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Synthesis and characterization of low generation halogenated linear poly(arylpropargyl)ether (PAPE) branches via selective palladium catalyzed coupling reactions

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Abstract—A rapid convergent synthesis of first- and second-generation halogenated linear poly(arylpropargyl ether) branches **7** and **10** is described. The key step of the sequence studied involves a selective Sonogashira–Linstrumelle (S–L) cross-coupling reaction of aryl iodides with alkynes bearing an sp^2-carbon–iodine bond. Application to the synthesis of functionalized first-generation poly(arylpropargylether) stars having a benzene-1,3,5-tricarboxylic acid core has been realized.

Over the last 30 years, the palladium–copper-catalyzed coupling reaction of terminal alkynes with organic halides has been extensively used for the introduction of an alkynyl moiety in organic molecules.[1] This procedure named Sonogashira–Linstrumelle (S–L) is of great interest since the preparation of organometallic acetylide species is not required and allows a huge range of functionalized 1-alkynes to couple chemoselectively under very mild conditions. Although selective coupling reactions of multiple halogenated aryl or heteroaryl halides with terminal alkynes are now well documented,[2] selective S–L coupling of aryl halides with arylalkynes bearing an sp^2-carbon–halogen bond has received little attention. In most cases reported in the literature, excellent selectivities were obtained when the coupling was carried out between aryl iodides and alkynes bearing an sp^2-carbon–fluorine, carbon–chlorine or carbon–bromine bond.[3] However, to our knowledge, there is no example of the coupling of aryl iodides with alkynes bearing an sp^2-carbon–iodide bond, probably because of the difficulty to control the reactivity of the two carbon–iodine bonds during the oxidative addition step to a palladium(0) species. Herein, we report the results of this study aimed at the synthesis of low generation poly(arylpropargylether) linear branches **2** suitable for the preparation of functionalized, chemically well-defined three-dimensional poly(arylpropargylether) stars **1**. As there is no increase in the number of branches from one generation to another, the term 'hyperbranched stars' seems to be more appropriate than the term 'dendrimer' to characterize our macromolecules **1**.

As part of a research field concerning novel dendrimers for drug delivery[4] we have initiated a program on the synthesis of low generation poly(arylpropargylether)[5] stars **1** (Scheme 1). The construction of these macromolecules involves an anchoring step of branches **2** possessing a primary alcohol function of variable chain length with central cores derived from 1,3,5-benzene tricarboxylic acid (**3**, X = OH). Each successive generation in the synthesis of branches **2** allows the incorporation of an arylpropargylether unit, in which the triple bond of the non-conjugated heteroatom-containing flexible linkage provides a focal point for further structural manipulation. Furthermore, ramification, materialized by the introduction of a *para*-substituted phenyl group, may potentiate the interaction with an active drug depending on the nature of the functionalities. A further particularity of star macromolecules is the ease of ^{1}H NMR analysis due to the absence of complicated multiplicity.

Thus, the construction of these functionalized star macromolecules **1** required a rapid and flexible method

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Keywords: Palladium; Copper; Alkyne; Halogenated poly(arylpropargylether); Poly(arylpropargylether) stars.

