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Influence of an 8-trifluoroacetyl group on flavanol couplings

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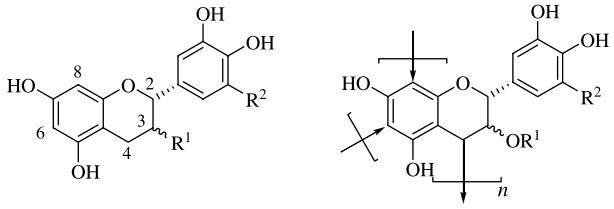
Abstract—The effect of an electron attracting substituent in the Lewis acid catalyzed oligomerization of flavanols was investigated. The results showed that the presence of a $COCF_3$, at the 8 position of a (+)-catechin unit strongly influenced the attack of the 6 free nucleophile flavanol position by the electrophile generated from a 4-*O*-alkyloxy protected catechin unit. This was observed either with $TiCl_4$ or TMSOTf as Lewis acids in which the carbon–carbon bond formation was inhibited and the corresponding dimer was detected in small amount. On the contrary, the formation of a carbon–oxygen bond was observed and the corresponding C-4→*O*→C-3 ether linked procyanidin dimer was isolated in a good yield. In order to avoid the participation of the C-3 hydroxyl group in the dimerization reaction, the two flavanol units were forced into C-4→C-8 coupling by use of an internal link. The structural elucidation of the isolated compounds was achieved through MS and NMR spectroscopy.

1. Introduction

Proanthocyanidins (condensed tannins) are a class of bioactive polyphenolic natural compounds found in a variety of plant foods and beverages. They have been attributed numerous therapeutic properties and many clinical researches suggest that their pronounced biological activities might prevent age-related chronic diseases, cancers and heart diseases.[1–3] These beneficial health effects have led to several investigations on their chemical structures and have initiated a number of synthetic efforts to access condensed tannins.[4–12] Proanthocyanidins are generally mixtures of oligomers and polymers of flavan-3-ol units, linked either through carbon–carbon and/or carbon–oxygen bonds. The most encountered flavan-3-ols involved in proanthocyanidin formation are derived from catechin **1a**, epicatechin **1b**, gallocatechin **1c**, or epigallocatechin **1d** (Fig. 1). The synthesis of proanthocyanidins **2** is generally achieved by coupling the C-4 of an electrophilic flavanyl unit to a C-6/C-8 of a nucleophilic flavanyl unit. The nucleophilicity of the aromatic A ring may play a crucial role in these coupling reactions during which a new bond is established between the C-4 position of the electrophile and the C-6/C-8 of the nucleophile unit.



1a: R^1 = α-OH, R^2=H catechin
1b: R^1 = β-OH, R^2=H epicatechin
1c: R^1 = α-OH, R^2=OH gallocatechin
1d: R^1 = β-OH, R^2=OH epigallocatechin

2: *n*=2 to >100
R^1=H, G alloyl
R^2=H, OH

Figure 1. Structures of flavan-3-ols monomers (**1a**–**1d**) and oligo/polymers (**2**).

The stability of proanthocyanidins is primarily dependent on that of this newly established linkage, which is sensitive to acidic and alkalinic conditions and might a priori also be influenced by the type of flavanol unit. Additionally, the reactivity of the electrophilic/nucleophilic species involved in the coupling reaction could also be influenced by the flavanol types. While the synthesis of proanthocyanidins from natural flavanols is well documented,[4–12] little is known about the effect of an A ring substitution on the reactivity of a flavanol unit involved either as nucleophilic or electrophilic species during the coupling reaction and its impact on the proanthocyanidin synthesis course.[13] In an ongoing program directed to the synthesis of modified proanthocyanidins, we described the preparation of modified catechin derivatives involving introduction of substituents either at C-6 and/or C-8 positions.[14,15] In this paper, we report the results dealing with

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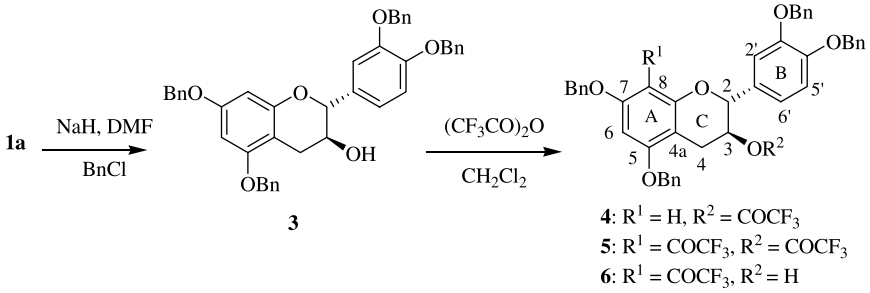


Scheme 1. Formation of tetrabenzylated trifluroacylated catechin derivatives **4**, **5**, **6**.

the effect of an electron deficient substituent linked to the C-8 position of a flavanol subunit on the Lewis acid catalyzed dimerisation of flavanols and offer new information on the reactivity of modified flavanols during such coupling reactions.

2. Results and discussion

2.1. Synthesis of modified flavanols

In the course of a program dealing with the synthesis and the reactivity of modified condensed tannins, we started an investigation on the synthesis of new procyanidin derivatives with modified monomeric subunits derived from catechin. Our objectives were to explore the impact of the A ring substitution on the course of Lewis acid catalyzed classic procyanidin formation reaction. For this study, the 8-trifluoroacetyltetrabenzyloxycatechin **6** was used as the electrophile acceptor in coupling reactions with a C-4 activated catechin derivative. Compound **6** was prepared by action of trifluoacetic anhydride on tetrabenzylated catechin **3** according to Scheme 1. During this reaction, the trifluoroacylation occurred first at the 3-OH giving the ester **4**. Compound **5** was then formed following a Friedel–Craft's reaction on the 8 nucleophile position. Hydrolysis of compound **5** gave the target product **6** with a yield of 64%. The structures of the three trifluoroacylated derivatives **4**, **5** and **6** were determined through UV, MS and NMR spectroscopy. Structure elucidation of compound **6**, which was used in the synthesis described below, was initiated by UV spectroscopy, which showed, in addition to the usual 280 nm flavan-3-ols maximum, another maximum located around 300 nm more probably due to the presence of the $COCF_3$ group. Its ESMS spectrum recorded in the positive ion mode showed signals located at *m/z*: 747, 764 and 769 amu corresponding to $[M+H]^+$, $[M+NH_4]^+$ and $[M+Na]^+$ ions, respectively, and indicating a molecular weight of 746 amu in agreement with the structure of compound **6**. The usual flavan-3-ols characteristic RDA fragmentation was also observed at *m/z*: 415 amu, $[M+H-332]^+$ ion and corresponding to the protonated A moiety (Fig. 2).

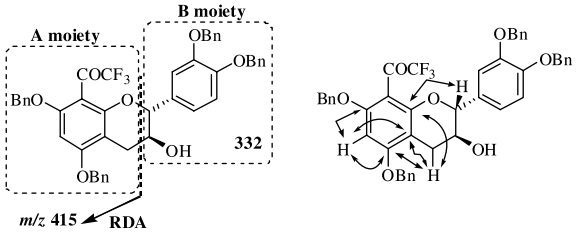


Figure 2. Main fragmentations and ^1H–^{13}C long range characteristic correlations observed for compound **6**.

