DOI: 10.1002/ejoc.201000053

Stereoselective Synthesis of Benzylated Prodelphinidins and Their Diastereomers with Use of the Mitsunobu Reaction in the Preparation of Their Gallocatechin Precursors

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Dedicated to Prof. Gerhard Höfle on the occasion of his 70th birthday

Keywords: Natural products / Phytochemistry / Polyphenols / Flavanoids / C-C coupling

The tetrabenzylated catechin **9** was prepared by benzylation of the commercially available pure (+)-catechin (**3**) and coupled with the commercially unavailable pentabenzylated (–)-gallocatechin **10**, prepared in a one-step Mitsunobu-type cyclization of the triol **8**. The highly stereoselective synthesis of benzylated prodelphinidins – catechin-(4α→8)-gallocatechin (**13**), gallocatechin-(4α→8)-gallocatechin (**14**), and gallocatechin-(4α→8)-catechin (**15**) – is reported for the first time. The ESI(+)-CID mass spectra of the coupling products were found to feature regioselective retro-Diels–Alder (RDA) reactions and unusual sequential losses of pairs of $C_7H_7^{\cdot}$ radicals (182 u) from the Na^+ adduct ions.

Introduction

Polyphenols are ingredients of agricultural products such as wine, tea, fruit, vegetables, and herbal medicines and play an important role due to their various biological functions.[1] The specific interactions of polyphenolic compounds with proteins have stimulated the search for new drugs derived from them.[2] Among polyphenolic compounds, flavonoids are considered to be particularly important because many have shown antibacterial,[3] anticancer,[4] antioxidant,[5] and antiviral[6] activities. The proanthocyanidins form an important subgroup of naturally occurring flavanoids. They show particularly rich variation in hydroxy substitution patterns, types of linkage between monomers, and degrees of polymerization, including interflavanyl bonds between the C^4–C^8 or C^4–C^6 positions of the flavan-3-ol units.[7,8]

The prodelphinidins form a specific class of proanthocyanidins in which the main building blocks are (–)-gallocatechin (**1**, Figure 1) and (+)-epigallocatechin (**2**). They are considered to be biologically particularly important polyphenolic secondary metabolites as a result of their anthelmintic,[9] antibacterial,[10] antiproliferative,[11] anti-HIV,[12] and antioxidant properties.[13–16] Some members of the prodelphinidins have inhibitory effects on membrane type 1 matrix metalloproteinase (MT 1-MMP),[17] others against glucose-mediated protein damage,[18] and some have trypsin

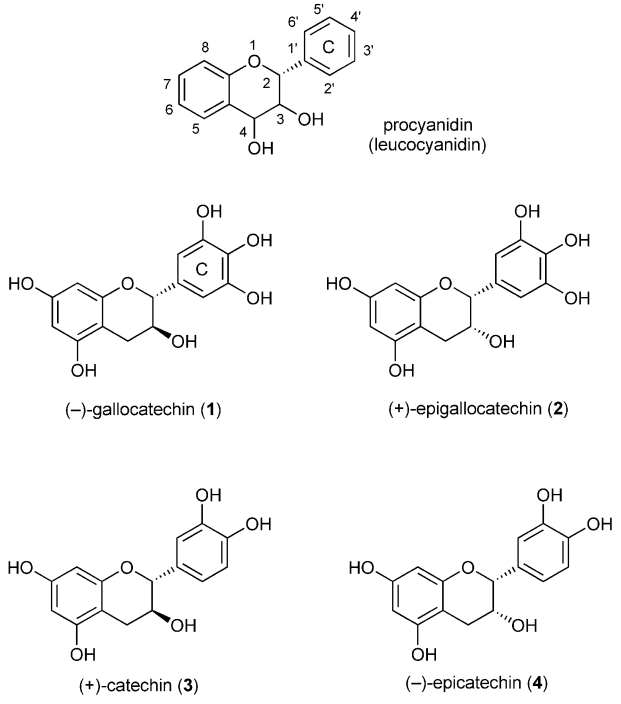

Figure 1. Structures of flavonoid monomers.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000053.

inhibitory activity. Analysis of the structure/activity relationships suggests that the strength of inhibition is significantly affected by the degree of polymerization, the number of phenolic hydroxy groups, and the 2,3-stereochemistry of the constituent units.[19] The prodelphinidins are also used as biochemical markers of HL60 cell differentiation[20] and reference compounds in HPLC analysis of different foodstuffs.[21] The proanthocyanidins (condensed tannins) have recently attracted considerable attention as antiviral, antibacterial, and antitumor agents.[22]

The polyphenolic proanthocyanidins are difficult to isolate from natural sources in pure form. The plant extracts generally produce mixtures of closely related compounds, not easily separable even with modern chromatographic methods. Their synthesis is therefore still very important and a topic of current research both for structure confirmation and for obtaining larger amounts of the pure compounds for biological testing.[7,8,23]

The main building blocks in the procyanidin class (also named leucocyanidins; for general structure see Figure 1) are (+)-catechin (**3**) and (–)-epicatechin (**4**), which are both commercially available in enantiomerically pure form. (–)-Gallocatechin (**1**) and (+)-epigallocatechin (**2**) are not commercially available and so it is not surprising that no prodelphinidin synthesis based on the condensation of these two building blocks has been reported. In a previous communication we described the enantioselective synthesis of the benzylated (–)-gallocatechin **10** (Scheme 1, below) by means of a Mitsunobu reaction.[24] We now report for the first time on the highly stereoselective synthesis of benzylated prodelphinidins: catechin-(4α→8)-gallocatechin (**13**, Scheme 2, below), gallocatechin-(4α→8)-catechin (**14**), and gallocatechin-(4α→8)-gallocatechin (**15**). These coupling products are present in food grains of barley and sorghum[25] and fresh leaves of *Camellia sinensis*[26] and impart a certain resistance to feeding by birds. Their presence has been associated with bloat prevention, especially in cattle that have been fed a high-soluble-protein diet.[27] The prodelphinidin **6** and **7** (Figure 2) and higher condensation products have been found to occur in the bark of *Quercus dentata*,[28] which serves as a source of tanning materials for the leather industry in China. Prodelphinidin B3 (**7**) is one of the active principle found in leaves of *Ribes nigrum*, traditionally used in Europe for the treatment of rheumatic diseases.[29] Beer is a beverage known to contain a wide variety of phenolic compounds, most of which originate from the raw materials of brewing: barley and hops. Stabilization of beer against clouding may be achieved by decreasing the simple flavanol content, thereby limiting further flavanol polymerization and complexation.[30] Prodelphinidin B3 (**7**) is present in beer and (–)-gallocatechin (**1**), (+)-epigallocatechin (**2**), and prodelphinidin B3 (**7**) are constituents of red wine.[31]

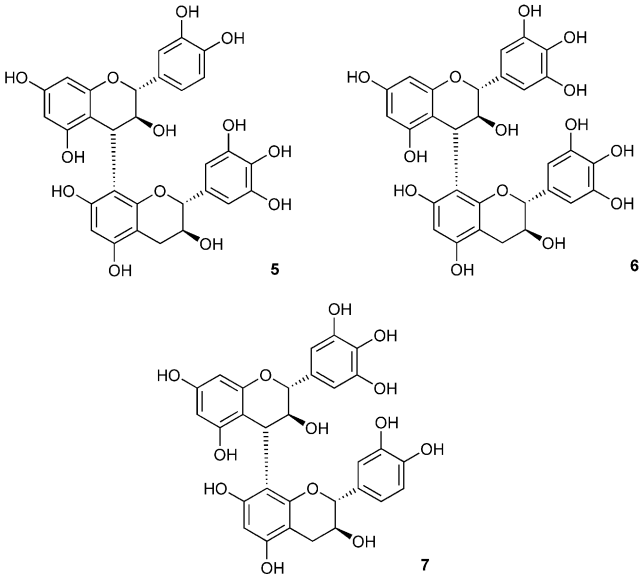


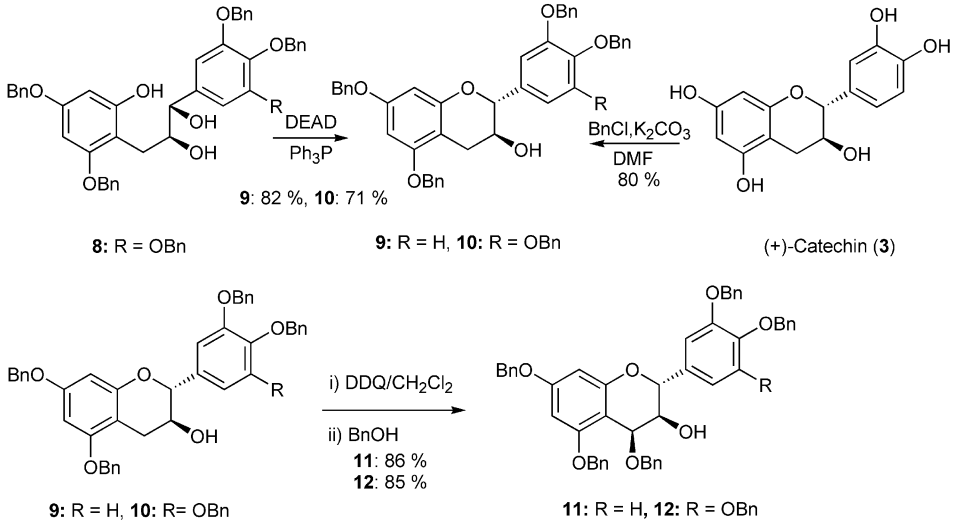
Figure 2. Structures of prodelphinidins and procyanidin.