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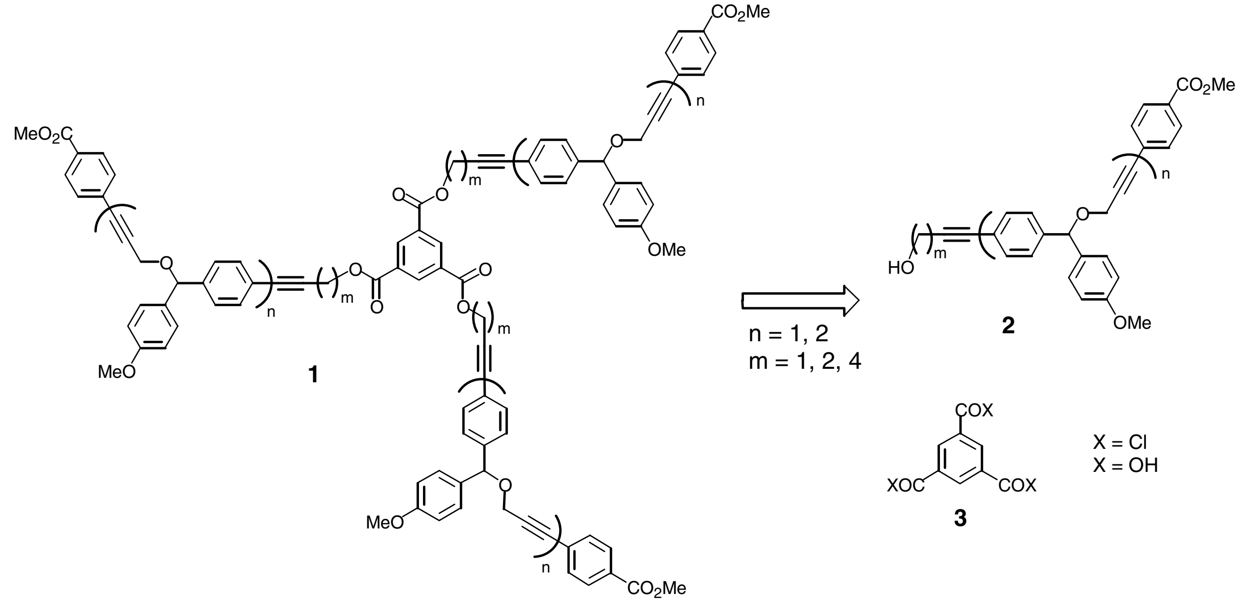
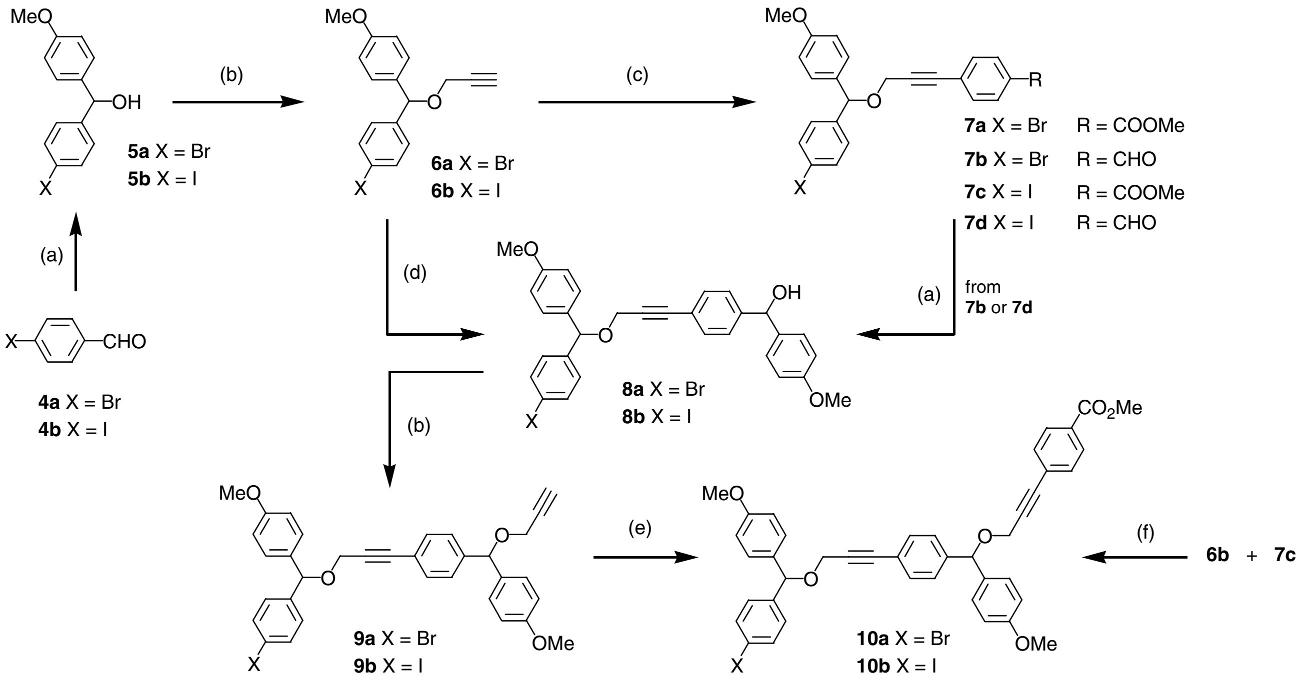


Scheme 1.