The position of the $COCF_3$ group on the aromatic A ring was elucidated by 2D NMR HMBC analysis. The usual pyran ring protons H-4 (2.67 and 3.08 ppm), H3 (3.95 ppm) and H-2 (4.78 ppm) were easily assigned by ^1H NMR analysis. The three B ring protons were observed between 6.89 and 7.01 ppm. For the aromatic A ring, only one proton signal appearing as a singlet at 6.28 ppm was present indicating a monosubstitution. The presence of the $COCF_3$ group was confirmed through ^{13}C NMR analysis showing a quartet at 184.31 ppm and corresponding to the carbonyl group. The protonated carbon chemical shifts were assigned through NMR DEPT analysis.

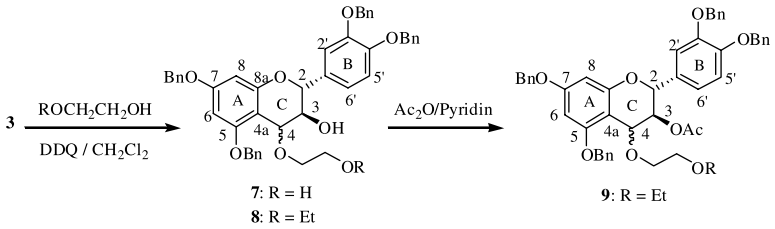
The definitive structure elucidation of compound **6** was achieved by HMBC experiment, which allowed assignment of all hydrogen and carbon atoms. In addition to their correlations with C-2 (81.94 ppm) and C-3 (67.63 ppm), H-4 protons (2.67 and 3.08 ppm) correlated with 3 carbons located at 103.19, 154.18 and 157.77 ppm. Carbons C-4a, C-8a and C-5 are in a favorable position to give such correlations. The signal observed at 103.19 ppm was attributed to C-4a due to its chemical shift position compared to C-8a and C-5, which are linked to an oxygen atom. The carbon signal located at 154.18 ppm also gave a correlation with H-2, which pointed to the C-8a carbon and thus the remaining signal observed at 157.77 ppm was attributed to C-5. The C-8a signal thus attributed did not show any correlation with the residual A ring aromatic protons, which is thus H-6. This was confirmed by the presence of a correlation between C-5 and the residual aromatic proton (Fig. 2).

2.2. Synthesis of activated catechin derivatives

Oxidation at the benzylic C-4 position of flavanols is a fundamental step in proanthocyanidin synthesis. Over the years, three main reagents have been used in the literature for this purpose, namely $K_2S_2O_8$, lead(IV) acetate and DDQ, which is now the most widely used.[16–22] In this study, DDQ was used as oxidant of tetrabenzylated catechin **3** in presence of ethylene glycol or 2-ethoxyethanol giving access to the corresponding 4-*O*-alkylated catechin **7**, **8** with yields up to 70% (Scheme 2).

2.3. $TiCl_4$-catalyzed flavanol coupling reaction

Lewis acids have been employed in literature to synthesize proanthocyanidins. Thus, $TiCl_4$, $AgBF_4$, $SnCl_4$, TMSOTf have been used to synthesize dimeric and oligomeric procyanidins of (+)-catechin and (−)-epicatechin

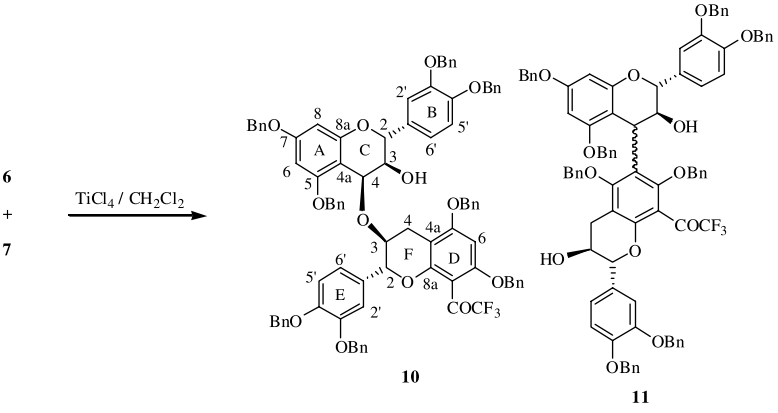


Scheme 2. Synthesis of the 4-activated catechin derivatives **7**, **8**, **9**.

units.[8,9,13,23–26] In these reactions, the role of Lewis acids is to promote the formation of the benzylic carbocation at C-4 of a flavanol subunit starting from a C-4 hetero substituted flavanol, which thereafter undergoes a Friedel–Craft-like addition on a second flavanol subunit. For this preliminary study, the Lewis acid $TiCl_4$ was first used as a carbocation promoting agent from the 4-(2-hydroxyethyloxy) flavan-3-ol **7**. Coupling reaction between compound **6** and **7** in a 6/1 molar ratio was investigated in CH_2Cl_2 according to Scheme 3. The reaction was monitored by CCM and HPLC and showed the disappearance of compound **6** and appearance of new compounds. Among the products formed, compound **10** was obtained in sufficient amounts to allow its structure investigation. This was achieved through UV, LC/ESMS, ES CAD MS/MS and NMR analysis.

The UV spectrum of compound **10** exhibited similar maxima (285 and 305 nm) to that of compound **6**, indicating that the original flavan structure with the $COCF_3$ group was retained. The mass spectrum obtained in the positive ion mode (Fig. 3) showed signals at *m/z*: 1395, 1412, 1417 and 1433 amu corresponding, respectively, to $[M+H]^+$, $[M+NH_4]^+$, $[M+Na]^+$ and $[M+K]^+$ indicating a molecular weight of 1394 amu in agreement with a dimeric structure consisting of tetrabenzylated (+)-catechin **3** linked to its trifluoroacylated derivative **6**. However, the remaining problem was the establishment of the position of linkage to compound **6**, as the tetrabenzylated catechin moiety is linked through its 4 position.

In addition to the signals indicated above, the mass spectrum of compound **10** also showed signals at *m/z*: 747 and 649 amu



Scheme 3. $TiCl_4$-catalyzed formation of compounds **10**, **11**.

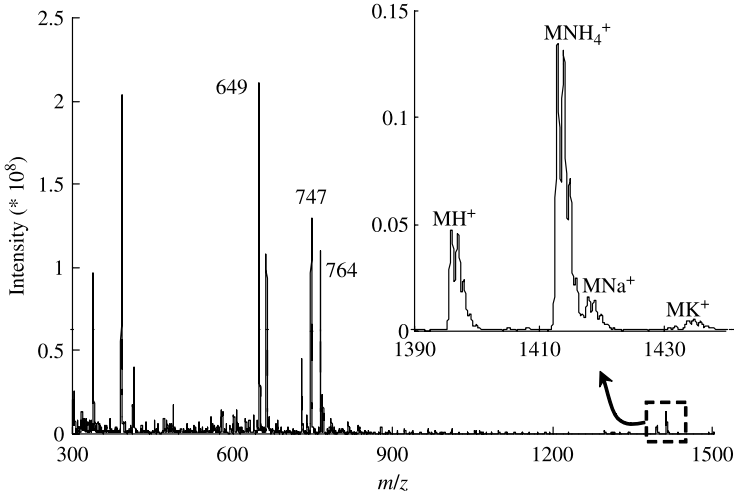


Figure 3. MS spectrum of **10** recorded in a positive ion mode.

corresponding to the fission of the bond between the two constitutive units. Among the other observed signals two of them were located at *m/z*: 1063 and 981 amu and were also observed in the spectrum obtained through positive ES CAD MS/MS fragmentation of the signal located at *m/z*: 1395 amu ($[M+H]^+$ ion). The signal observed at *m/z*: 1063 amu was attributed to the characteristic RDA fragmentation corresponding to the $[M+H-332]^+$ ion as what was observed for compound **6** through a loss of the B moiety. The second fragmentation observed at *m/z*: 981 amu correspond in fact to the $[M+H-414]^+$ ion, meaning a loss of the A moiety of compound **6** unit (Fig. 4) and corresponding to another RDA fragmentation. The occurrence of this fission indicated the presence of the A moiety in the structure of compound **10**. In other words, this means that the isolated compound is not a C-4→C-6 dimer since only one RDA fragmentation corresponding to the $[M+H-332]^+$ ion could be possible in this case. The possible linkage is thus expected to occur via the 2 or 3 position of the F ring or possibly the 2′, 5′ or 6′ positions of the ring E.