Results and Discussion

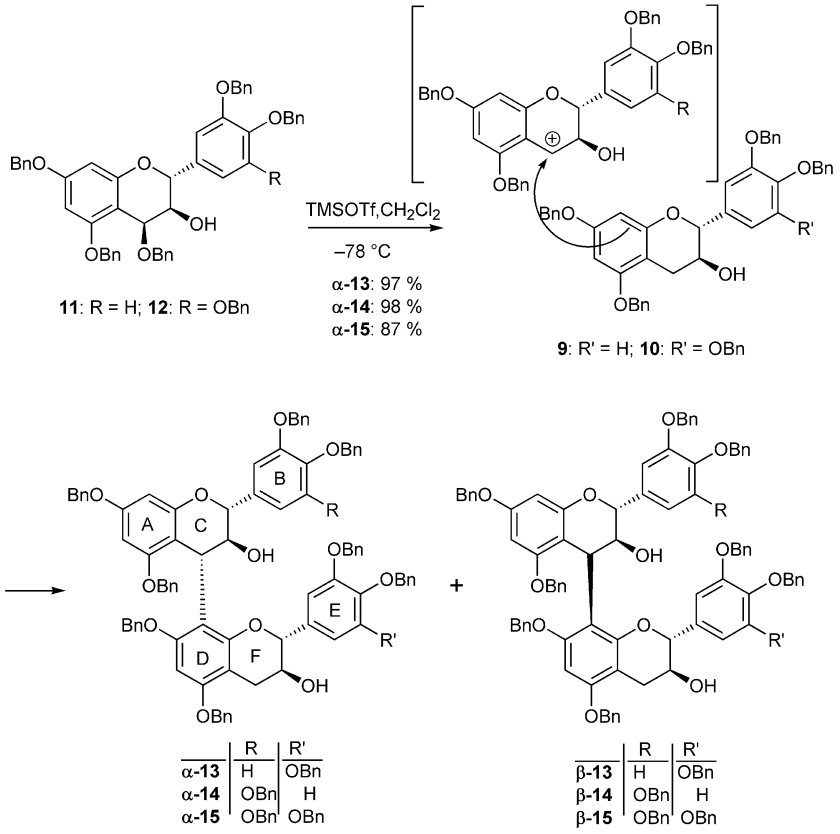
Synthesis

Couplings of monomeric flavans are usually performed in Friedel–Crafts-type reactions (see Scheme 2). Electron-rich trioxygenated aromatics such as the benzylated catechin **9** and gallocatechin **10** (Scheme 1) represent the nucleophilic units, whereas their benzyloxylated counterparts **11** or **12**, after activation with a Lewis acid, act as the electrophiles (see Scheme 2). The pentabenzylated (–)-gallocatechin **10** has already been prepared by our group[24] through a one-step Mitsunobu-type cyclization of the triol **8**[32] (Scheme 1). The phenol **8** was treated with diethyl azodicarboxylate and triphenylphosphane in anhydrous tetrahydrofuran to afford the (–)-pentabenzylated gallocatechin **10** with inversion of stereochemistry at C-2 and the expected 2,3-*trans* configuration. No loss of enantioselectivity was observed[33] and the theoretically possible five-membered cyclization products could not be detected. The tetrabenzylated catechin **9** was prepared in excess by the benzylation of commercially available pure (+)-catechin (**3**) with benzyl chloride and K_2CO_3 in DMF.[34] No formation of a *C*-benzylated product was observed.

The electrophiles **11** and **12** were prepared from their corresponding debenzyloxy compounds **9** and **10** by treatment with DDQ for benzylic oxidation.[8] DDQ oxidation at C-4 of the tetrabenzylated (+)-catechin **9** and the pentabenzylated (–)-gallocatechin **10** was performed with benzyl alcohol as the nucleophile and proceeded smoothly to give the 4-*O*-benzyl derivatives **11** and **12** in 85 and 86% isolated yields, respectively. The coupling reactions, starting only from the two flavans **9** and **10** with two or three benzyloxy groups rings on ring **B**, would thus theoretically give four pairs of diastereoisomers. We restricted the synthesis to those natural products prepared for the first time. Neither the mixed coupling products with two and three benzyloxy groups nor those with three benzyloxy groups on both ring B and E (for ring letter see Scheme 2 and ref.[2,8]) have previously been synthesized.



Scheme 1. Synthesis of the nucleophilic units **9** and **10** and the electrophiles **11** and **12**.



Scheme 2. TMSOTf-catalyzed condensations of **11/12** with **9/10** to afford the prodelphinidins **13**–**15**.

In principle, diastereomers can be formed during the coupling reaction. Procyanidin B3 and its diastereomers were prepared by the methods of Kawamoto and Vercauteren in 1.5:1 and 2.0:1 ratios, respectively.[7] Synthetic studies of (–)-procyanidin B3 based on condensation between two substituted catechin units have been reported by Roux et al.,[2] Kawamoto et al.,[35] and Vercauteren et al.,[36] but the stereoselectivity of the intermolecular condensation has only been described in detail by Ubukata et al.[7] Many Lewis acid catalysts have been employed for the synthesis of proanthocyanidins in the literature; they include $TiCl_4$ for epicatechin[37a] and the catechin coupling products[36] and $SnCl_4$ and $BF_3{\cdot}OEt_2$ for catechin "oligomers".[1,35] An improved synthesis of procyanidin dimers with controlled regio-and stereochemistry has recently been reported by the Fouquet group.[37b] The key step involves coupling between equimolar amounts of a tetraprotected monomer (the nucleophilic partner) and a C4-activated, C8-protected mono-

mer (the electrophilic partner) with $TiCl_4$ as the Lewis catalyst. However, we used larger amounts of the nucleophilic partners (which can be recovered), in order to avoid the need for protection steps and the formation of higher oligomers.[37a] For the condensation we followed the procedure of Saito et al.[23] with use of a solution of TMSOTf in CH_2Cl_2 (0.5 M), because it has been reported that the TMSOTf-catalyzed intermolecular condensation is very specific for the formation of the natural 3,4-*trans* isomers.

We first investigated the coupling reaction by starting with the benzyl ether **11**, prepared in fairly large amounts from the enantiomerically pure (+)-catechin (**3**) by benzylation with benzyl chloride and K_2CO_3 in DMF, as the electrophile.[34] The penta-*O*-benzylated gallocatechin **10** served as the nucleophilic part. Treatment of **11** with TMSOTf generated an intermediate cation that was attacked by the nucleophilic pentabenzyl ether **10** (Scheme 2) to form a mixture of the diastereomeric coupling products (4α)-**13** and (4β)-**13** in 97% combined yield. However, the minor *cis* isomer (4β)-**13** could not be isolated in pure form. Careful analysis of its ^{1}H NMR spectrum (after chromatographic enrichment) revealed a ratio of >50:1 in favor of the *trans* isomer (4α)-**13**. The ^{1}H NMR spectrum of the minor isomer clearly showed the gross structure of (4β)-**13**, but a clear assignment of all the signals of this complex molecule was not possible.

Similarly, the TMSOTf-catalyzed condensation between the hexa-*O*-benzylated gallocatechin **12** (electrophilic unit) and the penta-*O*-benzylated gallocatechin **10** (nucleophilic unit) proceeded smoothly to afford a mixture of (4α)-**15** and (4β)-**15** in 87% isolated yield in a >50:1 ratio. The prodelphinidin derivative with three oxygen functions on both rings B and E[28,29] had thus been prepared for the first time. For the synthesis of benzylated prodelphinidin B3 (**14**), the hexa-*O*-benzylated gallocatechin **12** was taken as the electrophilic part and the tetra-*O*-benzylated catechin **9** as the nucleophile to afford the naturally occurring benzylated prodelphinidin B3 (**14**)[28,30] in 98% combined yield. Again the ratio was >50:1 and neither (4β)-**14** nor (4β)-**15** could be isolated in pure form.

We also addressed the enantioselectivity of the coupling products. In cases in which the benzylated commercially available enantiomerically pure catechin derivative **10** was involved, enantiomerically pure coupling products **13** and **14** can reasonably be expected. However, although the enantiomeric purities of the building blocks **10** and **12** were checked by optical rotation, the absolute enantiomeric purities of these synthetic materials were not certain. All three coupling products (4α)-**13** to (4α)-**15** were therefore carefully checked by chiral HPLC under a large variety of solvent systems and conditions (see Exp. Section). Under none of these sets of conditions could peaks indicating deviation of any of the coupling products from enantiomeric purity be detected.

