Buffer-induced, selective mono-C-alkylation of phloroglucinol: application to the synthesis of an advanced intermediate of catechin

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Abstract—A straightforward mono-selective and C-specific alkylation of phloroglucinol with activated alkyl halides is presented. The use of water as solvent limits the amount of over-alkylated by-products. Provided some minor changes in the experimental conditions, hydrophobic cinnamyl halides can also be reacted, thus giving a direct access to advanced intermediates of natural flavonoids.

1. Introduction

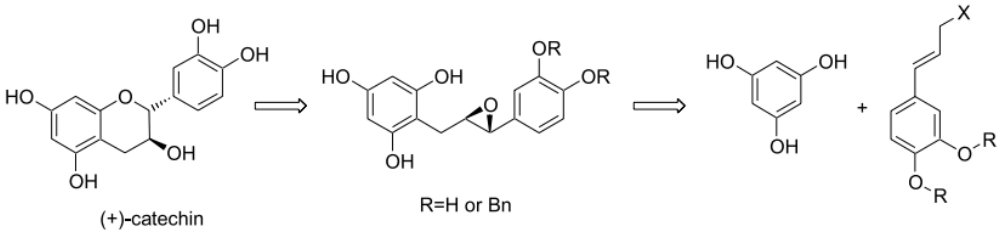
The flavonoids are a family of polyphenolic compounds found in the plant kingdom. They feature interesting antioxidative properties responsible for the health-benefits associated with a diet rich in vegetables and are found in large quantities in red wines and green teas.[1] However, due to the lack of reliable chemical methods for their synthesis, only natural extracts with ill-defined chemical compositions are usually evaluated for their biological activity. Undoubtedly, the poor overall stability of flavonoids is responsible for the lack of general methods for their chemical synthesis. Consequently, protecting-group free syntheses of polyphenols are scarce. The target molecules cannot often withstand the conditions required for removal of most of the conventional protecting groups. To the best of our knowledge, only benzyl derivatives have been used successfully as protecting groups in the total synthesis of natural flavonoids.[2] The phloroglucinol motif (1,3,5-benzenetriol) is ubiquitous in all natural flavonoids structures. As such, it constitutes the ultimate starting material en route to the synthesis of elaborated (un)natural polyphenols. Unfortunately, the benzylation of phloroglucinol is not selective and gives a mixture of both O- and C-benzylated products.[3] Hence, many efforts have been aimed at methods to achieve the specific mono-, di-, or tri-O-benzylation of phloroglucinol.[4] These methods are multi-step and require careful control of the reaction conditions. Most interestingly, the selective C-alkylation of phloroglucinol has never been reported, the only examples found in the literature concerning reactions with protected versions of phloroglucinol.[5] Though apparently simple, this transformation offers several synthetic challenges. As phloroglucinol contains six nucleophilic sites, an ideal reaction will be mono- and C-specific. Undoubtedly, such a reaction would constitute an easy and straightforward approach toward the synthesis of natural unprotected flavonoids like catechin whose retrosynthesis is depicted in the following scheme. Our approach to catechin is very concise and involves the intramolecular ring closing between a phenol of the phloroglucinol core and the epoxide as the last step. This epoxide intermediate is ideally synthesized in two steps starting from the selective alkylation of phloroglucinol followed by the epoxidation of the double bond. In this communication, we show that phloroglucinol can be C-specifically and mono-selectively alkylated with various activated alkyl halides in buffered aqueous solutions. The use of buffered aqueous solutions as the reaction media proved crucial to control the regio-selectivity of the reaction.

2. Results and discussion

The reaction of phloroglucinol with allyl bromide was investigated first (Table 1, entries 1–6). Interestingly, phloroglucinol is nucleophilic enough to undergo alkylation in aqueous ethanol in the absence of base, with allyl phloroglucinol **1a** being obtained in 36% yield (entry 1). No products resulting from the O-alkylation of phloroglucinol are detected in the crude reaction mixture. However, the reaction is not mono-selective and gives substantial amounts of the di-alkylated product **2a**. The extent of mono-alkylation as well as the yield of the desired compound **1a** is greatly improved in pure water (entry 2). The lower solubility of **2a** in water in comparison to the starting phloroglucinol may account for this better selectivity.