Through NMR analysis, the presence of two distinct catechin proton systems was observed. This was confirmed through 1D ^{1}H and 2D ^{1}H–^{1}H COSY NMR spectra, which showed the presence of an AMX and AA'MX spin systems corresponding to the two catechin units. Thus, the signals, which resonate at 2.52, 2.71, 4.48 and 4.90 ppm could be readily assigned to the H-4 (α and β), H-3 and H-2 of the F ring, while those located at 3.82, 4.85 and 5.10 ppm were assigned, respectively, to the H-3, H-4 and H-2 of the C ring.

In the HETCOR spectra, these aliphatic protons correlate with carbons located at 27.15, 70.80 and 76.69 ppm, respectively, for the first system and at 66.03, 70.17 and 80.52 ppm, respectively, for the second system. The furthest upfield carbon chemical shifts is in agreement with a carbon resonance deshielded by the presence of an oxygen atom. In addition, the HETCOR spectra showed correlations between the B and E rings protons and their corresponding carbons, which were thus assigned in connection with the results also obtained through ^{13}C and DEPT NMR analysis.

In the aromatic proton chemical shift region, the spectrum also showed two doublets ($J=1.8$ Hz) integrating one proton each located at 6.10 and 6.26 ppm and a singlet integrating one proton located at 6.20 ppm. The first doublets were assigned to H-6 and H-8 protons of the A ring while the singlet was assigned to H-6 of the D ring. This indicated that the interflavanyl linkage did not involve the D ring confirming thus the conclusion deduced from the MS results described above. It did not neither involve the E ring since the three corresponding protons were observed through ^{13}C and DEPT NMR spectra.

In conjunction with the absence of a doubly benzylic methylene proton characteristic of a C4→C6 linkage and taking into account the dimeric structure of the compound as supported by MS analysis, the NMR data collectively indicated a dimeric structure with an interflavanyl ether bond connecting the two heterocyclic C and F rings. Taking into account the fact that the linkage did not involve the H-2, H-3, H-4 F ring protons since they were all evidenced through NMR analysis, a (4-*O*-3) mode of linkage was thus concluded to occur between the two flavan-3-ols units. This was also confirmed by comparison of the chemical shifts of the H-4 and H-3 resonances of both the C and the F rings with those of their precursors. Finally, the structure of compound was univocally confirmed through HMBC analysis where several long range correlations were observed. In particular correlations involving proton and carbon of both C and F rings via the oxygen atom were observed and confirmed thus the ether linkage involved in compound **10**. Full assignment of the protons and carbon chemical shifts was achieved through HMBC analysis. Figure 4 showed some of the main correlations involving H/C of the C and F rings in agreement with the proposed structure.

It was concluded that a (4-*O*-3) linkage was occured between the two flavan-3-ol units. Moreover, coupling constants for the AMX spin system of the C ring protons ($J_{3,4}=3.2$ Hz) indicated a 3,4 cis relative configuration for this ring, that is a 4β linkage between both flavanol units. The complete stereoselectivity of the reaction remains, however, to be explained and should presumably be due to a participation of the hydroxy group at C-3 of **6**. However, its involvement in the stereochemical course of the reaction cannot be, in our case, related to the formation of a protonated

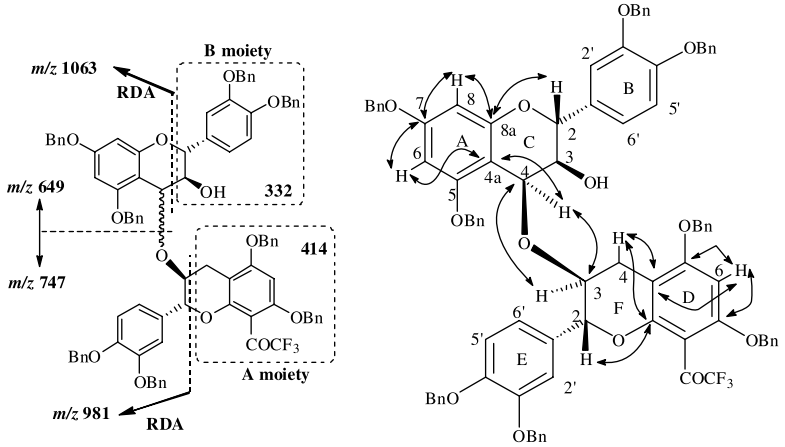


Figure 4. Main fragmentations and ^{1}H–^{13}C long range characteristic correlations observed for compound **10**.

epoxide similar to that reported by Bennie et al.,[27] in a work dealing with the dimerization of epioritin-4-ol derivatives.

Indeed, the stereochemical outcome of the reaction in our case should be rather more consistent with a chelation process of the Lewis acid by both hydroxy groups of **7** and **6**, therefore inducing the approach of the nucleophile from the β face of **7**. The possible participation of the oxygen atoms of the ethylene glycol moiety of **7**, in such a chelation process, thereby inducing a quasi-concerted process has also to be considered.

In order to verify the presence of other dimeric structures the mixture was explored by HPLC coupled to a mass spectrometry detection operating in the positive ion mode. An extracted ion current chromatogram recorded at *m/z*: 1395 and 1412 amu (Fig. 5) and corresponding to a dimeric structure molecular weight showed the presence, in addition to compound **10**, of a minor compound, which is possibly the carbon–carbon coupled dimer **11**. The fragmentations observed for compound **11** were in agreement with the proposed dimeric structure consisting of tetrabenzylated (+)-catechin **3** coupled to its trifluroacylated derivative **6** through a C4→C6 linkage (Fig. 6).

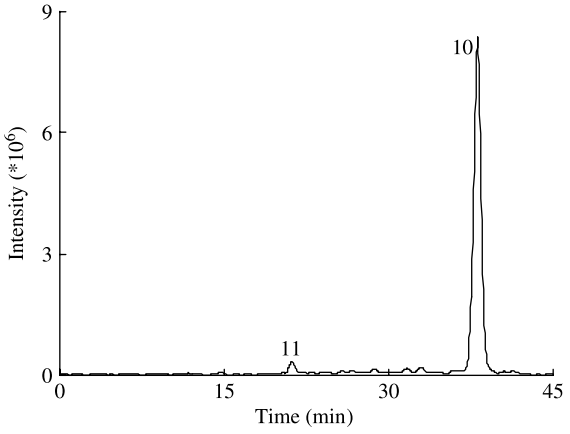


Figure 5. XIC recorded at *m/z*: 1395 amu showing the presence of the main 4-*O*-3 ether **10** and the probable C-4→C-6 linked dimers **11**.