Rotational isomers occurring with different ratios were observed in the NMR studies of all diastereomers in $CDCl_3$ solutions, as has also been reported in the literature[7,8,23,38] for such compounds possessing benzyl protecting groups. For (4α)-**13** we observed rotational isomers in a 4:1 ratio. Rotamers were also observed for (4α)-**14** and (4α)-**15**, in 2:1 and 7:1 ratios, respectively (see Exp. Section).

Mass Spectrometry

The mass spectrometric characterization of the oligobenzyl ethers (4α)-**13**, (4α)-**14**, and (4α)-**15** was achieved with the aid of $NaBF_4$-assisted electrospray ionization (ESI+) combined with collision-induced dissociation (CID) in an ion trap. The sodium cation adducts formed particularly readily when sodium tetrafluoroborate was added to methanol/chloroform solutions of the samples; both the correct accurate masses and the appropriate isotope patterns of the quasi-molecular $[M + Na]^+$ ions were determined in each case by FT-ICR mass spectrometry.

The collision-induced fragmentation of the $[M + Na]^+$ ions deserves special mention and is the subject of further investigation.[39] Unlike the *protonated* $[M + H]^+$ quasi-molecular ions, which show rather complicated fragmentation behavior, the sodium-cationized oligobenzyl ethers decompose through two very clear-cut fragmentation pathways: 1) apparently synchronous and repeated loss of two benzyl units (182 u), which strongly predominates over the loss of single $C_7H_7^{\cdot}$ residues, and 2) retro-Diels–Alder (RDA) fragmentation occurring with remarkable regioselectivity at the benzoannelated pyran ring. These processes were found to occur throughout with both the monomeric and the coupled oligobenzyl ethers, but we restrict the discussion here largely to two coupling products – the isomeric oligobenzyl ethers (4α)-**13** and (4α)-**14** – that were found to be distinguishable by the RDA process.

The ESI(+)-CID mass spectra of the $[M + Na]^+$ ions of isomers (4α)-**13** and (4α)-**14** (*m*/*z* 1427, nominally) are illustrated in Figures 3 and 4. In both cases the dominant fragmentation is the loss of 182 u, giving rise to ions at *m*/*z* 1245 and corresponding to the elimination either of molecular $C_{14}H_{14}$ or of two benzyl radicals ($C_7H_7^{\cdot}$). The occurrence of a minor peak at *m*/*z* 1336 in the spectrum of (4α)-**13** points to the latter process (see below). Subsequent loss of another apparent $C_{14}H_{14}$ entity of 182 u from the $[(M - 2\ C_7H_7) + Na]^+$ ions leads in both cases to the fragment ions $[(M - 4\ C_7H_7) + Na]^+$ at *m*/*z* 1063. Even a third such process is observed in the case of (4α)-**14**; it may be speculated on whether the collisional activation was somewhat more energetic than in the case of (4α)-**13** or whether structural factors are relevant here.[40] The overall sequence observed for the [(4α)-**14** + Na]$^+$ ions is shown in Scheme 3 and a mechanism for the quasi-pairwise loss of two benzyl radicals is depicted in Scheme 4 for the case of ions [(4α)-**14** + Na]$^+$. The origins of the different relative rates of the two subsequent $C_7H_7^{\cdot}$ losses obviously lie in their quite different energy requirements. The formation of the open-shell fragments $\{[M - n\,C_7H_7]^{\cdot} + Na\}^+$ {*n* = 1, 3, 5, *m*/*z* 1336, *m*/*z* 1154 and *m*/*z* 972 in the case of [(4α)-**13** + Na]$^+$ and [(4α)-**14** + Na]$^+$ ions} is energetically unfavorable and slow, whereas the formation of the closed-shell sodiated quinone-

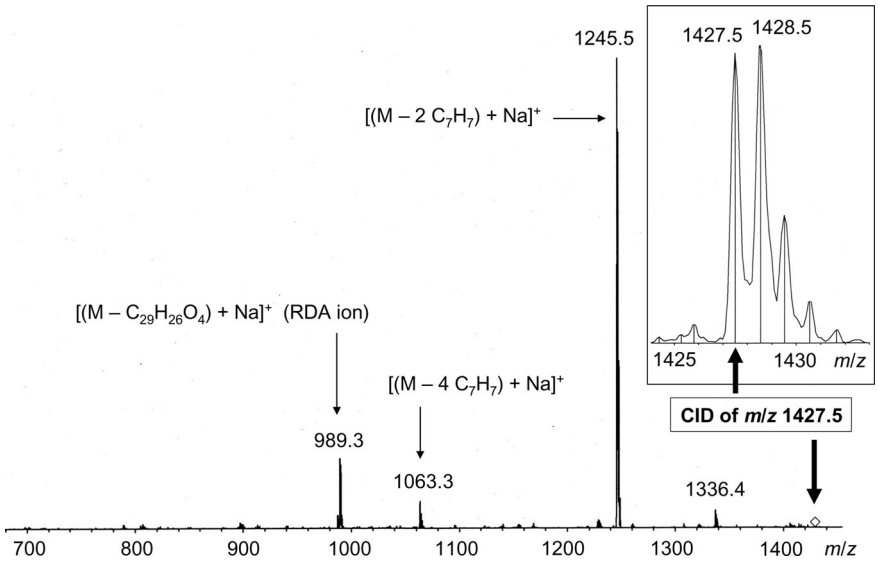


Figure 3. ESI(+)-CID mass spectrum of the $[M + Na]^+$ ions (*m*/*z* 1427) of the nonabenzyl ether (4α)-**13**. The inset shows the peak cluster of the quasi-molecular ions (*m*/*z* 1427–1431); CID was carried out on this peak cluster (arrows).

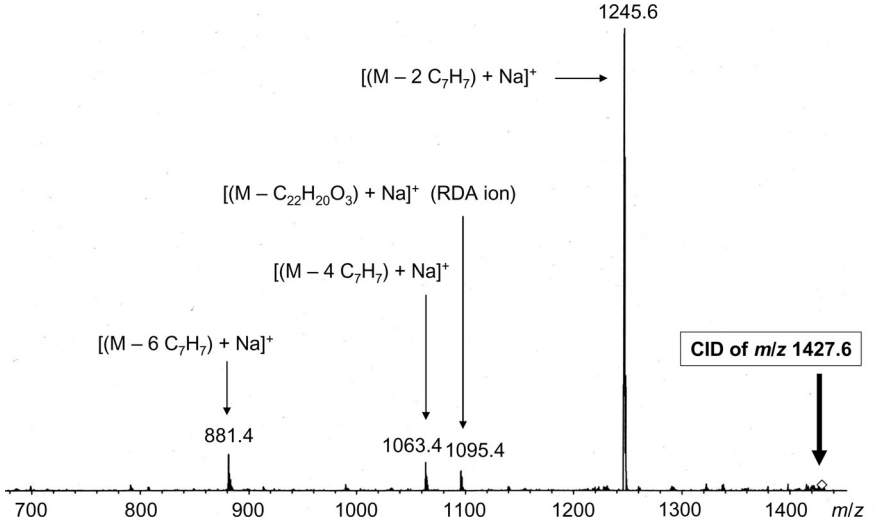
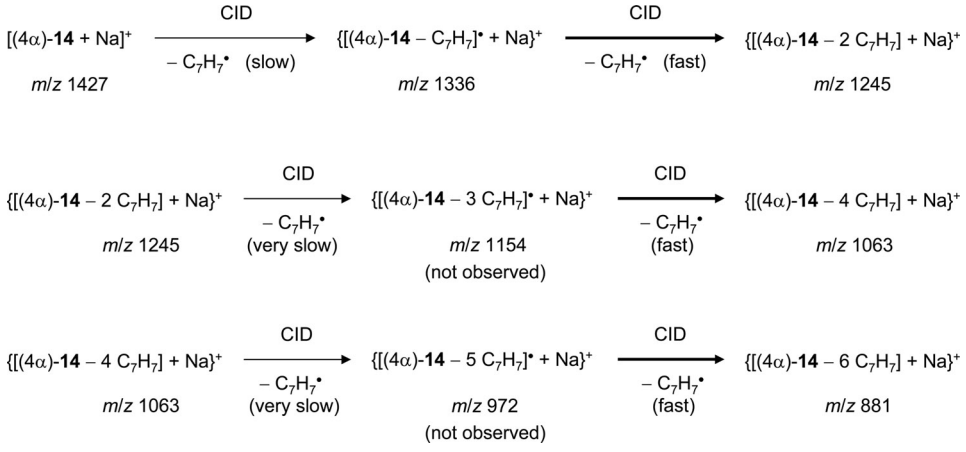
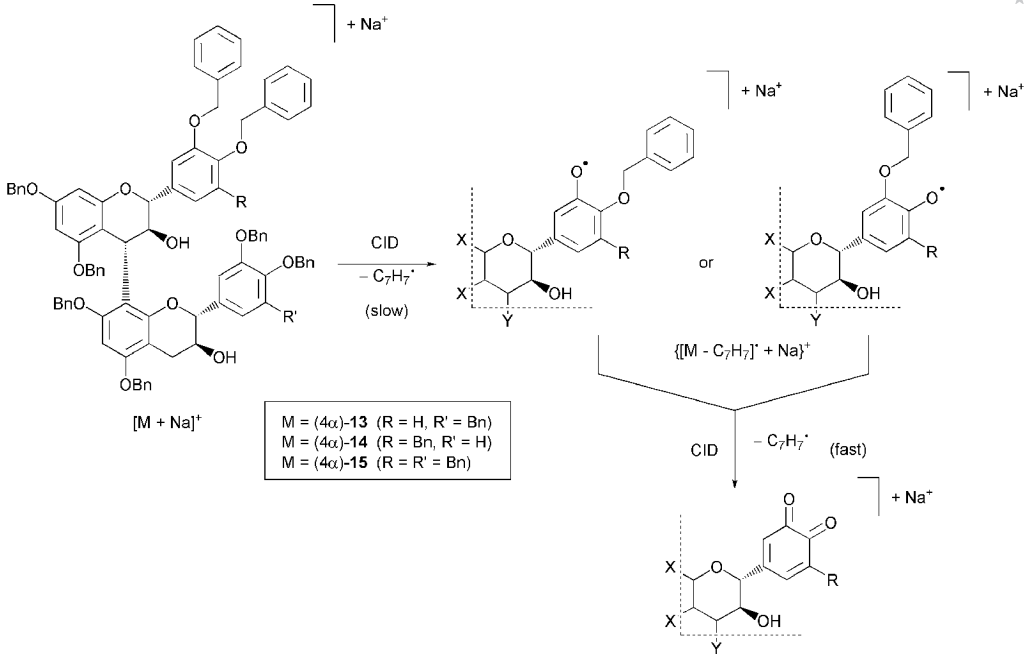