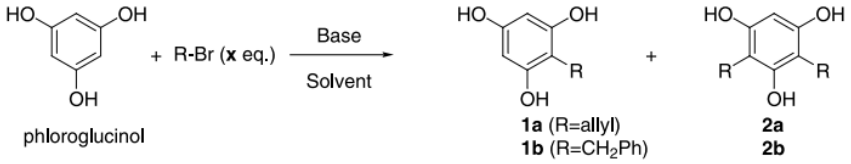
Although **1a** is obtained in good yield (68%, entry 2) in water, the pH of the reaction medium becomes increasingly acidic as the allyl phloroglucinol is formed. Since most of the polyphenols are pH-sensitive, milder conditions are required for the synthesis of

more elaborate adducts. Using stoichiometric amounts of sodium hydroxide, the phenolate of phloroglucinol is formed and the reaction is faster (entry 3).



Scheme 1. Retrosynthetic scheme of catechin.

Table 1. Conditions tested for the alkylation of phloroglucinol in water

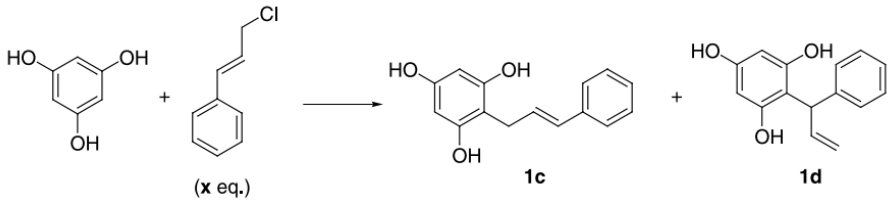


Entry	Base (equiv.)	x	R	Solvent	T (°C)	Time (h)	Yields (%)[a]	
							1	**2**
1	None	5	Allyl	$EtOH_{40\%}$	20	72	36	30
2	None	5	Allyl	H_2O	20	72	68	23
3	NaOH (1)	1.1	Allyl	H_2O	20	12	45	17
4	NaOH (2)	1.1	Allyl	H_2O	20	5	n.d.[b]	
5	Buffer[c]	4	Allyl	H_2O	20	4	62	24
6	Buffer[c]	4	Allyl	H_2O	10	10	35	12
7	Buffer[c]	2	Benzyl	H_2O	20	4	54	21
8	NaOH (2)	2	Benzyl	EtOH	20	4	40	26
9	TEA (3)	2	Benzyl	THF	20	5	42	23

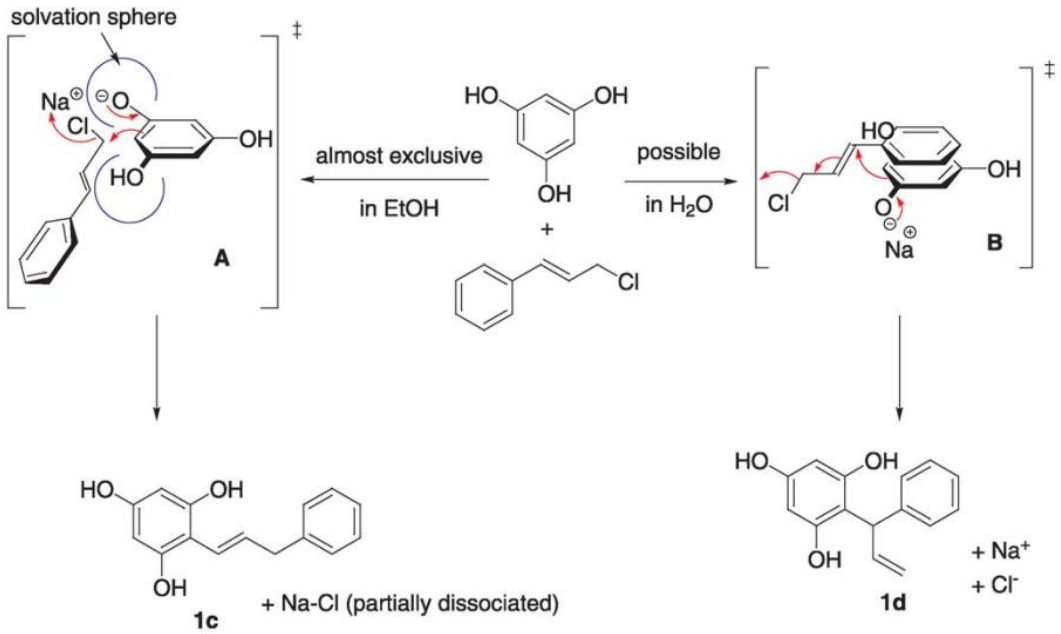
[a] Isolated yields.
[b] Not determined, see text.
[c] Phosphate buffer 0.2 M, pH 7.8.

