, *J* 8.1, 6′-H), 6.88 (1 H, dd, *J* 8.1 and 1.7, 5′-H), 7.02 (1 H, d, *J* 1.7, 2′-H); δ_C (75 MHz, [D_6]acetone) 27.9, 56.1, 68.0, 82.9, 95.4, 96.0, 100.7, 111.7, 115.3, 121.4, 131.7, 147.2, 148.0, 156.9, 157.1, 157.7; *m*/*z* (EI, 70 eV) 304 (59), 166 (100), 139 (76), 128 (72), 77 (73); *m*/*z* (CI, NH_3) 305 (100); HR *m*/*z* (EI) 304.0948 ± 0.4 ppm $C_{16}H_{16}O_6$.

(2*R*,3*S*)-2-(3′-Hydroxy-4′-methoxyphenyl)chroman-3,5,7-triol (22).[15b,28,30a,30b] Yield 87%; mp 152–153 °C (Found: C, 59.25; H, 5.82%; $C_{16}H_{16}O_6 \cdot H_2O$ requires C, 59.62; H, 5.63%; $[\alpha]_D^{20}$ +20.6° (*c* 0.65, acetone); δ_H (300 MHz, [D_6]acetone) 2.52 (1 H, dd, *J* 16.0 and 8.2, 4a-H), 2.91 (1 H, dd, *J* 16.0 and 5.4, 4b-H), 3.83 (3H, s, OMe), 3.97–4.03 (1 H, m, 3-H), 4.59 (1 H, d, *J* 7.5, 2-H), 5.88 (1 H, d, *J* 2.0, 8-H), 6.02 (1 H, d, *J* 2.0, 6-H), 6.84 (1 H, dd, *J* 8.3 and 1.8, 5′-H), 6.91 (1 H, d, *J* 8.3, 6′-H), 6. 92 (1 H, d, *J* 1.8, 2′-H); δ_C (75 MHz, [D_6]acetone) 29.0, 56.2, 68.2, 82.5, 95.4, 96.0, 100.5, 111.9, 114.9, 119.6, 133.4, 147.1, 148.0, 156.8, 157.1, 157.7; *m*/*z* (EI, 70 eV) 304 (M^+, 100%), 166 (99), 139 (95); *m*/*z* (CI, NH_3) 305 (100%); HR *m*/*z* (EI) 304.0951 ± 1.3 ppm $C_{16}H_{16}O_6$.

Synthesis of the compounds 23a,b

To a stirred solution of compounds **16a**,**b** (0.5 g, 1.12 mmol) in acetone (30 mL) was added potassium carbonate (0.16 g, 4.48 mmol) and methyl iodide (0.28 mL, 4.48 mmol). The reaction was stirred at room temperature for 12 h. Acetone was removed under vacuum and the resulting mixture was washed with water (20 mL). The aqueous layer was extracted with AcOEt (3 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished on oily product which was purified by flash column chromatography using AcOEt–hexane (40 : 60) as eluent to give a 50 : 50 mixture of products **23a**,**b**.

(2*R*,3*S*)-5,7-Dimethoxy-2-[3′-methoxy-4′-(di-*tert*-butylhydroxysilyloxy)phenyl]chroman-3-ol and 5,7-dimethoxy-2-[4′-methoxy-3′-(di-*tert*-butylhydroxysilyloxy)phenyl]chroman-3-ol (23a,b) (50 : 50 mixture). Yield 83%; oil; δ_H (300 MHz, $CDCl_3$) 1.13 (18 H, br s, *t*Bu), 2.54 (2 H, dd, *J* 16.3 and 8.2, 2 4a-H), 2.96 (1 H, d, *J* 16.3 and 5.5, 2 4b-H), 3.04 (1 H, d, *J* 16.3 and 5.4, OH), 3.74 (6 H, s, 2 OMe), 3.77 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.02–4.09 (2 H, m, 2 3-H), 4.66 (2 H, br d, 2 2-H), 6.09 (2 H, br d, 2 8-H), 6.12 (2 H, br d, 2 6-H), 6.85–7.08 (6 H, m, 2(6′-H and 5′-H and 2′-H)); δ_C (75 MHz, $CDCl_3$) 20.7, 27.3, 27.8, 55.4, 55.5, 55.9, 56.0, 68.3, 68.4, 81.2, 81.6, 93.8, 94.1, 102.1, 102.5, 121.2, 121.9, 131.9, 135.6, 136.4, 137.0, 145.5, 145.6, 149.3, 155.3, 155.4, 157.9, 159.0.

Synthesis of trimethylated catechin derivatives 24 and 25

The final deprotection of compounds **23a**,**b** was carried out as described previously for compounds **18a**,**b**. After purification by flash column chromatography with AcOEt–hexane (50 : 50) as eluent, a mixture of compounds **24** and **25** was separated by preparative HPLC. HPLC separations of the two trimethylated analogues were achieved on a 250 × 4.6 mm id column packed with 5 μm Hypersil ODS C18 stationary phase. The mobile phase consisted of acetonitrile–methanol 38 : 62, and with 0.2% formic acid. The column eluent was directed to a UV detector set at 280 nm.

(2*R*,3*S*)-5,7-Dimethoxy-2-(4′-hydroxy-3′-methoxyphenyl)-chroman-3-ol (24). Yield 35%; mp 157–158 °C; $[\alpha]_D^{20}$ −12.5° (*c* 0.15, MeOH); δ_H (300 MHz, $CDCl_3$) 2.58 (1 H, dd, *J* 16.2 and 9.0, 4a-H), 3.07 (1 H, dd, *J* 16.2 and 5.8, 4b-H), 3.74 (3H, s, OMe), 3.80 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.01–4.08 (1 H, m, 3-H), 4.63 (1 H, d, *J* 8.4, 2-H), 6.10 (1 H, d, *J* 2.2, 8-H), 6.13 (1 H, d, *J* 2.2, 6-H), 6.93–6.97 (3 H, br d, 6′-H and 5′-H and 2′-H); δ_C (75 MHz, $CDCl_3$) 27.7, 55.4, 55.5, 55.9, 68.3, 81.9, 91.9, 93.0, 101.7, 109.4, 114.6, 120.6, 129.6, 146.1, 146.9, 155.3, 158.7, 159.7.

(2*R*,3*S*)-5,7-Dimethoxy-2-(3′-hydroxy-4′-methoxyphenyl)-chroman-3-ol (25).[30a] Yield 40%; mp 154–155 °C; $[\alpha]_D^{20}$ −8.0° (*c* 1.00, acetone); δ_H (300 MHz, $CDCl_3$) 2.58 (1 H, dd, *J* 16.3 and 8.8, 4a-H), 3.02 (1 H, dd, *J* 16.3 and 5.5, 4b-H), 3.74 (3H, s, OMe), 3.79 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.02–4.12 (1 H, m, 3-H), 4.66 (1 H, d, *J* 8.1, 2-H), 6.09 (1 H, d, *J* 2.3, 8-H), 6.12 (1 H, d, *J* 2.3, 6-H), 6.87 (1 H, d, *J* 8.2, 5′-H), 6.93 (1 H, dd, *J* 8.2 and 1.9, 6′-H), 7.02 (1 H, d, *J* 1.9, 2′-H); δ_C (75 MHz, $CDCl_3$) 27.3, 55.3, 55.5, 56.0, 68.1, 81.5, 91.9, 93.0, 101.5, 110.7, 113.1, 119.2, 131.0, 146.0, 146.9, 155.2, 158.7, 159.7.

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