Figure 4. ESI(+)-CID mass spectrum of the $[M + Na]^+$ ions (*m*/*z* 1427) of the nonabenzyl ether (4α)-**14**.



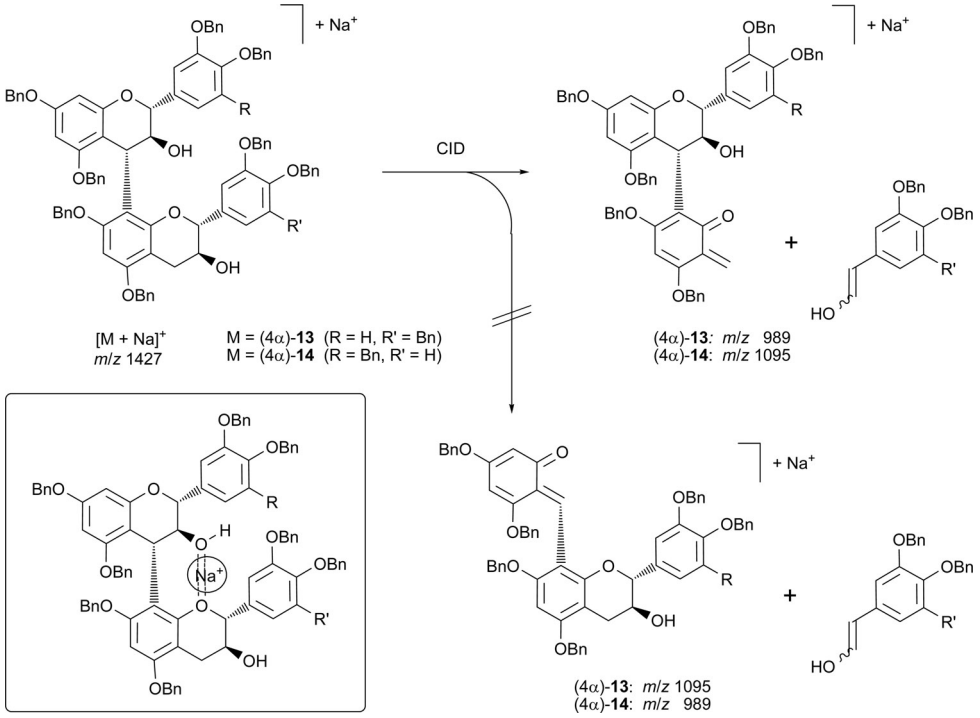
Scheme 3. Fragmentation of $[(4\alpha)$-**14** $+ Na]^+$ ions through consecutive losses of $C_7H_7^{\cdot}$ radicals.



Scheme 4. Proposed mechanism for the fragmentation of [(4α)-**13** + Na]$^+$, [(4α)-**14** + Na]$^+$, and [(4α)-**15** + Na]$^+$ ions through consecutive losses of $C_7H_7^•$ radicals. The starting site of the fragmentation is chosen arbitrarily; dashed lines indicate the backbone (X, X, Y) of the molecule.

type ions {[M – 2*n*C_7H_7] + Na}$^+$ (*n* = 1 and 2, *m*/*z* 1245 and *m*/*z* 1063, respectively) is favorable and relatively fast. However, it remains unclear why the loss of six benzyl radicals from ions [(4α)-**14** + Na]$^+$, giving rise to the fragment ions *m*/*z* 881, is also very fast, in spite of the lack of a third *ortho*-benzyloxybenzene unit.

Whereas the consecutive losses of $C_{14}H_{14}$ (or pairs of C_7H_7) units appear to be characteristic for both isomeric [(4α)-**13** + Na]$^+$ and [(4α)-**14** + Na]$^+$ ions, an independent fragmentation pathway that allows us to distinguish between the two isomers is open. In contrast to the [(4α)-**13** + Na]$^+$ ions, which expel 438 u corresponding to a $C_{29}H_{26}O_4$



Scheme 5. Specific fragmentation of the isomeric [(4α)-**13** + Na]$^+$ and [(4α)-**14** + Na]$^+$ ions through regioselective retro-Diels–Alder fragmentation. The insert illustrates a conceivably preferred coordination mode of the sodium cation.

molecule to give the characteristic fragment ions *m*/*z* 989, the $[(4\alpha)$-**14** + Na$]^+$ ions lose only 332 u, corresponding to a $C_{22}H_{20}O_3$ molecule. Undoubtedly, these fragmentations can be traced to retro-Diels–Alder processes occurring in the 3-hydroxychroman moieties. Ignoring possible tautomerization steps, we assume that 3,4,5-tri(benzyloxy)-2-hydroxystyrene is eliminated in the first case and 3,4-bis-(benzyloxy)-2-hydroxystyrene in the second, as depicted in Scheme 5.

One explanation for the occurrence of the regioselective retro-Diels–Alder process may be a favorable coordination mode of the sodium cation in the interior region of the bis(hydroxychroman) unit (see insert in Scheme 5). Although many other "tautomeric" $[M + Na]^+$ adducts might be formed prior to fragmentation, including species with dominating cation–π interactions,[41,42] the coordination between the 3-hydroxy and the 1′′-ether oxygen centers would be expected to be most efficient to stabilize the adduct ions. It appears reasonable to assume that in this "inner" adduct the release of the hydroxystyrene fragment from the hydroxy-coordinated chroman moiety is prevented, leaving the retro-Diels–Alder fragmentation of the other hydroxychroman unit as the only remaining pathway. Further investigations to unravel the intriguing and characteristic fragmentation behavior of sodium-cationized oligobenzyl ethers under the conditions of ESI-CID mass spectrometry are underway.[39,43,44]

Conclusions

In conclusion, the prodelphinidins[28,30] **13**–**15** with varying numbers of benzyloxy groups (two or three) on rings B and E or with three benzyloxy groups on both rings have been synthesized for the first time, through TMSOTf-catalyzed intermolecular condensations. The mass spectrometric characterization of these oligobenzyl ethers by ESI(+) techniques revealed that the $[M + Na]^+$ adduct ions undergo unexpected sequential losses of pairs of benzyl radicals as well as structure-specific, regioselective retro-Diels–Alder (RDA) reactions.

Experimental Section

General: TMSOTf-catalyzed intermolecular condensations were performed under argon. TLC was performed on precoated TLC plates (silica gel). Melting points were measured with a Gallenkamp apparatus and are not corrected. NMR spectra were recorded with a Bruker Avance 500 instrument at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C). Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as an internal standard. Upper case letters (A–F) designate the rings as shown in Scheme 2. Optical rotations were measured at 25 °C with a Perkin–Elmer Polarimeter 241. Mass spectra were recorded with a Finnigan MAT 8430 spectrometer in the electron impact mode at 70 eV and with chemical ionization, and are reported as *m*/*z* values and relative abundances. The infrared spectra were recorded with a Nicolet 510 P FT-IR spectrometer. The HPLC system used was: Summit (Dionex), pump: P 580 A (Dionex), detector: UVD 170S, autosampler: ASI 100 (Dionex), column oven: STH 585 (Dionex).