Yet, the mono-alkylation selectivity is low. This can be ascribed to the better solubility of the phenolate of **1a** in water in comparison to its neutral form. Consequently, **1a** is more likely to over-react in basic solutions and lesser monoselectivity is observed (entry 3). A complex mixture of products is obtained with excess quantities of base (entry 4). Partial migration of the double bond of **1a** and **2a** in (conjugate) benzylic position takes place under these conditions. Alternatively, use of a buffered, ca. neutral, aqueous solution proved very successful. Since the pH is maintained throughout the course of the reaction, the reaction time is short and the yield of **1a** remains quite good (entry 5). Reducing the reaction temperature to 10°C not only slows product formation but also results in lower selectivity and overall yield (entry 6). Under the same conditions (0.2 M phosphate buffer, pH 7.8, 25°C), the reaction of phloroglucinol with benzyl bromide gave **1b** and **2b** in 54 and 21% yield, respectively. As for allyl bromide (results not shown), no O-benzylated phloroglucinol was obtained in ethanol or THF (entry 8 and 9),[6] and the reaction must be carried out in DMF to observe the formation of benzyl ethers (results not shown).[7] Hence, water does not influence the C-selectivity of the reaction. Indeed, both the phloroglucinol and activated alkyl halides are known to favor C-alkylation.[8,9] This is in sharp contrast to the reaction of non-activated alkyl bromides with phloroglucinol where water has a marked influence both on the C- and on the mono-selectivity.[10] The reaction of phloroglucinol with cinnamyl halides (Table 2) readily gives access to the skeleton of natural flavonoids (Scheme 1). Yet, these adducts are quite acid-sensitive. This may in turn explain why the synthesis of simple intermediates like **1c** have only been reported in a low 30% yield,[9,11] or not achieved at all.[12] The reaction of cinnamyl halides is actually even more challenging. In addition to the classical mono- and C-/O-alkylation issues encountered so far with allyl and benzyl halides, cinnamyl halides can give two additional regioisomers upon reaction with a nucleophile. Indeed, both regioisomers **1c** and **1d** are formed in equal amounts under our buffered reaction conditions (Table 2, entry 1). We found the desired isomer **1c** is cleanly obtained in a mixture of ethanol and aqueous sodium hydroxide. Several factors may account for this selectivity. First, the dielectric constant of the solution decreases with increasing amounts of ethanol. Hence, the dissociation of ion pairs is less likely in solutions containing higher concentration of ethanol. The sodium counter-ion of the phenolate and the chlorine of cinnamyl chloride may be in close vicinity throughout the reaction pathway in ethanol-rich aqueous solutions as in transition state **A**, which leads to **1c** (Scheme 2).