to prepare linear branches **2** bearing various hydroxyalkyne aryl substituents. To this end, we focused our attention on a straightforward approach based on the use of aryl halides **7** and **10**, which could represent useful building blocks to introduce hydroxyalkyne moieties of various chain length by a palladium–copper S–L coupling reaction. The synthesis of the first- and second-generation of these branches involves an iterative, three-step sequence based on Grignard addition, Williamson alkylation and then S–L coupling (Scheme 2). Following this synthetic scheme, compounds **6**, easily accessible starting from the corresponding aldehydes **4** by a Grignard 1,2-addition followed by a Williamson propargylation, are characterized by the presence of both a terminal alkyne group and an sp^2-carbon–halogen bond. These functionalities are able to undergo auto-coupling processes under the S–L reaction conditions. For the success of



Scheme 2. Reagents and conditions: (a) p-$MeOC_6H_4MgBr$ (2 equiv), THF, −40 °C (**5a**: 94%, **5b**: 91%, **8a**: 84%, **8b**: 89%); (b) NaH 60% (2 equiv), $BrCH_2C{\equiv}CH$ (2 equiv), THF-DMF (1:1 v/v), 20 °C (**6a**: 90%, **6b**: 92%, **9a**: 77%, **9b**: 77%); (c) ArI or ArBr (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N, 60 °C (**7a**: 74%, **7b**: 63% without CuI, **7c**: 80%, **7d**: 73%); (d) **6a** (1.5 equiv), **5b** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N, 60 °C, 1 h (**8a**: 88%); (e) p-$IC_6H_4CO_2Me$ (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N, 60 °C (**10a**: 64%, **10b**: 58%); (f) **6b** (1.5 equiv), **7c** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N, 60 °C, 1 h (**10b**: 24%, **11**: 14%).

this strategy, cross-coupling must be favored with respect to auto-coupling. Since terminal alkynes react at a higher rate with aryl iodides than with aryl bromides we initially investigated the preparation of brominated derivatives **7a**–**b** and **10a**.

To avoid its auto-coupling, brominated alkyne **6a** was slowly added, at 80 °C, to a solution containing methyl 4-iodobenzoate, $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %) in triethylamine. Under these conditions, the S–L cross-coupling reaction occurred selectively on the carbon–iodine bond and resulted in the formation of brominated first generation **7a** in good yield (74%). Under similar conditions, coupling **6a** with 4-bromobenzaldehyde allowed the formation of **7b** with a lower yield (52%) whereas in the absence of copper iodide[6a] the yield of **7b** increased to 63%.

When starting from **7b**, brominated higher generation **10a** was obtained according to the three-step sequence described above based on Grignard addition (**8a**: 84%), Williamson propargylation (**9a**: 77%) and S–L coupling reaction (**10a**: 64%). It should be noted that the intermediate **8a** may be obtained in a one-step sequence in good yield (88%) when the coupling is performed between bromoalkyne **6a** and iodo alcohol **5b**.

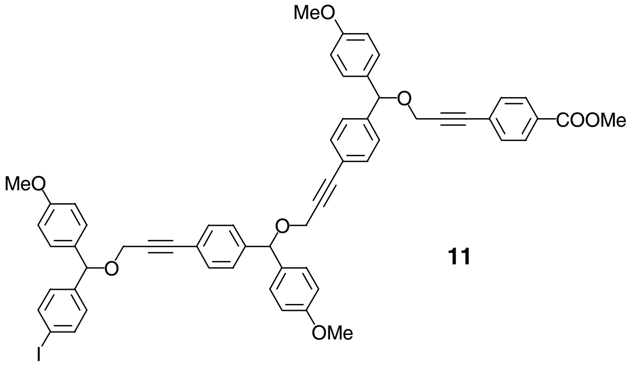
Having in our hands brominated derivatives **7a** and **10a**, we next studied the introduction of propargylic and homopropargylic alcohol chains under S–L coupling reactions to obtain linear branches **2**. All our attempts to perform such coupling reactions employing various combinations[6] of Pd/solvent/amine mixtures (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$/PPh_3 or $P(t\text{Bu})_3$, THF, DMF, dioxane, Et_3N, Et_2NH, $i\text{Pr}_2NH$ or piperidine with or without CuI) were however, unsuccessful. In most cases, starting materials were recovered or degradation occurred. These difficulties in obtaining **2** from brominated derivatives **7a** and **10a** led us to explore coupling reactions with the corresponding iodides **7c** and **10b**.

Since the carbon–iodide bond is more reactive than the corresponding bromide and in order to avoid auto-coupling reactions, various conditions were examined for performing selective alkynylation of activated aryl iodides such as methyl 4-iodobenzoate or 4-iodobenzaldehyde with substrate **6b**. It was found that when **6b** was added slowly to the reaction mixture containing activated aryl iodides[7] in triethylamine at 60 °C in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10%), the cross-coupling reaction occurred selectively on the carbon–iodide bond of the activated aromatic ring affording iodinated first-generation derivatives **7c**–**d**[8] in 80% and 73% yields, respectively.