Mass Spectrometry: ESI mass spectra were recorded with an Esquire 3000 ion trap mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) fitted with a standard nanoESI source. Samples were introduced through self-made nanospray needles. Nitrogen, generated by a Bruker nitrogen generator (NGM 11), was used as a drying gas. Helium served as a cooling gas for the ion trap and collision gas for MS^n experiments. The spectra shown were recorded with the aid of Bruker Daltonik Esquire NT 5.2 Esquire Control software by accumulation and averaging of several single spectra. DataAnalysis™ 3.4 was used for spectra processing. Under similar ESI conditions, accurate masses were measured by use of a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer APEX III (Bruker Daltonik GmbH, Bremen, Germany) fitted with a 7.0 T, 160 mm bore superconducting magnet (Bruker Analytik GmbH – Magnetics, Karlsruhe, Germany) and an infinity cell, and interfaced to an external nanoESI source. Scan accumulation and Fourier transformation were performed with XMASS NT (7.08) on a PC workstation; for further data processing DataAnalysis™ 3.4 was used.

2,3-*trans*-5,7,3′,4′-Tetrakis(benzyloxy)flavan-3-ol (9): A stirred solution of (+)-catechin (**3**, 3.00 g, 10.33 mmol), benzyl chloride (6.62 g, 6.00 mL, 52.10 mmol), and K_2CO_3 (9.00 g, 65.1 mmol) in DMF (30 mL) was heated for 4 h at 120–130 °C (monitored by TLC). The mixture was poured into water (100 mL), and the resulting solution was extracted with ethyl acetate (250 mL) and dried with Na_2SO_4. Evaporation of the solvent gave a thick, brown oil, which was subjected to column chromatography on silica gel to provide pure (+)-3′,4′,5,7-tetra-*O*-benzylcatechin (**9**) as a white solid in 80% yield (5.30 g, 8.15 mmol); m.p. 121–122 °C (ref.[34] 116 °C). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.68 (dd, *J* = 16.4, 8.6 Hz,1 H, 4-H-α), 3.14 (dd, *J* = 16.4, 5.5 Hz, 1 H, 4-H-β), 4.03 (m, 1 H, 3-H), 4.65 (d, *J* = 8.3 Hz, 1 H, 2-H), 5.01 (s, 2 H, O*CH*$_2$Ph), 5.05 (s, 2 H, O*CH*$_2$Ph), 5.19 (s, 2 H, O*CH*$_2$Ph), 5.20 (s, 2 H, O*CH*$_2$Ph), 6.23 (d, *J* = 2.5 Hz, 1 H, 6-H), 6.29 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.98 (d, *J* = 8.5 Hz, 1 H, 5′-H), 7.01 (dd, *J* = 8.5, 2.1 Hz, 1 H, 6′-H), 7.05 (d, *J* = 2.1 Hz, 1 H, 2′-H), 7.28–7.48 (m, 20 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 27.6 (C-4), 68.2 (C-3), 69.9 (O*CH*$_2$Ph), 70.1 (O*CH*$_2$Ph), 71.2 (O*CH*$_2$Ph), 71.3 (O*CH*$_2$Ph), 81.5 (C-2), 93.85 (C-6), 94.4 (C-8), 102.3 (C-4a), 113.9 (C-2′), 115.0 (C-5′), 120.6 (C-6′), 127.1, 127.2, 127.4, 127.5, 127.8, 127.8, 127.9, 128.4, 128.5, 128.5 (C-Ar), 130.9 (C-1′), 136.8, 136.9, 137.0, 137.1 (C-Ar) 149.1 (C-3′), 149.3 (C-4′), 155.2 (C-8a), 157.7 (C-5), 157.8 (C-7) ppm.

2,3-*trans*-3,4-*cis*-4,5,7,3′,4′-Pentakis(benzyloxy)flavan-3-ol (11): DDQ (2 equiv., 140 mg, 0.61 mmol) was slowly added at 0 °C to a solution of tetra-*O*-benzylcatechin (**9**, 500 mg, 0.78 mmol) and benzyl alcohol (0.80 mL, 7.60 mmol) in CH_2Cl_2 (6 mL). After the system had been stirred overnight at room temperature, excess 4-(dimethylamino)pyridine (200 mg, 1.63 mmol) was added to the solution at 0 °C and the mixture was stirred for another 30 min. The resulting mixture was filtered, and the filtrate was washed with water (50 mL) and brine (20 mL) and dried with Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel column chromatography to give (2*S*,3*S*,4*S*)-4,5,7,3′,4′-pentabenzyloxyflavan-3-ol (**11**) as a white solid in 86% yield (514 mg, 0.67 mmol); m.p. 127–128 °C (ref.[8] 124–125 °C). $[\alpha]_D$ = +53.7 (*c* = 0.48, $CHCl_3$) [ref.[8] +56.4 (*c* = 0.48, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.90 (dt, *J* = 3.4, 9.7 Hz, 1 H, 3-H), 4.66 (d, *J* = 11.5 Hz, 1 H, O*CH*$_2$Ph), 4.78 (d, *J* = 11.5 Hz, 1 H, O*CH*$_2$Ph), 4.96 (d, *J* = 3.4 Hz, 1 H, 4-H), 4.98 (d, *J* = 9.7 Hz, 1 H, 2-H), 5.00 (d, *J* = 9.7 Hz, 1 H,

OCH_2Ph), 5.01 (d, J = 11.2 Hz, 1 H, OCH_2Ph), 5.05 (d, J = 11.2 Hz, 1 H, OCH_2Ph), 5.13 (s, 4 H, OCH_2Ph), 6.18 (d, J = 2.2 Hz, 1 H, 8-H), 6.28 (d, J = 2.2 Hz, 1 H, 6-H), 6.94 (d, J = 8.3 Hz, 1 H, 5′-H), 6.99 (dd, J = 2.0, 8.3 Hz, 1 H, 6′-H), 7.07 (d, J = 2.0 Hz, 1 H, 2′-H), 7.18–7.45 (m, 25 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 67.8 (C-4), 69.8 (OCH_2Ph), 70.9 (OCH_2Ph), 71.3 (C-3), 71.5 (OCH_2Ph), 71.4 (OCH_2Ph), 71.7 (OCH_2Ph), 81.5 (C-2), 93.85 (C-6), 94.4 (C-8), 102.3 (C-4a), 113.9 (C-2′), 115.0 (C-5′), 120.6 (C-6′), 127.1, 127.2, 127.4, 127.5, 127.8, 127.8, 127.9, 128.4, 128.5, 128.5 (C-Ar), 130.9 (C-1′), 136.8, 136.9, 137.0, 137.1 (C-Ar) 149.1 (C-3′), 149.3 (C-4′), 155.2 (C-8a), 157.7 (C-5), 157.8 (C-7) ppm. MS (EI, 70 eV): m/z (%) = 156 (44) $[M]^{+\cdot}$, 756.1 (4), 648 (30), 620 (12), 557 (15), 529 (28), 332 (19), 256 (22), 211 (19), 181 (62), 108.1 (100).

2,3-*trans*-5,7,3′,4′,5′-Pentakis(benzyloxy)flavan-3-ol (10): Triphenylphosphane (15 mg, 0.057 mmol) was added to a solution of triol **8** (30 mg, 0.038 mmol) in anhydrous THF (2 mL). The mixture was stirred for 10 min and diethyl azodicarboxylate (0.01 mL, 0.057 mmol) was then added dropwise. After stirring for 2.5 h at room temperature, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a white residue. The obtained residue was purified by silica gel column chromatography to afford 2,3-*trans*-5,7,3′,4′,5′-pentakis(benzyloxy)flavan-3-ol (**10**) as a white solid in 71% yield (26 mg, 0.033 mmol); m.p. 116–118 °C.[24] $[\alpha]_D$ = –8.96 (c = 1.0, $CHCl_3$), ref.[33] –7.21 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.76 (br. s, 1 H, 3-OH), 2.75 (dd, J = 16.5, 9.0 Hz, 1 H, 4-H_a), 3.15 (dd, J = 16.5, 6.0 Hz, 1 H, 4-H_b), 4.01 (ddd, J = 9.0, 8.1, 6.0 Hz, 1 H, 3-H), 4.65 (d, J = 8.1 Hz, 1 H, 2-H), 5.04 (s, 2 H, OCH_2Ph), 5.07 (s, 2 H, OCH_2Ph), 5.10 (s, 2 H, OCH_2Ph), 5.11 (s, 2 H, OCH_2Ph), 5.14 (s, 2 H, OCH_2Ph), 6.29 (d, J = 2.4 Hz, 1 H, 8-H), 6.34 (d, J = 2.4 Hz, 1 H, 6-H), 6.78 (s, 2 H, 2′-H, 6′-H), 7.30–7.55 (m, 25 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 27.9 (C-4), 68.5 (C-3), 70.2 (OCH_2Ph), 70.4 (OCH_2Ph), 71.4 (OCH_2Ph), 82.1 (C-2), 94.2 (C-8), 94.6 (C-6), 102.6 (C-4a), 106.9 (C-2′, C-6′), 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.0, 133.6, 137.1, 137.2, 138.0, 138.9 (Ar), 153.1 (C-4′), 153.3 (C-3′, C-5′), 155.4 (C-5), 158.0 (C-8a), 159.1 (C-7) ppm. IR (film): $\tilde{\nu}$ = 3550, 3029, 1592, 1536, 1374, 1295, 1116, 773 cm^{-1}. MS (EI): m/z (%) = 756 (1) $[M]^{+\cdot}$, 725 (1), 665 (3), 575 (1), 528 (1), 463 (1), 433 (4), 319 (10), 306 (7), 215 (2), 181 (25), 91 (100), 44 (8). HRMS calcd. for $C_{50}H_{44}O_7$ $[M]^{+\cdot}$ 756.30872; found 756.30645.