Table 2. Cinnamylation of phloroglucinol in aqueous solutions



Entry	Conditions	x	Yields (%)	
			1c	**1d**
1	Phosphate buffer 0.2 M, pH 7.8	2	35	35
2	NaOH (1.25 equiv.), H_2O/EtOH 15/85 (v/v)	1.25	69	Traces

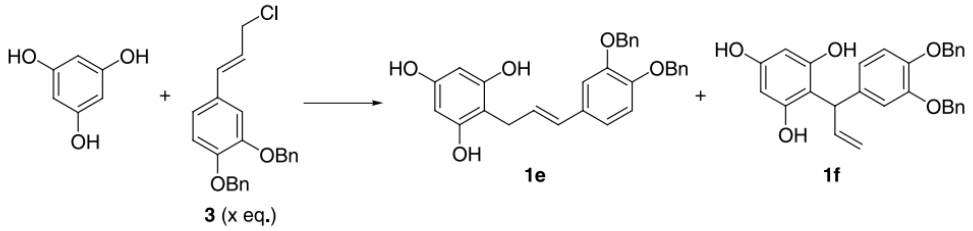


Scheme 2. Solvent-dependant transition states in the cinnamylation of phloroglucinol.

However, the strong hydrophobic effect and high cohesive energy density expected in water alone as a solvent should favor transition state **B** and thus produce **1d**.[13] Yet, the phenols are also thoroughly solvated in water. This should favor the attack on the less crowded terminal position of the alkyl halide leading to **1c**. These two opposing effects, hydrophobicity and solvation of the phenols, may account for the absence of selectivity in water.

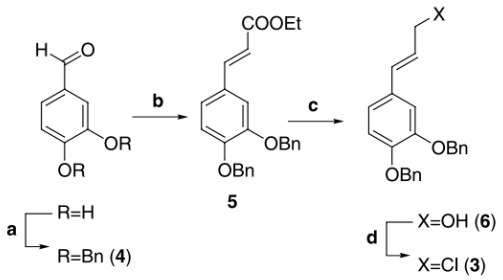
With this result in hand, we then synthesized the advanced intermediate of catechin **1e** starting from the highly hydrophobic functionalized cinnamyl chloride 3 (Table 3). This compound is efficiently synthesized in four steps starting from the commercially available 3,4-dihydroxybenzaldehyde (Scheme 3). The cinnamyl chloride **3** was then reacted with the phloroglucinol under a variety of aqueous ethanolic conditions (Table 3).

Table 3. Synthesis of an advanced intermediate of catechin



	Conditions	x	Yields (%)	
			1e	**1f**
1	NaOH (1.3 equiv.), $EtOH_{90\%}$ (vol.), 2 h	1.25	0	0
2	NaOH (1.3 equiv.), $EtOH_{90\%}$ (vol.), 0.1 h	1.25	45	12
3	NaOH (2 equiv.), $EtOH/H_2O/THF$ 72/14/14, 20–50 °C, 9 h	0.33[a]	53	Traces

[a] **3** in a minimum of THF was added slowly to the reaction over a 4 h period.



Scheme 3. Synthesis of the cinnamyl chloride **3**. Reagents: (a) NaH, BnBr, DMF; (b) NaH, triethylphosphonoacetate, THF; (c) LAH, Et_2O, −15 °C; (d) $SOCl_2$, Net_3, CH_2Cl_2, 0 °C.

In contrast to allyl bromide and cinnamyl chloride, the substituted cinnamyl chloride **3** is not soluble in ethanol or water. Consequently, no adduct is formed under the conditions optimized with cinnamyl chloride (entry 1). Under ultrasonic irradiation, the desired product **1e** is formed, yet not selectively (entry 2), the other regioisomer **1f** being obtained in substantial amounts.[14] When a solution of **3** in a minimum of THF is added slowly to the phloroglucinol in aqueous ethanol under gentle heating, only trace amounts of the undesired **1f** are observed and **1e** is obtained pure in a satisfactory 53% yield after flash chromatography (entry 3). This product has already been synthesized in low yield (17%) from phloroglucinol and the corresponding palladium p-acetate.[8] This advanced intermediate of natural flavonoids is obtained in our case in 53% yield under very simple and straightforward conditions.