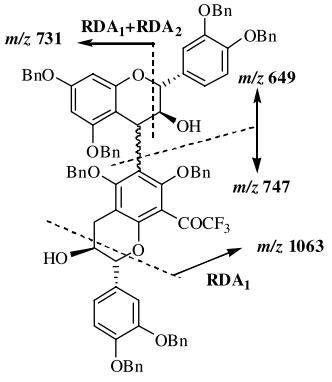


Figure 6. Main fragmentations observed for compound **11**.

The almost exclusive, high yielding formation, in these conditions of the novel ether linked procyanidins as main compound rather than its carbon–carbon C-4→C-6 coupled analogue reflects the importance of electronic features in the formation of flavan-3-ol dimers. The poor nucleophilicity of the A ring monomeric precursor, caused by the presence of the $COCF_3$ group, permits alternative centers to participate in the interflavanyl bond formation.

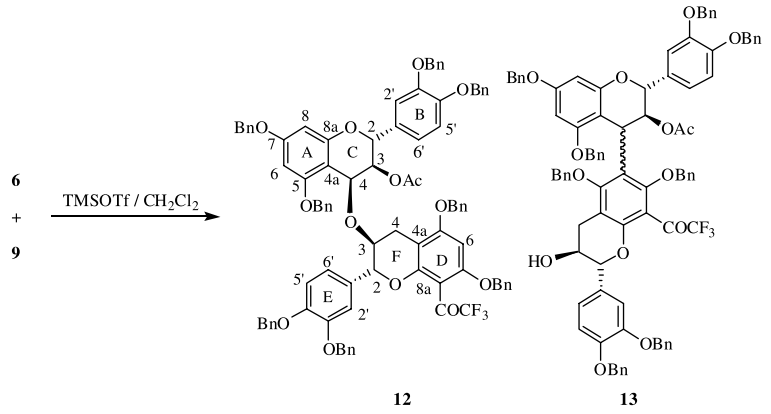
2.4. TMSOTf-catalyzed flavanol coupling reaction

As indicated above, various Lewis acids were used as coupling agents for proanthocyanidin synthesis. After having used $TiCl_4$, the same reaction was investigated using TMSOTf, which was recently used to synthesize octabenzylated procyanidin-B3 with high levels of setereoselectivity and in excellent isolated yields.[7,8,28] The reaction was conducted by using the acetylated compound **9** as electrophile, which was prepared through DDQ mediated oxidation of tetrabenzylated catechin **3** in presence of ethoxyethanol followed by an acetylation using acetic anhydride (Scheme 2). The structures of the compounds obtained were confirmed by MS and NMR analysis. The coupling reaction in the presence of TMSOTf was achieved at −78 °C using the same 8-trifluoroacetylated adduct **6** as nucleophile. After isolation by column chromatography eluting with ethylacetate/cyclohexane mixture, the major compound obtained was submitted to spectral analysis. The mass spectrum obtained in the positive ion mode showed signals at *m/z*: 1437, 1454 and 1459 amu and corresponding to $[M+H]^+$, $[M+NH_4]^+$ and $[M+Na]^+$ ions, respectively, in agreement with a dimeric structure consisting of an acetoxy-tetrabenzyloxy- and a trifluoroacetyl-tetrabenzyloxy catechin. The full structure elucidation of compound **12** was achieved using 1D and 2D NMR analysis. The presence of the three A and D rings aromatic protons was observed indicating that they were not involved during the coupling reaction and that the interflavanic bond was not a C-4→C-6 type. Further NMR analysis similar to those described for compounds **10** was used to confirm the regiochemistry of the reaction and indicated the predominant formation of a C-4→*O*→C-3 ether bond type between the two flavanol moieties. The 3,4 stereochemistry of the upper unit was also determined by NMR and was shown to be cis (Scheme 4).

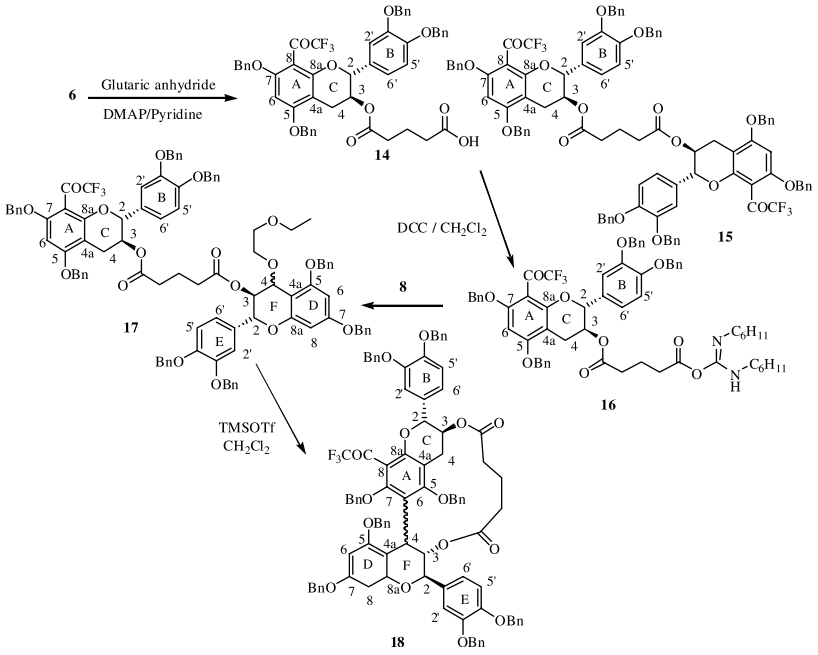
The formation of the ether linked procyanidins as main products of dimerisation rather than the carbon–carbon C-4→C-6 coupled analogues showed that the inhibition effect of the trifluoroacetyl group when using $TiCl_4$ as catalysing Lewis acid was also observed in the case of TMSOTf. This confirms the effect of the A ring substitution on the nucleophilicity of the flavanol, so allowing other nucleophilic centers to participate to the coupling reaction.

2.5. TMSOTf-catalyzed intramolecular flavanol coupling reaction

After having tested these two Lewis acid in the condensation reaction and after having showed the participation of the 3-hydroxyl group as a nucleophilic site in interflavanyl linkage formation, we decided to protect this group and to try to achieve coupling reaction with increased C–C linkage formation yield. To avoid the undesirable intervention of the 3-hydroxyl group in the chain elongation process, this group was protected in both the electrophilic and the nucleophilic



Scheme 4. TMSOTf-catalyzed formation of compounds **12**, **13**.



Scheme 5. TMSOTf-catalyzed formation of compounds **18**.

reaction partner by a diester linker glutaric anhydride in two steps (Scheme 5) and the TMSOTf-catalyzed condensation reaction was reinvestigated.

The 8-trifluoroacetyl derivative **6** was first treated with glutaric anhydride to yield the corresponding esterified compound **14**, in addition to which compound **15** resulting from a double esterification was also obtained. The isolated carboxylic mono-ester **14** was further coupled with the electrophile unit **8** in presence of DCC to give the desired diester **17**. In this reaction, the intermediate **16** was also isolated and identified. Having the 4-*O*-alkoxy derivative **17** in hand, the stage was set for its possible conversion to the corresponding C–C coupled adduct **18** (Scheme 5) through intramolecular TMSOTf-catalyzed coupling reaction.[7] The reaction was conducted in CH_2Cl_2 at −78 °C to give coupled product **18** with a low yield. In order to increase the reaction yield, several attempts were made in various conditions; however the C–C bond formation was always observed with a low yield. The mass spectrum of compound **18** showed signals at *m/z*: 1491 and 1598 amu corresponding to $[M+H]^+$ and $[M+NH_4]^+$ ions, respectively, and where the fragment *m/z*: 731 resulting from two successive RDA scissions was observed showing the presence of the C-4→C-6 linkage. In the ^1H NMR spectrum, the particular disappearance of the H-6A proton was observed confirming such C–C linkage. The low yield obtained in the coupling reaction confirms once again the negative effect of the 8-trifluoroacetyl substituent on the nucleophilicity of the C-6 center. This could also be due to geometrical factors, which are obviously important in such coupling reaction.