2,3-*trans*-3,4-*cis*-4,5,7,3′,4′5′-Hexakis(benzyloxy)flavan-3-ol (12): DDQ (2 equiv., 60 mg, 0.26 mmol) was slowly added at 0 °C to a solution of tetra-*O*-benzylcatechin (**10**, 100 mg, 0.132 mmol) and benzyl alcohol (0.10 mL, 0.96 mmol) in CH_2Cl_2 (5 mL). After the system had been stirred overnight at room temperature, excess 4-(dimethylamino)pyridine (40 mg, 0.32 mmol) was added at 0 °C and the mixture was stirred for another 30 min. The resulting mixture was filtered, and the filtrate was washed with water (50 mL) and brine (20 mL) and dried with Na_2SO_4. After filtration the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel column chromatography to give 2,3-*trans*-3,4-*cis*-4,5,7,3′,4′5′-hexakis(benzyloxy)flavan-3-ol (**12**) as a white foam in 85% yield (96 mg, 0.111 mmol); m.p. 121–123 °C. $[\alpha]_D$ = +53.25 (c = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.93 (m, 1 H, 3-H), 4.22 (d, J = 8.1 Hz, 1 H, 4-H), 4.68 (d, J = 11.4 Hz, 1 H, OCH_2Ph), 4.77 (d, J = 11.4 Hz, 1 H, OCH_2Ph), 4.94 (d, J = 3.4 Hz, 1 H, 4-H), 4.97 (d, J = 9.6 Hz, 1 H, 2-H), 5.00 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 5.01 (d, J = 11.2 Hz, 1 H, OCH_2Ph), 5.05 (d, J = 11.2 Hz, 1 H, OCH_2Ph), 5.13 (s, 4 H, OCH_2Ph), 6.22 (d, J = 2.2 Hz, 1 H, 8-H), 6.31 (d, J = 2.2 Hz, 1 H, 6-H), 6.84 (d, J = 2.1 Hz, 2 H, 2′,6′-H), 7.20–7.48 (m, 30 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 68.9 (C-4), 70.5 (C-3), 70.63 (OCH_2Ph), 70.66 (OCH_2Ph), 71.1 (OCH_2Ph), 71.3 (OCH_2Ph), 72.5 (OCH_2Ph), 75.2 (OCH_2Ph), 77.2 (C-2), 93.5 (C-6), 94.5 (C-8), 106.9 (C-2′), 107 (C-6′), 115.0 (C-5′), 127.5, 127.5, 127.7, 127.8, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.6, 133.9, 136.3, 136.6, 137.1, 137.9, 138.9 (C-Ar), 138.9 (C-4′), 152.3 (C-5′), 156.2 (C-3′), 158.7 (C-5), 161.0 (C-7) ppm. MS (EI): m/z (%) = 862 (2) $[M]^{+\cdot}$, 846 (4), 754 (1), 663 (5), 614 (3), 523 (1), 505 (7), 396 (12), 361 (3), 265 (2), 193 (10), 181 (23), 108 (96), 91 (100), 44 (3). HRMS calcd. for $C_{57}H_{50}O_8$ $[M]^{+\cdot}$ 862.35057; found 862.35093.

Catechin-(4α→8)-Gallocatechin [(4α)-13]: 2,3-*trans*-5,7,3′,4′,5′-Pentakis(benzyloxy)flavan-3-ol (**10**, 150 mg, 0.198 mmol, 3 equiv.) and 2,3-*trans*-3,4-*cis*-4,5,7,3′,4′-pentakis(benzyloxy)flavan-3-ol (**11**, 50 mg, 0.066 mmol) were dissolved in CH_2Cl_2 (20 mL) and TMSOTf (0.5 M solution in CH_2Cl_2, 0.2 mL) was added dropwise at –78 °C. After stirring for 5 min at 0 °C, the reaction mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate (1 mL). The aqueous solution was extracted with chloroform (15 mL) and the organic phase was washed with water (10 mL) and brine (10 mL) and dried with Na_2SO_4. After filtration, the organic phase was concentrated on a rotary evaporator. A mixture of diastereomers was obtained in 97% yield and was purified by preparative silica gel TLC (Macherey–Nagel, 1.0 mm, CH_2Cl_2/EtOAc 100:0.5, 4 developments) to afford a thick, pale yellow oil. $[\alpha]_D$ = –86.66 (c = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 4:1 mixture of rotational isomers.

Major Isomer: δ = 1.35–1.67 (m, 2 H, OH), 2.36 (dd, J = 9.3, 16.2 Hz, 1 H, 4F-H-β), 3.05 (dd, J = 5.2, 16.2 Hz, 1 H, 4F-H-α), 3.60 (d, J = 8.0 Hz, 1 H, 2F-H), 3.63–3.71 (m, 1 H, 3F-H), 4.26 (dd, J = 8.0, 9.8 Hz, 1 H, 3C-H), 4.50 (d, J = 9.8 Hz, 1 H, 4C-H), 4.55 (d, J = 10.7 Hz, 2 H, OCH_2Ph), 4.67 (d, J = 8.8 Hz, 1 H, 2C-H), 4.69–4.74 (m, 2 H, OCH_2Ph), 4.79–4.83 (m, 2 H, OCH_2Ph), 4.86–5.13 (m, 12 H, OCH_2Ph), 6.10 (d, J = 2.2 Hz, 1 H, 6A-H), 6.18 (d, J = 2.2 Hz, 1 H, 8A-H), 6.23 (s, 1 H, 6D-H), 6.68 (dd, J = 2.0, 8.7 Hz, 1 H, 6B-H), 6.84–6.94 (m, 7 H, Ar-H), 6.96–7.00 (m, 2 H, 2B-H, 6B-H), 7.11–7.15 (m, 2 H, 2E-H, 6E-H), 7.27–7.48 (m, 38 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 27.88 (4F-CH_2), 37.14 (4C-CH), 68.50 (3F-CH-OH), 69.87 (OCH_2Ph), 70.00 (OCH_2Ph), 70.04 (OCH_2Ph), 70.38 (OCH_2Ph), 71.17 (OCH_2Ph), 71.23 (OCH_2Ph), 71.39 (OCH_2Ph), 71.48 (OCH_2Ph), 73.36 (3C-CH),75.24 (OCH_2Ph), 80.62 (2C-CH), 82.19 (2F-CH), 91.51, 94.21, 94.96, 102.28, 106.54, 108.72, 112.03, 113.60, 114.88, 115.99, 121.30, 127.08 (×2), 127.12, 127.23, 127.47, 127.51, 127.56, 127.62, 127.68, 127.75, 127.80, 127.87, 128.09, 128.15, 128.17, 128.27 (×2), 128.32, 128.36, 128.38, 128.44, 128.46, 128.54, 128.59, 131.75, 134.19, 136.71, 136.97, 137.06, 137.13, 137.18, 137.29, 137.32, 137.70, 137.95, 138.44, 149.14, 149.32, 152.83, 153.59, 155.60, 158.02 ppm. MS [ESI(+), $CHCl_3$/MeOH, $NaBF_4$]: m/z (%) = 1427.5 (96) $[M + Na]^+$, 1428.5 (100) $[(^{13}C_1)\text{-}M + Na]^+$, 1429.5 (44) $[(^{13}C_2)\text{-}M + Na]^+$, 1430.6 (14) $[(^{13}C_3)\text{-}M + Na]^+$, 1431.6 (4), $[(^{13}C_4)\text{-}M + Na]^+$. HRMS calcd. for $C_{93}H_{80}O_{13}Na$ 1427.54911; found 1427.54905.