To achieve the synthesis of iodinated second generation **10b**, **7d** was subjected to the iterative reaction sequence. Grignard addition afforded **8b** in 89% yield. Propargylation of the latter (**9b**: 77%) followed by coupling of the resulting alkyne **9b** with methyl 4-iodobenzoate selectively gave iodinated second generation **10b** in 58% yield.[9]

An alternative and rapid approach to **10b** based on a one-step coupling of **7c** (bearing a non-activated carbon–iodine bond compared to methyl 4-iodobenzoate) with substrate **6b** was also explored. To this end, a coupling reaction was attempted under the similar conditions described above ($PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10%), Et_3N, 60 °C) but only gave a 24% yield of iodinated second generation linear branch **10b** together with 14% of iodinated third generation linear branch **11** (Scheme 3). Despite the low yield of this transformation, it represents a rapid entry to **10b** (overall yield 20% in three steps from **4b** compared to 24% overall yield in six steps from **4b**).

We then studied the coupling reaction of iodinated linear chains **7c** and **10b** with various hydroxy-terminal alkyne derivatives (Table 1). All the reactions were conducted in triethylamine at 60 °C in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %). Iodinated first generation **7c** reacted with propargylic and homopropargylic alcohols with excellent yields (88–91%, entries 1 and 2) and with hex-5-yn-1-ol with a lower yield (49%, entry 3). Under similar conditions, the second-generation of linear branch derivatives **2d**–**e** were obtained in good yields (77–81%, entries 4 and 5). This synthetic scheme was successful and afforded five different hydroxyl linear branches[10] from only two iodinated derivatives **7c** and **10b**. It should be noted that all compounds synthesized including first- and second-



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Scheme 3.

Table 1. Synthesis of linear branches **2**[a]

$$\textbf{7c}\ \text{or}\ \textbf{10b}\ \xrightarrow[\substack{5\%\ PdCl_2(PPh_3)_2,\ 10\%\ CuI \\ Et_3N,\ 60^\circ C,\ 1\ \text{to}\ 2\ h}]{R\!-\!\!\equiv\ (2\ \text{equiv})}\ \textbf{2}$$

Entry	Iodinated branch	R	2	Yield[b] (%)
1	**7c**	CH_2OH	**2a**	91
2	**7c**	$(CH_2)_2OH$	**2b**	88
3	**7c**	$(CH_2)_4OH$	**2c**	49
4	**10b**	CH_2OH	**2d**	81
5	**10b**	$(CH_2)_2OH$	**2e**	77

[a] All reactions were performed with 1-alkyne (2 equiv) in the presence of $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %) in Et_3N at 60 °C.

[b] Yield of isolated products.

generation derivatives **7**, **10** and **2** were fully characterized using NMR spectroscopy (^{1}H and ^{13}C), mass spectrometry (electrospray ESI) and elemental analysis. As expected with these linear branches, the ^{1}H NMR spectra show signals corresponding to the different monomer layers and the integration clearly indicates which generation is involved.

After synthesis of linear branches **2**, their attachment to a chosen core was carried out. The first (**2a**–**b**) and the second (**2d**) generation compounds were thus reacted with 1,3,5-benzenetricarbonyl chloride under various conditions[11] including Et_3N, pyridine or DMAP in CH_2Cl_2 or toluene. Surprisingly, the above-mentioned reaction conditions did not yield the desired first- and second-generation poly(arylpropargylether) stars **1**. Inseparable mixtures of products were obtained, despite running the reactions for longer times and at higher temperatures. However, under Mitsunobu conditions, we found for instance that the coupling of **2b** with 1,3,5-benzenetricarboxylic acid in the presence of DEAD (4.2 equiv) and PPh_3 (5.4 equiv) in THF for 2 h at 60 °C afforded the first generation poly(arylpropargylether) stars **1a**[12] ($n = 1$ and $m = 2$) in good isolated yield (62%). This PAPE star was characterized by classical analytical methods including ^{1}H, ^{13}C NMR and mass spectrometry.