3. Conclusion

Our results delineate thus the influence of an electron deficient substituent on C-8 of the aromatic A ring of a catechin subunit on the course of the Lewis acid catalyzed classical procyanidin formation reaction. The results obtained showed that the presence of a $COCF_3$ substituent linked to the 8 position of a (+)-catechin unit strongly influenced the attack on the flavanol moiety by the electrophile generated from a 4-*O*-alkyloxy protected catechin unit and indicates the importance of electronic

features in the establishment of the carbon–carbon interflavanic bond. When using either $TiCl_4$ or TMSOTf as Lewis acids, C–C bond formation was inhibited and the corresponding C→C dimer was detected only in a very small amount. By contrast the formation of a carbon–oxygen bond was observed and the corresponding C-4→*O*→C-3 ether linked procyanidin dimer was isolated in a good yield. The poor nucleophilicity of the A ring electrophile acceptor subunit probably caused by the presence of the electron deficient $COCF_3$ group, allows alternative nucleophilic sites of the molecules to participate in interflavanyl bond formation.

Our results report the production of ether linked dimeric procyanidins based on (+)-catechin skeleton and obtained in good yield. Its formation is a new concept in proanthocyanidin synthesis since until now only flavanols with pyrogallol moiety were described as precursors of 4-*O*-4 and 4-*O*-3 ether linked proanthocyanidins. They finally open perspectives for further investigations of similar compounds. A number of properties such as temperature and hydrolytic stability, in addition to its biological activities, remain of a high interest, and will be investigated.

4. Experimental

4.1. General

All reactions were performed under argon and monitored by TLC and analytical HPLC. Unless otherwise indicated, the ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively (proton decoupling mode for carbon). ^1H NMR spectra were referenced to the signal at $\delta=$ 7.27 ppm of residual $CHCl_3$. ^{13}C NMR spectra were referenced to signals of $CDCl_3$ ($\delta=77.0$ ppm). Resonances of the benzyl group are not mentioned. FT-IR spectra were recorded with a Nicolet Avatar 320 FT-IR spectrophotometer. UV–visible spectra were recorded with a Kontron Uvikon 930 spectrophotometer fitted with a quartz cell.

Analytical TLC was performed on Merck silica gel 60 F254 plates. Column chromatography was performed using a mixture of ethyl acetate/cyclohexane as eluent on silica gel 60 Å 70–200 μm (SDS, 13124 PEYPIN, France). Analytical HPLC analysis was performed on a Varian apparatus including a 9012 solvent delivery system, a 9100 autosampler and a 9065 polychrom diode array detector. Analysis were performed on a C18 column eluting with a mixture of solvents A: acetonitrile and B: water with 0.5% orthophosphoric acid eluting from 15 to 100% A in 18 min followed by a washing and a reequilibrating of the column. LC/MS analysis were performed with a chromatographic system (Alliance) consisted of a Waters 2695 separations module equipped with an autosampler and a Waters 2487 dual lambda absorbance detector (Waters, Milford, MA, USA). The column was a 150×2.1 mm Interchrom UP5ODB#15E (Uptisphere 5 μm ODB) with a 10× 2.1 mm precolumn from Interchim (Montluçon, France). Chromatography was ran in isocratic mode using a 60/40 mixture of acetonitrile (RS-Plus quality for HPLC from Carlo Erba) and water with 0.2% acetic acid. The flow rate was 0.2 mL/min, the analyses were performed with the column and the samples kept at ambient temperature and 5.0–10 μL was injected for each analysis. The effluent from the UV detector was introduced without any split into the mass spectrometer. The HPLC system was coupled on line to a Quattro LC MS/MS triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with a pneumatically assisted electrospray source ionisation (ESI). Data acquisition and processing were performed using a MassLynx NT 3.5 data system. The electrospray source parameters were fixed as follow: electrospray capillary voltage 3.25 kV in positive mode and 3 kV in negative mode, source block temperature 120 °C, desolvation gas temperature 400 °C. Nitrogen was used as drying gas and nebulising gas at flow rates of approximately 50 and 450 L/h.

4.2. Synthesis

4.2.1. 3′,4′,5,7-Tetrabenzyloxycatechin (3). To a stirred suspension of NaH (144.5 mmol) in dry DMF (170 mL) under nitrogen at −78 °C, was sequentially added a solution of (+)-catechin **1a** (10 g, 34 mmol) in anhydrous DMF (170 mL) and benzyl chloride (170 mmol). The mixture was stirred at −78 °C for 15 min then at room temperature for 7 h. Progress of the reaction was monitored by TLC and was quenched by addition of 1 N HCl and water. The aqueous layer was extracted with EtOAc and the organic layer washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (eluent, cyclohexane/EtOAc, 80:20) afforded 3′,4′,5,7-tetrabenzyloxycatechin **3** (33 mmol, 97%) as white amorphous powder. Spectral data were similar to those previously described.[29]

4.2.2. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin (6). To a solution of tetra-*O*-benzylated catechin **3** (2 g, 3.0 mmol) in CH_2Cl_2 (12 mL) was added dropwise $(CF_3CO)_2O$ (20 mL) at 0 °C. The mixture was stirred at room temperature and the progress of the reaction was followed by TLC. The formation of **4** as primary product of the reaction was first observed. The formation of compound **5** was then observed. Hydrolysis of compound **5** gave the target product **6**. The crude mixture so obtained was concentrated and chromatographed on silica gel (eluent, cyclohexane/EtOAc, 80:20) giving 1.43 g (1.9 mmol, 64%) of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6**. The purity of **6** was controlled through analytical HPLC. ^1H NMR (300 MHz, $CDCl_3$) 7.01 (d, $J=1.6$ Hz, 1H, H-2′), 6.89 (dd, $J=1.6$, 8.4 Hz, 1H, H-6′), 6.95 (d, $J=8.4$ Hz, 1H, H-5′), 6.28 (s, 1H, H-6), 4.72 (d, $J=7.8$ Hz, 1H, H-2), 3.95 (m, 1H, H-3), 3.08 (dd, $J=5.4$, 16.5 Hz, 1H, H-4β), 2.67 (dd, $J=8.7$, 16.5 Hz, 1H, H-4α). ^{13}C NMR (125 MHz, $CDCl_3$) 184.3 (CO), 160.6 (C-7), 157.8 (C-5), 154.2 (C-8a), 149.5 (C-4′), 149.2 (C-3′), 130.4 (C-1′), 121.1 (CF_3), 120.4 (C-6′), 115.1 (C-5′), 113.8 (C-2′), 105.7 (C-8), 103.2 (C-4a), 81.9 (C-2), 91.3 (C-6), 67.6 (C-3), 27.5 (C-4). ESI-MS *m/z*: 747 $[M+H]^+$, 764 $[M+NH_4]^+$, 769 $[M+Na]^+$.