Minor Isomer: δ = 1.35–1.67 (m, 0.50 H, OH), 2.64 (dd, J = 9.3, 16.2 Hz, 0.25 H, 4F-H-β), 3.23 (dd, J = 5.2, 16.2 Hz, 0.25 H, 4F-H-α), 4.39 (d, J = 8.0 Hz, 0.25 H, 2F-H), 3.63–3.71 (m, 0.25 H, 3F-H), 4.15 (dd, J = 8.0, 9.8 Hz, 0.25 H, 3C-H), 4.53 (d, J = 9.8 Hz, 0.25 H, 4C-H), 4.65–4.74 (m, 0.50 H, OCH_2Ph), 4.77 (d, J = 8.8 Hz, 0.25 H, 2C-H), 4.69–4.83 (m, 1.5 H, OCH_2Ph), 4.85–5.14 (m, 3 H, OCH_2Ph), 5.92 (d, J = 2.2 Hz, 0.25 H, 6A-H), 6.16 (d, J

= 2.2 Hz, 0.25 H, 8A-H), 6.35 (s, 0.25 H, 6D-H), 6.99 (dd, *J* = 2.0, 8.7 Hz, 0.25 H, 6B-H), 6.84–6.94 (m, 1.75 H, Ar-H), 7.10–7.23 (m, 0.5 H, 2B-H, 6B-H), 7.27–7.47 (m, 10 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 29.69 (4F-CH_2), 37.19 (4C-CH), 68.50 (3F-CH-OH), 70.00 (OCH_2Ph), 70.15 (OCH_2Ph), 70.42 (OCH_2Ph), 71.22 (OCH_2Ph), 71.29 (OCH_2Ph), 71.33 (OCH_2Ph), 71.48 (OCH_2Ph), 71.49 (OCH_2Ph), 73.80 (3C-CH), 75.21 (OCH_2Ph), 80.63 (2C-CH), 82.22 (2F-CH), 91.54, 94.17, 94.99, 102.28, 106.58, 107.61, 108.71, 112.00, 113.59, 114.92, 115.97, 121.29, 127.12 (×2), 127.23, 127.47, 127.51, 127.56, 127.62 (×2), 127.68, 127.75, 127.80, 127.91, 128.09, 128.15, 128.17, 128.27 (×3), 128.32, 128.36, 128.38, 128.44, 128.46, 128.54, 128.59, 131.79, 134.25, 136.68, 136.99, 137.07, 137.14, 137.20, 137.29, 137.32, 137.72, 137.99, 138.51, 149.17, 149.35, 152.82, 153.50, 155.66, 158.02 ppm.

Gallocatechin-(4α→8)-catechin [(4α)-14]: 2,3-*trans*-5,7,3′,4′-Tetrakis(benzyloxy)flavan-3-ol (**9**, 90 mg, 0.139 mmol, 3 equiv.) and 2,3-*trans*-3,4-*cis*-5,7,3′,4′,5′-hexakis(benzyloxy)flavan-3-ol (**12**, 40 mg, 0.046 mmol) were dissolved in CH_2Cl_2 (20 mL), and TMSOTf (0.5 M solution in CH_2Cl_2, 0.2 mL) was added dropwise at –78 °C. After stirring for 5 min at 0 °C, the reaction mixture was quenched by addition of saturated sodium hydrogen carbonate (1 mL). The aqueous solution was extracted with chloroform (15 mL) and the organic phase was washed with water (10 mL) and brine (10 mL) and dried with Na_2SO_4. After filtration of the organic phase it was concentrated on a rotary evaporator. A mixture of diastereomers was obtained in 98% yield and purified by preparative silica gel TLC (Macherey–Nagel, 1.0 mm, CH_2Cl_2/EtOAc 100:0.5, 4 developments) as a thick, pale yellow oil. $[\alpha]_D$ = –92.97 (*c* = 0.32, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 2:1 mixture of rotational isomers.

Major Isomer: δ = 1.28–1.61 (m, 2 H, OH), 2.39 (dd, *J* = 9.1, 16.2 Hz, 1 H, 4F-H-β), 3.03 (dd, *J* = 5.7, 16.2 Hz, 1 H, 4F-H-α), 3.61 (d, *J* = 8.5 Hz, 1 H, 2F-H), 3.63–3.75 (m, 1 H, 3F-H), 4.21 (dd, *J* = 8.6, 9.3 Hz, 1 H, 3C-H), 4.48 (d, *J* = 9.3 Hz, 1 H, 4C-H), 4.56 (d, *J* = 11.3 Hz, 2 H, OCH_2Ph), 4.67 (d, *J* = 8.6 Hz, 1 H, 2C-H), 4.68–4.75 (m, 2 H, OCH_2Ph), 4.80–4.89 (m, 2 H, OCH_2Ph), 4.90–5.16 (m, 12 H, OCH_2Ph), 6.13 (d, *J* = 2.4 Hz, 1 H, 6A-H), 6.18 (d, *J* = 2.4 Hz, 1 H, 8A-H), 6.25 (s, 1 H, 6D-H), 6.81 (dd, *J* = 1.9, 8.2 Hz, 1 H, 6E-H), 6.96 (d, *J* = 1.9 Hz, 1 H, 6B-H), 6.84–6.94 (m, 7 H, Ar-H), 7.19–7.25 (m, 2 H, Ar-H), 7.25–7.47 (m, 38 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 31.22 (4F-CH_2), 37.13 (4C-CH), 68.36 (3F-CH-OH), 69.88 (OCH_2Ph), 69.93 (OCH_2Ph), 70.16 (OCH_2Ph), 70.94 (OCH_2Ph), 71.03 (OCH_2Ph), 71.17 (OCH_2Ph), 71.25 (OCH_2Ph), 71.68 (OCH_2Ph), 73.26 (3C-CH), 77.57 (OCH_2Ph), 80.67 (2C-CH), 82.08 (2F-CH), 91.55, 94.30, 94.95, 102.61, 106.93, 112.01, 113.94, 114.01, 114.37, 114.92, 120.19, 120.65, 127.05 (×2), 127.13 (×3), 127.25, 127.42, 127.51, 127.58, 127.68, 127.80, 127.82, 127.89, 127.90, 128.07, 128.09, 128.17, 128.18, 128.25, 128.32, 128.36, 128.38, 128.43 (×2), 128.49, 128.55, 128.60, 130.85, 131.55, 134.16, 136.68, 137.02, 137.11, 137.20, 137.28, 137.95 (×2), 138.69, 148.99, 149.11, 152.81, 152.90, 153.98, 153.99, 155.55 (×2), 155.60, 156.68, 157.61, 158.05 ppm. MS [ESI(+), $CHCl_3$/MeOH, $NaBF_4$]: *m*/*z* (%) = 1427.5 (94) [M + Na]$^+$, 1428.6 (100) [($^{13}C_1$)-M + Na]$^+$, 1429.6 (49) [($^{13}C_2$)-M + Na]$^+$, 1430.6 (16) [($^{13}C_3$)-M + Na]$^+$, 1431.6 (3) [($^{13}C_4$)-M + Na]$^+$. HRMS calcd. for $C_{93}H_{80}O_{13}Na$ 1427.54911; found 1427.54954.

Minor Isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.35–1.70 (m, 1 H, OH), 2.64 (dd, *J* = 9.1, 16.2 Hz, 0.50 H, 4F-H-β), 3.17 (dd, *J* = 5.7, 16.2 Hz, 0.50 H, 4F-H-α), 3.63–3.75 (m, 0.50 H, 3F-H), 4.18 (d, *J* = 8.5 Hz, 0.50 H, 2F-H), 4.46 (dd, *J* = 8.6, 9.3 Hz, 0.50 H, 3C-H), 4.51 (d, *J* = 9.3 Hz, 0.50 H, 4C-H), 4.68–4.77 (m, 1 H, OCH_2Ph), 4.79 (d, *J* = 8.6 Hz, 0.50 H, 2C-H), 4.85–5.14 (m, 8 H, OCH_2Ph), 6.05 (d, *J* = 2.4 Hz, 0.50 H, 6A-H), 6.09 (d, *J* = 2.4 Hz, 0.50 H, 8A-H), 6.35 (s, 0.50 H, 6D-H), 6.48 (dd, *J* = 1.9, 8.2 Hz, 0.50 H, 6E-H), 6.56 (d, *J* = 1.9 Hz, 0.50 H, 6B-H), 7.12–7.16 (m, 3.50 H, Ar-H), 7.27–7.47 (m, 20 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 33.55 (4F-CH_2), 37.22 (4C-CH), 68.56 (3F-CH-OH), 69.91 (OCH_2Ph), 70.01 (OCH_2Ph), 70.35 (OCH_2Ph), 71.06 (OCH_2Ph), 71.20 (OCH_2Ph), 71.30 (OCH_2Ph), 71.34 (OCH_2Ph), 71.69 (OCH_2Ph), 73.37 (3C-CH), 77.58 (OCH_2Ph), 80.68 (2C-CH), 82.35 (2F-CH), 91.93, 94.31, 94.95, 103.34, 107.21, 112.02, 113.96, 114.01, 114.93, 120.20, 120.65, 127.05, 127.10 (×2), 127.13, 127.22 (×3), 127.25, 127.26, 127.42, 127.46, 127.52, 127.54, 127.58, 127.69, 127.80, 127.83, 127.89, 127.91, 128.07, 128.09, 128.17, 128.18, 128.25, 128.33, 128.36, 128.38, 128.44, 128.49, 128.56, 128.60, 130.85, 131.65, 134.16, 136.68, 137.03, 137.11, 137.21, 137.28, 137.95 (×2), 138.69, 148.99, 149.11, 152.81, 152.90, 153.99, 155.55 (×2), 155.61, 156.68, 157.77, 158.07 ppm.