In conclusion, a mild, high-yielding C-specific and monoselective alkylation of phloroglucinol with activated alkyl halides has been developed. The C-specificity of this reaction comes from the fact that both phloroglucinol and activated alkyl halides favor C-alkylation. On the other hand, the solubility of mono-C-adducts are limited in water, thereby, preventing over-alkylation reactions and giving good mono-alkylation selectivity. With minor changes in the experimental conditions, these aqueous conditions have been utilized with highly hydrophobic substrates to afford an advanced intermediate of catechin. The subsequent epoxidation of the double bond of **1e** has not been successful so far due to the high reactivity of the phloroglucinol toward oxidants. Yet, preliminary results indicate that iodination of the double bond is feasible. We are now concentrating our efforts on trying to make this reaction more selective and then achieve a straightforward, protection-free, total synthesis of catechin.

3. Experimental

3.1. General

3.1.1. **2-Allylphloroglucinol** (**1a**). To a solution of phloroglucinol·2H2O (0.1 g, 0.61 mmol) in 10.98 mL 0.2 M Na_2HPO_4 and 1.02 mL of 0.2 M NaH_2PO_4 is added the allyl bromide (0.21 mL, 2.44 mmol). The reaction is stirred for 3 h and the aqueous phase is extracted twice with ether. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (25–35% AcOEt/hexane). $C_9H_{10}O_3$ (166.06); R_f 0.45 (40% AcOEt/hexane); ^1H (200 MHz, ε CD_3OD/ $CDCl_3$): δ 3.34 (d, ^3J=5.2 Hz, 2H, H5), 5.00–5.14 (m, 2H, H_7), 5.85–6.07 (m, 1H, H_6), 5.91 (s, 2H, H_2). ^{13}C (75 MHz, ε

$CD_3OD/CDCl_3$): δ 27.6, 96.2, 104.6, 116.0, 136.5, 153.5, 154.4. IR (neat): ν_{max}=3454 (br, OH), 2924 (Ar.), 1621 (Ar-O), 1452, 1212 (br), 1112 cm^{-1}. MS (NH_4^+): *m/z*: 167 $[M+H]^+$.

3.1.2. **2,4-Diallylphloroglucinol** (**2a**). $C_{12}H_{14}O_3$ (206.24); R_f 0.7 (60% AcOEt/hexane); ^1H (200 MHz, $CDCl_3$): δ 3.42 (m, 4H), 5.13–5.25 (m, 4H), 5.94–6.07 (m, 2H), 6.01 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 27.1, 95.8, 104.2, 115.5, 136.6, 155.5, 155.9; IR: ν_{max}=3492 (br, OH), 2924 (Ar.), 1623 (Ar-O), 1464, 1150 cm^{-1}; MS (NH_4^+): *m/z*: 207 $[M+H]^+$.

3.1.3. **2-Benzylphloroglucinol** (**1b**). Same procedure as for **1a** (benzyl bromide as the electrophile). $C_{13}H_{12}O_3$ (216.23); R_f 0.4 (60% AcOEt/hexane); ^1H (200 MHz, ε CD_3OD/ $CDCl_3$): δ 3.96 (s, 2H), 5.95 (s, 2H), 7.12–7.26 (m, 5H); ^{13}C (50 MHz, ε $CD_3OD/CDCl_3$): δ 28.4, 96.0, 106.5, 126.2, 128.2, 128.6, 140.3, 155.4, 155.8; IR (neat): ν_{max}=3359 (br, OH), 2927 (Ar.), 1615 (br, Ar-O), 1456, 1144 cm^{-1}; MS (NH_4^+): *m/z*: 217 (100) $[M+H]^+$, 234 (49.8) $[M+NH_4]^+$, 251 (10.8) $[M+NH_3+NH_4]^+$.