4.2.3. 3′,4′,5,7-Tetrabenzyloxy-4-(2-hydroxyethoxy)-catechin (7). To a solution of 3′,4′,5,7-tetrabenzyloxycatechin **3** (1.3 g, 2.0 mmol) in anhydrous CH_2Cl_2 (13 mL) was added at room temperature 0.6 mL (11.5 mmol) of

ethylene glycol and then all at once and with a good stirring 0.9 g (3.9 mmol) of DDQ. A black-green colour appeared instantaneously and gradually faded to a dark brown. After 120 min of vigorous stirring at room temperature under a $CaCl_2$ tube, excess of 4-(dimethylamino)-pyridine was added to the solution at 0 °C and the mixture was stirred for 5 min. The resulting purple solid was removed by filtration and the filtrate was washed with water and brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, hexane/EtOAc, 1:2–2:3) gave 3′,4′,5,7-tetrabenzyloxy-4-(2-hydroxyethoxy)catechin **7** (990 mg, 1.4 mmol, 70%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) 7.13 (d, J=1.6 Hz, 1H, H-2′B), 7.08 (d, J=8.1 Hz, 1H, H-5′B), 7.02 (dd, J=1.6, 8.1 Hz, 1H, H-6′B), 6.50 (d, J=2.1 Hz, 1H, H-6A), 6.25 (d, J=2.1 Hz, 1H, H-8A), 5.10 (d, J=10.0 Hz, 1H, H-2C), 4.95 (m, 1H, H-3C), 4.82 (d, J=7.1 Hz, 1H, H-4C), 3.50–3.90 (m, 4H, OCH_2-CH_2O). ^{13}C NMR (125 MHz, $CDCl_3$) 161.5 (C-7A), 160.7 (C-5A), 157.6 (C-8aD), 147.5 (C-3′B), 147.3 (C-4′B), 131.2 (C-1′B), 121.2 (C-6′B), 116.3 (C-5′B), 113.8 (C-2′B), 105.8 (C-4aA), 94.2 (C-8A), 93.2 (C-6A), 78.8 (C-2C), 74.2 (C-3C), 71.3 (C-4C), 68.3 (OCH$_2$CH$_2$OH), 61.8 (OCH$_2$$CH_2$-OH). ESI-MS m/z: 711 $[M+H]^+$, 728 $[M+NH_4]^+$, 733 $[M+Na]^+$.

4.2.4. 3′,4′,5,7-Tetrabenzyloxy-4-(2-ethoxyethoxy)-catechin (8). DDQ oxidation according to the above procedure using 3′,4′,5,7-tetrabenzyloxycatechin **3** (500 mg, 0.77 mmol), DDQ (350 mg, 1.54 mmol) and 2-ethoxyethanol (1.5 mL) in CH_2Cl_2 (15 mL) for 2 h afforded **8** as a pale yellow solid, which was crystallized from hexane/EtOAc to give 550 mg (0.75 mmol, 97%) of 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** as colourless needles. ^{1}H NMR (300 MHz, $CDCl_3$) 7.20 (d, J=1.7 Hz, 1H, H-2′B), 7.01 (d, J=8.0 Hz, 1H, H-5′B), 6.97 (dd, J=1.7, 8.0 Hz, 1H, H-6′B), 6.17 (d, J=2.0 Hz, 1H, H-6A), 6.03 (d, J=2.0 Hz, 1H, H-8A), 4.98 (d, J=10.05 Hz, 1H, H-2C), 4.89 (m, 1H, H-3C), 4.85 (d, J=7.0 Hz, 1H, H-4C), 3.50–3.90 (m, 4H, OCH_2CH_2O), 3.30 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 1.20 (t, J=7.0 Hz, 2H, OCH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 161.2 (C-7A), 160.3 (C-5A), 156.6 (C-8aD), 148.3 (C-3′B), 148.1 (C-4′B), 131.1 (C-1′B), 121.1 (C-6′B), 115.6 (C-5′B), 114.1 (C-2′B), 104.7 (C-4aA), 94.5 (C-8A), 93.6 (C-6A), 76.5 (C-2C), 74.2 (C-3C), 72.1 (C-4C), 70.8 (OCH$_2$), 70.2 (CH$_2$O), 66.5 (CH$_2$CH$_3$), 14.0 (CH$_2$$CH_3$). ESI-MS m/z: 739 $[M+H]^+$, 756 $[M+NH_4]^+$, 761 $[M+Na]^+$.

4.2.5. 3-Acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxy-ethoxy)catechin (9). Acetylation using 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** (500 mg, 0.67 mmol), Ac_2O and 4-(dimethylamino)pyridine afforded 510 mg (0.65 mmol) of 3-acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **9** as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) 7.30 (d, J=1.6 Hz, 1H, H-2′B), 7.10 (d, J=8.1 Hz, 1H, H-5′B), 6.96 (dd, J=1.6, 8.1 Hz, 1H, H-6′B), 6.20 (d, J=2.0 Hz, 1H, H-6A), 6.10 (d, J=2.0 Hz, 1H, H-8A), 5.30 (m, 1H, H-3C), 5.20 (d, J=10.17 Hz, 1H, H-2C), 4.80 (d, J=7.4 Hz, 1H, H-4C), 3.30–3.7 (m, 4H, OCH_2CH_2O), 3.20 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 1.7 (s, 3H, CH_3CO), 1.10 (t, J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 170.2 (CH$_3$$C$O), 161.0 (C-7A), 160.5 (C-5A), 156.8 (C-8aD), 147.5 (C-3′B), 147.0 (C-4′B), 130.6 (C-1′B), 120.9 (C-6′B), 116.5 (C-5′B), 114.5 (C-2′B), 105.3 (C-4aA), 94.2 (C-8A), 93.4 (C-6A), 76.3 (C-3C), 75.8 (C-3C), 71.2 (C-4C), 70.1 (OCH$_2$), 70.0 (CH$_2$O), 66.3 (CH$_2$CH$_3$), 20.1 (CH$_3$CO), 14.2 (CH$_2$$CH_3$). ESI-MS m/z: 7381 $[M+H]^+$, 803 $[M+Na]^+$.