Gallocatechin-(4α→8)-gallocatechin [(4α)-15]: 2,3-*trans*-5,7,3′,4′,5′-Pentakis(benzyloxy)flavan-3-ol (**10**, 105 mg, 0.139 mmol, 3 equiv.) and 2,3-*trans*-3,4-*cis*-4,5,7,3′,4′,5′-hexakis(benzyloxy)flavan-3-ol (**12**, 40 mg, 0.046 mmol) were dissolved in CH_2Cl_2 (20 mL). TMSOTf (0.5 M solution in CH_2Cl_2, 0.2 mL) was added dropwise to this solution at –78 °C. After stirring for 5 min at 0 °C, the reaction mixture was quenched by addition of saturated sodium hydrogen carbonate solution (1 mL). The aqueous solution was extracted with chloroform (15 mL) and the organic phase was washed with water (10 mL) and brine (10 mL) and dried with Na_2SO_4. After filtration the organic phase was concentrated on a rotary evaporator. A mixture of diastereomers was obtained in 87% yield and purified by preparative silica gel TLC (Macherey–Nagel, 1.0 mm, CH_2Cl_2/EtOAc 100:0.5, 4 developments) as a thick, pale yellow oil. $[\alpha]_D$ = –83.75 (*c* = 0.26, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7:1 mixture of rotational isomers.

Major Isomer: δ = 1.30–1.42 (m, 2 H, OH), 2.38 (dd, *J* = 9.2, 16.2 Hz, 1 H, 4F-H-β), 3.03 (dd, *J* = 5.6, 16.2 Hz, 1 H, 4F-H-α), 3.59 (d, *J* = 8.4 Hz, 1 H, 2F-H), 3.62–3.73 (m, 1 H, 3F-H), 4.21 (d, *J* = 9.0 Hz, 1 H, 4C-H), 4.53 (dd, *J* = 8.7, 9.0 Hz, 1 H, 3C-H), 4.66–4.72 (m, 3 H, OCH_2Ph), 4.73 (d, *J* = 8.7 Hz, 1 H, 2C-H), 4.77–4.86 (m, 3 H, OCH_2Ph), 4.90–4.97 (m, 4 H, OCH_2Ph), 4.99–5.13 (m, 8 H, OCH_2Ph), 6.13 (d, *J* = 2.3 Hz, 1 H, 6A-H), 6.19 (d, *J* = 2.3 Hz, 1 H, 8A-H), 6.25 (s, 1 H, 6D-H), 6.85–6.88 (m, 4 H, Ar-H), 7.18–7.47 (m, 38 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 32.17 (4F-CH_2), 37.08 (4C-CH), 68.13 (3F-CH-OH), 69.71 (OCH_2Ph), 70.03 (OCH_2Ph), 70.17 (OCH_2Ph), 70.37 (OCH_2Ph), 71.09 (OCH_2Ph), 71.37 (OCH_2Ph), 71.87 (OCH_2Ph), 73.34 (3C-CH), 75.15 (OCH_2Ph), 75.22 (OCH_2Ph), 80.65 (2C-CH), 82.44 (2F-CH), 91.51, 94.34, 102.39, 103.05, 106.64, 107.06, 112.37, 113.73, 114.05, 114.57, 120.10, 120.65, 127.05, 127.11 (×2), 127.45, 127.49, 127.68, 127.76, 127.81 (×2), 127.82, 127.89, 127.93, 128.08 (×3), 128.15, 128.18, 128.30, 128.35, 128.39, 128.45, 128.51, 128.55 (×2), 128.60, 128.61, 130.95, 131.63, 134.23, 136.68, 136.69, 136.95, 137.00, 137.11, 137.21, 137.28, 137.95 (×2), 138.69, 148.99, 152.60, 152.81, 152.98, 153.21, 153.47, 155.43 (×2), 155.57, 156.10, 157.23, 158.09 ppm. MS [ESI(+), $CHCl_3$/MeOH, $NaBF_4$]: *m*/*z* (%) = 1533.7 (68) [M + Na]$^+$, 1534.6 (100) [($^{13}C_1$)-M + Na]$^+$, 1535.6 (50) [($^{13}C_2$)-M + Na]$^+$, 1536.6 (15) [($^{13}C_3$)-M + Na]$^+$, 1537.6 (5) [($^{13}C_4$)-M + Na]$^+$. HRMS calcd. for $C_{100}H_{86}O_{14}Na$ 1533.59089; found 1533.58914.

Minor Isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.30–1.42 (m, 0.28 H, OH), 2.65 (dd, *J* = 9.2, 16.2 Hz, 0.14 H, 4F-H-β), 3.22

(dd, J = 5.6, 16.2 Hz, 0.14 H, 4F-H-α), 4.42 (d, J = 8.4 Hz, 0.14 H, 2F-H), 3.62–3.73 (m, 0.14 H, 3F-H), 4.14 (d, J = 9.0 Hz, 0.5 H, 4C-H), 4.53 (dd, J = 8.7, 9.0 Hz, 0.14 H, 3C-H), 4.66–4.74 (m, 0.28 H, OCH_2Ph), 4.78 (d, J = 8.7 Hz, 0.14 H, 2C-H), 4.81–4.88 (m, 0.42 H, OCH_2Ph), 4.90–5.13 (m, 1.14 H, OCH_2Ph), 5.96 (d, J = 2.3 Hz, 0.14 H, 6A-H), 6.18 (d, J = 2.3 Hz, 0.14 H, 8A-H), 6.30 (s, 0.14 H, 6D-H), 6.87–6.93 (m, 0.56 H, Ar-H), 7.18–7.47 (m, 5.42 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 33.81 (4F-CH_2), 37.32 (4C-CH), 68.36 (3F-CH-OH), 70.01 (OCH_2Ph), 70.06 (OCH_2Ph), 70.23 (OCH_2Ph), 71.04 (OCH_2Ph), 71.20 (OCH_2Ph), 71.37 (OCH_2Ph), 71.92 (OCH_2Ph), 73.37 (3C-CH), 75.16 (OCH_2Ph), 75.22 (OCH_2Ph), 80.67 (2C-CH), 82.47 (2F-CH), 91.54, 94.36, 102.43, 103.10, 106.65, 107.06, 107.11, 112.37, 113.73, 114.11, 114.82, 120.10, 120.65, 127.05, 127.13 (×2), 127.45, 127.50, 127.68, 127.76, 127.81 (×2), 127.82, 127.90, 127.93, 128.14 (×3), 128.09, 128.15, 128.19, 128.30, 128.36, 128.39, 128.47, 128.51, 128.56 (×2), 128.60, 128.61, 130.95, 131.63, 134.23, 136.68, 136.69, 136.95, 137.03, 137.11, 137.21, 137.28, 137.95 (×2), 138.69, 149.11, 152.71, 152.90, 152.98, 153.27, 153.71, 155.43 (×2), 155.93, 156.17, 157.23, 158.31 ppm.

HPLC Measurement Conditions for Compounds (4α)-13 to (4α)-15: Compounds (4α)-**13** to (4α)-**15** were tested with a variety of different HPLC columns and elution systems to check their enantiomeric purities. In no case could any splitting of the compound signal into peaks for enantiomers be detected. The following conditions were used:

1) Column: EC 250 × 4.6 mm NUCLEOCEL Alpha S, eluent: *n*-heptane/propan-2-ol (80:20), flow rate: 0.5 mL min^{-1}, temperature: 25 °C, detection: UV, 230 and 254 nm, pressure: 50 bar, injection volume: 5 μL. Retention time (4α)-**13**: 11.15 min and (4α)-**15**: 41.54 min (see Supporting Material for examples of HPLC elution profiles).

2) Column: EC 250 × 4.6 mm NUCLEOCEL Alpha RP-S, eluent: acetonitrile/water (50:50), flow rate: 0.5 mL min^{-1}, temperature: 25 °C, detection: UV, 230 and 254 nm, pressure: 100 bar, injection volume: 5 μL.

3) Column: EC 250 × 4.6 mm NUCLEOCEL Delta S, eluent: *n*-heptane/propan-2-ol (80:20), flow rate: 0.5 mL min^{-1}, temperature: 25 °C, detection: UV, 230 and 254 nm. pressure: 30 bar, injection volume: 5 μL.

4) Column: EC 250 × 4.6 mm NUCLEOCEL Delta RP-S, eluent: acetonitrile/water (50:50), flow rate: 0.5 mL min^{-1}, temperature: 25 °C, detection: UV, 230 and 254 nm, pressure: 70 bar, injection volume: 5 μL.

5) Column: EC 250 × 4.0 mm NUCLEOSIL Chiral 2, eluent: *n*-heptane/propan-2-ol/TFA (95: 5:0.05 v/v), flow rate: 0.8 mL min^{-1}, temperature: 25 °C, detection: UV, 230 and 254 nm, pressure: 80 bar, injection volume: 5 μL.

Supporting Information (see also the footnote on the first page of this article): HPLC chromatograms for compound (4α)-**13** (Figure S1) and (4α)-**15** (Figure S2) under separation conditions 1.

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Received: January 15, 2010
Published Online: March 23, 2010