3.1.4. **2,4-Dibenzylphloroglucinol** (**2b**). $C_{20}H_{18}O_3$ (306.36); R_f 0.7 (60% AcOEt/hexane); ^1H (200 MHz, $CDCl_3$): δ 3.99 (s, 4H), 4.81 (s, 3H, OH), 5.99 (s, 1H), 7.12–7.30 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ 28.9, 96.2, 106.7, 126.4, 128.2, 128.7, 139.8, 153.4, 154.1; IR (neat): ν_{max}=3526 (br, OH), 3028, 2924 (Ar.), 1619 (br, Ar-O), 1447, 1186, 1039 cm^{-1}; MS (NH_4^+): *m/z*: 307 (100) $[M+H]^+$, 323 (54.6) $[M+NH_4]^+$.

3.1.5. **2-Cinnamylphloroglucinol** (**1c**). The cinnamyl chloride (7.62 mL, 54.00 mmol) is added to the phloroglucinol·$2H_2O$ (7 g, 43.17 mmol) in solution in 200 mL of ethanol and 25 mL of 2 M NaOH. After 3 h, the ethanol is partially evaporated under reduced pressure. The resulting aqueous solution is first washed with 200 mL of hexane and extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (25–40% AcOEt/hexane). $C_{15}H_{14}O_3$ (242.27); R_f 0.45 (60% AcOEt/hexane); ^1H (200 MHz, ε $CD_3OD/CDCl_3$): δ 3.57 (d, ^3J=5.4 Hz, 2H), 6.01 (s, 2H), 6.36 (dt, ^3J=15.9 Hz, 3J2¼5.6 Hz, 1H), 6.53 (d, ^3J=15.9 Hz, 1H), 7.22–7.39 (m, 5H); ^{13}C (75 MHz, ε $CD_3OD/CDCl_3$): d 26.2, 96.0, 104.7, 126.2, 127.2, 128.0, 128.5, 130.7, 137.4, 155.4, 155.8; IR (neat): ν_{max}=3381 (br, OH), 2986, 2870 (Ar.), 1612 (Ar-O), 1142 cm^{-1}; MS (NH_4^+): *m/z*: 243 (56.9) $[M+H]^+$, 260 (100) $[M+NH_4]^+$, 277 (20.3) $[M+NH_3+NH_4]^+$.

3.1.6. **2-(1-Phenyl-allyl)-phloroglucinol** (**1d**). $C_{15}H_{14}O_3$ (242.27); R_f 0.5 (60% AcOEt/hexane); ^1H (300 MHz, ε $CD_3OD/CDCl_3$): δ 5.07–5.39 (m, 2H), 5.21 (br s, 2H, OH), 5.31 (d, ^3J=5.9 Hz, 1H), 5.96 (s, 2H), 7.24–7.34 (m, 5H); IR (neat): ν_{max}=3446 (br, OH), 2983 (Ar.), 1615 (Ar-O), 1217 cm^{-1}; MS (NH_4^+): *m/z*: 243 $[M+H]^+$, 260 $[M+NH_4]^+$.

3.1.7. **2-[3-(3,4-Bisbenzyloxy-phenyl)-allyl]-phloroglucinol** (**1e**). The cinnamyl chloride 3 (0.3 g, 0.82 mmol) in 1.5 mL of THF is slowly added (0.35 mL/h) to the phloroglucinol·$2H_2O$ (0.4 g, 2.47 mmol) in 8 mL of ethanol and 1.5 mL of water and NaOH (0.2 g, 5 mmol). The reaction is stirred at 50 °C for 4 h and the ethanol is partially evaporated under reduced pressure. The resulting aqueous solution is first washed with 200 mL of hexane and extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (30–40% AcOEt/hexane). $C_{29}H_{26}O_5$ (454.51); R_f 0.45 (60% AcOEt/hexane); ^1H (300 MHz, ε $CD_3OD/CDCl_3$): δ 3.39 (d, ^3J=5.0 Hz, 2H), 5.02, 5.03 (s, 4H), 5.89 (s, 2H), 6.11 (dt, ^3J=15.9 Hz, ^3J=5.9 Hz, 1H), 6.28 (d, ^3J=15.9 Hz, 1H), 6.78 (dd, ^3J=8.4 Hz, ^4J =1.9 Hz, 1H), 6.84 (d, ^3J=8.4 Hz, 1H), 6.97 (d, ^4J=1.9 Hz, 1H), 7.23– 7.41 (m, 10H); ^{13}C (75 MHz, ε $CD_3OD/CDCl_3$): δ 26.8, 72.3, 72.4, 95.4, 106.1, 113.5, 116.3, 120.5, 128.4, 128.5, 128.6, 129.1, 129.2, 133.7, 138.3, 148.7, 149.9, 156.9, 157.4; IR (neat): ν_{max}=3388 (br, OH), 3032, 2925 (Ar.), 1606 (Ar-O), 1509, 1262, 1133 cm^{-1}; MS (NH_4^+): *m/z*: 472 $[M+NH_4]^+$.