4.2.6. 3′,4′,5,7-Tetrabenzyloxycatechin-(4β→*O*→3)-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin (10). To a solution of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (895 mg, 1.2 mmol, 6 equiv) and 3′,4′,5,7-tetrabenzyloxy-4-(2-hydroxyethoxy)catechin **7** (142 mg, 0.2 mmol) in CH_2Cl_2 (40 mL) was added dropwise 0.2 mmol of $TiCl_4$ at 0 °C. The reaction mixture was stirred for 5 min and then quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with EtOAc and the combined organic phase was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration and silica gel column chromatography (eluent cyclohexane/EtOAc, 80:20) afforded 180 mg of **10** (0.13 mmol, 66%). The purity of **10** was controlled through analytical HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) 7.08 (d, J=1.8 Hz, 1H, H-2′B), 7.01 (d, J=8.2 Hz, 1H, H-5′B), 7.00 (dd, J=1.8, 8.2 Hz, 1H, H-6′B), 6.80 (d, J=8.2 Hz, 1H, H-5′E), 6.78 (d, J=1.3 Hz, 1H, H-2′E), 6.63 (dd, J=1.3, 8.2 Hz, 1H, H-6′E), 6.27 (d, J=2.2 Hz, 1H, H-6A), 6.20 (s, 1H, H-6D), 6.12 (d, J=2.2 Hz, 1H, H-8A), 5.06 (m, 1H, H-4C), 4.99 (m, 1H, H-2F), 4.85 (d, J=10 Hz, 1H, H-2C), 4.49 (m, 1H, H-3F), 3.83 (m, 1H, H-3C), 2.78 (dd, J=4.4, 16.7 Hz, 1H, H-4βF), 2.61 (dd, J=4.4, 16.7 Hz, 1H, H-4αF). ^{13}C NMR (125 MHz, $CDCl_3$) 188.9 (CO, q, J=38 Hz), 165.6 (C-7A), 165.3 (C-5D), 162.7 (C-5A), 161.9 (C-7D), 161.0 (C-8aA), 158.8 (C-8aD), 153.7 (C-3′B), 153.6 (C-4′B), 153.4 (C-3′E), 152.9 (C-4′E), 136.7 (C-1′B), 136.2 (C-1′E), 125.3 (C-6′B), 123.5 (C-6′E), 119.1 (C-5′B), 118.6 (C-5′E), 118.6 (C-2′B), 116.4 (C-2′E), 115.7 (CF_3, q, J=292 Hz), 109.6 (C-8D), 106.8 (C-4aA), 106.6 (C-4aD), 98.8 (C-8A), 97.6 (C-6A), 95.2 (C-6D), 84.6 (C-2F), 80.8 (C-2C), 74.6 (C-3F), 74.0 (C-3C), 70.3 (C-4C), 27.2 (C-4F). ESI-MS m/z: 1395.9 $[M+H]^+$, 1412 $[M+NH_4]^+$, 1417 $[M+Na]^+$, 1433 $[M+K]^+$.

4.2.7. 3-Acetoxy-3′,4′,5,7-tetrabenzyloxycatechin-(4β→*O*→3)-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin (12). To a solution of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (895 mg, 1.2 mmol, 6 equiv) and 3-acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **9** (156 mg, 0.2 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.4 mL, 0.2 mmol, 0.5 M solution in CH_2Cl_2) at −78 °C. After stirring for 5 min, the reaction mixture was quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with EtOAc and the organic phase was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration and silica gel column chromatography (cyclohexane/EtOAc, 80:20) afforded 143 mg of **12** (0.1 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.11 (m, 2H, H-2′B, H-5′E), 7.00 (m, 2H, H-6′B, H-2′E), 6.81 (d, J=8.7 Hz, 1H, H-5′B), 6.63 (m, 1H, H-6′E), 6.26 (d, J=2.0 Hz, 1H, H-8A), 6.20 (s, 1H, H-6D), 6.10 (d, J=2.0 Hz, 1H, H-6A), 5.10 (m, 1H, H-2F), 4.90 (m, 1H, H-4C), 4.85 (d, J=10.2 Hz, 1H, H-2C), 4.48 (m, 1H, H-3F), 3.82 (m, 1H, H-3C), 2.71 (dd, J=6.6, 16.5 Hz, 1H, H-4βF), 2.52 (dd, J=4.5, 16.5 Hz, 1H, H-4αF), 1.9 (s, 3H, CH_3CO). ^{13}C NMR (125 MHz,

$CDCl_3$) 184.5 (CF_3CO), 169.8 (CH_3CO), 161.3 (C-7D), 160.8 (C-7A), 158.4 (C-5D), 157.6 (C-5A), 156.7 (C-8aD), 154.3 (C-8aA), 149.5 (C-4′E), 149.3 (C-4′B), 149.2 (C-3′E), 148.8 (C-3′B), 132.1 (C-1′E), 131.8 (C-1′B), 122.2 (CF_3), 121.4 (C-6′E), 119.7 (C-6′B), 115.1 (C-5′E), 114.9 (C-5′B), 114.8 (C-2′E), 112.6 (C-2′B), 110.2 (C-4aA), 105.6 (C-8D), 102.7 (C-4aD), 94.3 (C-6A), 93.3 (C-8A), 92.5 (C-6D), 80.5 (C-2C), 76.7 (C-2F), 70.8 (C-3F), 70.2 (C-4C), 66.0 (C-3C), 27.2 (C-4F), 21.1 (CH_3CO). ESI-MS *m/z*: 1437 $[M+H]^+$, 1454 $[M+NH_4]^+$, 1459 $[M+Na]^+$.

4.2.8. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate (14). A mixture of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (400 mg, 0.53 mmol), glutaric anhydride (183 mg, 1.6 mmol) and 4-(dimethylamino)-pyridine (5 mg) in pyridine (15 mL) was stirred at 0 °C for 1 h. After stirring for 48 h at room temperature, the reaction was quenched with water, and extracted with EtOAc. The combined organic acid phases were washed with brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, hexane/EtOAc, 1:1) gave 210 mg (0.24 mmol, 45%) of **14** and 160 mg of **15** (0.1 mmol, 19%). ^{1}H NMR of **14** (300 MHz, $CDCl_3$) 6.99 (d, $J=1.5$ Hz, 1H, H-2′), 6.91 (d, $J=8.4$ Hz, 1H, H-5′), 6.84 (dd, $J=1.5$, 8.4 Hz, 1H, H-6′), 6.24 (s, 1H, H-6), 5.3 (m, 1H, H-3), 4.95 (d, $J=7.8$ Hz, 1H, H-2), 2.81 (dd, $J=5.1$, 16.0 Hz, 1H, H-4β), 2.72 (dd, $J=5.7$, 16.0 Hz, 1H, H-4α), 2.4 (m, 4H, CH_2COOR, CH_2COOH), 1.7 (m, 2H, CH_2-CH_2CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) 184.7 ($COCF_3$), 177.5 (COOH), 172.2 (COOR), 159.6 (C-7), 158.0 (C-5), 153.2 (C-8a), 149.2 (C-3′), 148.7 (C-4′), 130.4 (C-1′), 124.3 (C-6′), 117.8 (CF_3), 116.5 (C-5′), 114.4 (C-2′), 105.6 (C-8), 102.0 (C-4a), 91.1 (C-6), 78.5 (C-2), 68.4 (C-3), 35.5 (CH_2COOH), 33.6 (CH_2COOR), 27.9 (C-4), 19.9 (CH_2-CH_2COOH). ESI-MS *m/z*: 861 $[M+H]^+$, 883 $[M+Na]^+$.

4.2.9. Di-(5,7,3′,4′-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl) glutarate (15). ^{1}H NMR (300 MHz, $CDCl_3$) 7.10 (d, $J=1.5$ Hz, 2H, H-2′), 6.96 (d, $J=8.2$ Hz, 2H, H-5′), 6.90 (dd, $J=1.5$, 8.2 Hz, 2H, H-6′), 6.20 (s, 2H, H-6), 5.20 (d, $J=7.8$ Hz, 2H, H-2), 4.89 (m, 2H, H-3), 3.02 (dd, $J=5.1$, 15.0 Hz, 2H, H-4β), 2.72 (dd, $J=5.7$, 15.0 Hz, 2H, H-4α), 2.3 (m, 4H, CH_2CO), 1.8 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$) 185.0 ($COCF_3$), 172.1 (COOR), 160.6 (C-7), 158.0 (C-5), 153.7 (C-8a), 149.2 (C-3′), 148.5 (C-4′), 130.2 (C-1′), 121.0 (C-6′), 117.9 (CF_3), 117.5 (C-5′), 115.1 (C-2′), 105.6 (C-8), 102.0 (C4a), 91.1 (C-6), 78.5 (C-2), 68.4 (C-3), 33.5 (CH_2CO), 27.5 (C-4), 20.5 (CH_2CH_2CO). ESI-MS *m/z*: 1589 $[M+H]^+$, 1611 $[M+Na]^+$.