3.1.8. **2-[3-(3,4-Bisbenzyloxy-phenyl)-allyl]-phloroglucinol** (**1f**). $C_{29}H_{26}O_5$ (454.51); R_f 0.55 (60% AcOEt/ hexane); ^1H (300 MHz, $CDCl_3$): δ 5.01–5.28 (m, 2H), 5.07, 5.10 (s, 4H), 5.19 (d, ^3J=6.2 Hz, 1H), 5.92 (s, 2H), 6.30–6.41 (m, 1H), 6.77–6.90 (m, 3H), 7.26–7.43 (m, 10H); MS (NH_4^+): *m/z*: 472 $[M+NH_4]^+$.

3.1.9. **3,4-Dibenzyloxybenzaldehyde** (**4**). A first portion of sodium hydride (60%, 7 g) is added to the 3,4-dihydroxybenzaldehyde (18.65 g, 135 mmol) in 300 mL of dry DMF. After the evolution of gas had ceased, the benzyl bromide (32.92 mL) is added dropwise on the solution. After 1 h, the rest of the NaH is added (5.88 g, 297 mmol total). The reaction is stirred for four additional hours and 600 g of ice is added to the reaction mixture. The aqueous solution is extracted three times with ether. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The brown solid thus obtained is triturated with methanol to afford 36.4 g (85%) of **4**. $C_{21}H_{18}O_3$ (318.37); R_f 0.55 (30% AcOEt/ hexane); ^1H (200 MHz, $CDCl_3$): δ 5.22 (s, 2H), 5.26 (s, 2H), 7.03 (d, ^3J=8.0 Hz, 1H), 7.26–7.51 (m, 11H), 9.82 (s, 1H); ^{13}C (50 MHz, $CDCl_3$): δ 70.8, 71.0, 112.5, 113.1, 126.6, 127.0, 127.3, 128.0, 128.1, 128.5, 128.6, 130.3, 136.2, 136.5, 149.2, 154.3, 190.8; IR (neat): ν_{max}=3034, 2825, 2729, 1683, 1262, 1130 cm^{-1}; MS (NH_4^+): *m/z*: 319 $[M+H]^+$.

3.1.10. **3-(3,4-Bis-benzyloxy-phenyl)-acrylic acid ethyl ester** (**5**). NaH (5.26 g, 130 mmol) is added to a solution of triethylphosphonoacetate (24.05 mL, 120 mmol) in 300 mL of THF. After the evolution of gas had ceased, the 3,4- dibenzyloxybenzaldehyde (36.4 g, 114 mmol) is added and the reaction is stirred for 10 min. 400 g of ice is added to the reaction mixture and the aqueous solution is extracted three times with ethyl acetate. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was rapidly filtered (AcOEt) on a short pad of silica to afford 44.2 g (100%) of the acrylate. $C_{25}H_{24}O_4$ (388.46); R_f 0.45 (20% AcOEt/ hexane); ^1H (200 MHz, $CDCl_3$): δ 1.33 (t, ^3J=7.2 Hz, 3H), 4.25 (q, ^3J=7.2 Hz, 2H), 5.19 (s, 2H), 5.20 (s, 2H), 6.25 (d, ^3J=15.9 Hz, 1H), 6.92 (d, ^3J=8.4 Hz, 1H), 7.07 (dd, ^3J=8.4 Hz, ^4J =2.2 Hz, 1H), 7.13 (d, ^4J =2.2 Hz, 1H), 7.32–7.48 (m, 10H), 7.80 (d, ^3J=15.9 Hz, 1H); ^{13}C (50 MHz, $CDCl_3$): δ 14.4, 60.4, 71.0, 71.3, 113.7, 114.3, 116.2, 122.8, 127.2, 127.3, 128.0, 128.6, 136.8, 144.4, 148.9, 151.0, 167.2. IR (neat): ν_{max}=2972, 2926, 2866, 1739, 1716, 1511, 1230 cm^{-1}. MS (NH_4^+): *m/z*: 389 $[M+H]^+$.