4.2.10. 3′,4′,5,7-Tetrabenzyloxy-4-(2-ethoxyethoxy)-catechin-3-yl-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate (17). A solution of 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** (150 mg, 0.20 mmol), 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate **14** (300 mg, 0.40 mmol), DCC (82.6 mg, 0.40 mmol) and DMAP (10.00 mg) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 1 h. After stirring for 12 h at room temperature, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, cyclohexane/EtOAc, 80:20) gave 50 mg (0.05 mmol, 12.5%) of the intermediate compound **16** and 126 mg (0.08 mmol, 40%) of the target product **17**, which was obtained as amorphous powder. ^{1}H NMR (300 MHz, $CDCl_3$) 7.21 (d, $J=8.1$ Hz, 1H, H-5′E), 7.06 (d, $J=1.5$ Hz, 1H, H-2′E), 6.95 (dd, $J=1.5$, 8.1 Hz, 1H, H-6′E), 6.84 (d, $J=1.7$ Hz, 1H, H-2′B), 6.74 (d, $J=8.4$ Hz, 1H, H-5′B), 6.26 (dd, $J=1.7$, 8.4 Hz, 1H, H-6′B), 6.19 (s, 1H, H-6A), 6.16 (d, $J=2$ Hz, 1H, H-6D), 6.03 (d, $J=2$ Hz, 1H, H-8D), 4.95–5.31 (m, 4H, H-2C, H-3C, H-2F, H-3F), 4.87 (d, $J=3$ Hz, 1H, H-4F), 3.4 (q, $J=7$ Hz, 2H, CH_2CH_3), 3.33–3.52 (m, 4H, OCH_2CH_2O), 2.82 (dd, $J=6.4$, 16.2 Hz, 1H, H-4βC), 2.65 (dd, $J=5.4$, 16.2 Hz, 1H, H-4αC), 1.98–2.40 (m, 6H, $CH_2CH_2CH_2$), 1.1 (t, $J=7$ Hz, 3H, CH_3CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) 185.6 ($COCF_3$), 171.3 (COO), 170.9 (COO), 160.6 (C-7A), 159.9 (C-7D), 158.1 (C-5A), 157.4 (C-5D), 155.4 (C-8aA), 153.0 (C-8aD), 148.9 (C-3′B), 148.5 (3C, C-4′B, C-3′E, C-4′E), 130.1 (C-1′B), 129.9 (C-1′E), 120.9 (C-6′B), 118.8 (C-6′E), 117.4 (CF_3), 114.4 (2C, C-5′B, C-5′E), 114.3 (2C, C-2′B, C-2′E), 103.3 (C-4aA), 101.4 (C-4aD), 94.0 (C-8D), 93.4 (C-6D), 90.5 (C-6A), 78.2 (C-2C), 77.6 (C-2F), 74.5 (C-3C), 72.8 (C-3F), 70.2 (OCH_2CH_2O), 70.0 (OCH_2CH_2O), 66.5 (OCH_2CH_3), 35.1 (2C, CH_2CO), 27.1 (C-4), 19.8 ($CH_2CH_2CH_2$), 13.9 (CH_3CH_2). ESI-MS *m/z*: 1581 $[M+H]^+$, 1603 $[M+Na]^+$.

4.2.11. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl-dicyclohexyl-carbodiimidoyl-glutarate (16). ^{1}H NMR (300 MHz, $CDCl_3$) 7.05 (d, $J=1.5$ Hz, 1H, H-2′), 6.95 (d, $J=8.4$ Hz, 1H, H-5′), 6.78 (dd, $J=1.5$, 8.2 Hz, 1H, H-6′), 6.20 (s, 1H, H-6), 5.1 (d, $J=7.8$ Hz, 1H, H-2), 4.90 (m, 1H, H-3), 2.90 (dd, $J=5.1$, 16.0 Hz, 1H, H-4β), 2.60 (dd, $J=5.7$, 16.0 Hz, 1H, H-4α), 2.4 (m, 4H, CH_2CO), 1.6 (m, 2H, $CH_2CH_2CH_2$), 1.1–2.8 (m, 22H, H Cyclo). ^{13}C NMR (125 MHz, $CDCl_3$) 184.6 ($COCF_3$), 172.5 (COO), 172.2 (COOC=N), 160.6 (C-7), 158.0 (C-5), 154.1 (C-8a), 153.7 (C=N), 149.2 (C-3′), 149.1 (C-4′), 130.6 (C-1′), 120.6 (C-6′), 117.4 (CF_3), 116.5 (C-5′), 114.3 (C-2′), 105.6 (C-8), 102.0 (C-4a), 91.1 (C-6), 78.4 (C-2), 68.4 (C-3), 55.7 (CH–N=), 50.0 (CH–NH), 34.1 (CH_2–CO), 33.8 (CH_2–CO), 33.5 (CH_2 Cyclo), 33.5 (CH_2 Cyclo), 32.8 (CH_2 Cyclo), 32.7 (CH_2 Cyclo), 31.1 (CH_2 Cyclo), 31.0 (CH_2 Cyclo), 27.3 (C-4), 25.6 (CH_2 Cyclo), 25.5 (CH_2 Cyclo), 24.9 (CH_2 Cyclo), 23.2 (CH_2 Cyclo), 20.5 ($CH_2CH_2CH_2$). ESI-MS *m/z*: 1067.6 $[M+H]^+$, 1089.6 $[M+Na]^+$.

4.2.12. Octabenzyloxy-3,3′-*O*-glutarylcatechin-(4→6)-8-trifluoroacetylcatechin (18). To a solution of **17** (100 mg, 0.06 mmol) in CH_2Cl_2 (20 mL) was added dropwise TMSOTf (0.11 mL, 0.06 mmol, 0.5 M solution in CH_2Cl_2) at 0 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($MgSO_4$). Filtration, concentration and short silica gel column chromatography (eluent, cyclohexane/EtOAc, 80:20) afforded 2 mg (0.001 mmol, 2.2%) of **18** as amorphous powder. ^{1}H NMR (300 MHz, $CDCl_3$) 7.01 (1H, d, $J=1.5$ Hz, 1H, H-2′E), 6.90 (1H, dd, $J=1.5$, 8.1 Hz, 1H, H-6′E), 6.75 (1H, d, $J=1.6$ Hz, 1H, H-2′B), 6.70 (1H, d, $J=8.1$ Hz, 1H, H-5′E), 6.40 (1H, dd, $J=1.6$, 8.3 Hz, 1H, H-6′B), 6.21 (1H, d, $J=8.3$ Hz, 1H, H-5′B), 6.10 (1H, d, $J=2.0$ Hz, 1H, H-6D), 6.05 (1H, d, $J=2.0$ Hz, 1H, H-8D),

5.05 (m, 1H, H-2F), 4.95 (m, 1H, H-4F), 4.80 (d, J= 10.2 Hz, 1H, H-2C), 4.42 (m, 1H, H-3F), 3.85 (m, 1H, H-3C), 2.76 (dd, J=6.6, 16.3 Hz, 1H, H-4βF), 2.45 (dd, J= 4.5, 16.3 Hz, 1H, H-4αF), 2.20–2.40 (m, 4H, $CH_2CH_2CH_2$), 1.70–1.92 (m, 2H, $CH_2CH_2CH_2$). ESI-MS *m/z*: 1491 $[M+H]^+$, 1513 $[M+Na]^+$.

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