3.1.11. **3',4'-Dibenzyloxycinnamyl alcohol** (**6**). $LiAlH_4$ (0.195 g, 5.15 mmol) is added over 5 min to a solution of the acrylate (2.00 g, 5.15 mmol) in 60 mL anhydrous ether at -15 °C (RM: to avoid the precipitation of the acrylate, the addition must start right after the flask is cooled).

The reaction is stirred for 2 h and a few drops of conc. $Na_2S_2O_5$ and 5 g of Na_2SO_4 are added. The residue is rapidly filtered (AcOEt) on a short pad of silica to afford 1.34 g (75%) of pure **6**. $C_{23}H_{22}O_3$ (346.42); R_f 0.25 (40% AcOEt/hexane); ^{1}H (200 MHz, $CDCl_3$): δ 4.27 (dd, ^3J=5.9 Hz, ^4J =1.5 Hz, 2H), 5.18, 5.17 (s, 4H), 6.18 (dt, ^3J=15.9 Hz, ^3J=5.9 Hz, 1H), 6.50 (dt, ^3J=15.9 Hz, ^4J =1.5 Hz, 1H), 6.90–7.04 (m, 3H), 7.28–7.51 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ 61.9, 69.4, 69.5, 111.1, 113.1, 118.5, 125.0, 125.4, 125.5, 126.0, 126.1, 126.7, 126.8, 128.6, 129.0, 135.4, 147.0, 147.2; IR (neat): ν_{max}=3065 (br, OH), 3035, 2920, 1512, 1259 cm^{-1}; MS (NH_4^+): *m/z*: 364 $[M+NH_4]^+$.

3.1.12. **3-(3,4-Bis-benzyloxy-phenyl)-1-chloro-prop-2- ene** (**3**). Thionyl chloride (0.93 mL, 12.71 mmol) is added dropwise to the cinnamyl alcohol (4 g, 11.56 mmol) and triethylamine (1.85 mL, 13.29 mmol) in 100 mL of dichloromethane at 0 °C. After 1 h, 100 mL of water is added and the resulting aqueous solution is extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by a rapid flash chromatography on silica gel (50% AcOEt/hexane) to give 3.72 g (88%) of the cinnamyl chloride **3**. $C_{23}H_{21}Cl_1O_2$ (364.86). ^{1}H (200 MHz, $CDCl_3$): δ 4.22 (dd, ^3J=7.3 Hz, ^3J =1.3 Hz, 2H), 5.18, (s, 4H), 6.14 (dt, ^3J=15.7 Hz, ^3J=7.3 Hz, 1H), 6.55 (d, ^3J=15.7 Hz, 1H), 6.88–7.03 (m, 3H), 7.31–7.50 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ 46.1, 71.6, 71.9, 113.6, 115.3, 121.1, 123.6, 127.7, 127.8, 128.3, 128.9, 130.0, 134.3, 137.5, 149.5, 149.8; IR (neat): ν_{max}=3032, 2936, 1511, 1263, 1135 cm^{-1}; MS (NH_4^+): *m/z*: 382 $[M+NH_4]^+$.

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