In conclusion, we have succeeded in developing a convenient route to low generation halogenated linear poly(arylpropargylether) branches **7** and **10** based on S–L selective coupling of activated aryl iodides with halogenated alkynes. Iodinated linear branches **7c**–**d** and **10b** were used successfully for the synthesis of various hydroxyl linear branches **2**, which can serve as building blocks for the synthesis of chemically well-defined, multi-dimensional poly(arylpropargylether) stars. Preliminary results demonstrated that Mitsunobu conditions could be an alternative solution to classical acylation for the preparation of functionalized first generation poly(arylpropargylether) stars **1**. Further investigation of these macromolecules with regard to their biocompatibility and cell cytotoxicity is in progress.

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7. Under similar conditions, coupling of **6b** with the corresponding activated aryl bromides resulted exclusively in auto-coupling of **6b**.
8. Preparation and characterization of iodinated first generation **7c**: To a solution of methyl 4-iodobenzoate (1.45 mmol, 381 mg), $PdCl_2(PPh_3)_2$ (0.036 mmol, 25 mg) and CuI (0.07 mmol, 14 mg) in freshly distilled Et_3N (5 mL) was slowly added, at 60 °C, via a syringe pump (addition time 1 h) a solution of iodinated alkyne **6b** (0.72 mmol, 275 mg) in Et_3N (5 mL). The reaction mixture was stirred at 60 °C and monitored by TLC analysis until complete consumption of terminal alkyne **6b** (30 min) before being concentrated in vacuo. The residue was dissolved in AcOEt (15 mL), washed successively with aqueous HCl (0.5 M), H_2O (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (cyclohexane/AcOEt 9:1, $R_f = 0.23$) afforded pure **7c** (0.57 mmol, 295 mg, 80%). IR 2950–2836, 1718, 1606, 1585, 1509 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.91 (s, 3H), 4.36 (s, 2H), 5.59 (s, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.98 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.2, 55.2, 56.5, 81.1, 85.7, 88.1, 93.1, 114.0, 127.2, 128.7, 129.0, 129.4, 129.8, 131.6, 132.6, 137.4, 141.4, 159.4, 166.4; MS (ESI): m/z (%) = 579 (100), 535 (20) $[M+Na]^+$; $C_{25}H_{21}IO_4$ (512.05): calcd C 58.61, H 4.13; found C 58.74, H 4.18.
9. Compound **10b**: IR 3000–2836, 1719, 1607, 1585, 1509 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 4.32 (s, 2H), 4.36 (s, 2H), 5.60 (s, 1H), 5.64 (s, 1H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 2H), 7.24 (m, 4H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.47 (d,

$J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 52.2, 55.2, 56.5, 80.8, 81.3, 85.2, 85.7, 86.4, 88.3, 93.1, 114.0, 121.7, 127.0, 128.7, 129.1, 129.4, 131.7, 131.8, 132.8, 137.4, 141.6, 142.2, 159.3, 166.3; MS (ESI): *m*/*z* (%) = 785 (100) [M+Na]$^+$; $C_{42}H_{35}IO_6$ (762.15): calcd. C 66.15, H 4.63; found C 65.52, H 4.75.

10. Selected characterization data of the first and second generation linear branches.

    Compound **2a**: IR 3466, 2951, 1718, 1606, 1509 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.80 (br s, 1H), 3.78 (s, 3H); 3.91 (s, 3H), 4.36 (s, 2H), 4.47 (s, 2H), 5.64 (s, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.97 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 51.4, 52.1, 55.2, 56.4, 81.3, 85.3, 85.6, 87.4, 88.2, 113.9, 121.7, 126.9, 127.2, 128.7, 129.4, 129.6, 131.6, 132.7, 142.0, 159.3, 166.4; MS (ESI): *m*/*z* (%) = 458 (5) [M+NH$_4$]$^+$, 251 (100); $C_{28}H_{24}O_5$ (440,16): calcd. C 76.35, H 5.49; found C 74.19, H 5.60.

    Compound **2b**: IR 3504, 2951, 2361, 1718, 1606, 1509 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.85 (br s, 1H), 2.67 (t, $J = 6.2$ Hz, 2H), 3.78 (s, 3H), 3.79 (t, $J = 6.2$ Hz, 2H), 3.92 (s, 3H), 4.36 (s, 2H), 5.63 (s, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.98 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 23.8, 52.2, 55.3, 56.5, 61.2, 81.4, 82.3, 85.7, 86.4, 88.2, 113.9, 122.6, 127.0, 127.3, 128.8, 129.4, 129.7, 131.7, 132.9, 141.5, 159.4, 166.5; MS (ESI): *m*/*z* (%) = 472 (20) [M+NH$_4$]$^+$, 455 (10) [M+H]$^+$, 265 (100); $C_{29}H_{26}O_5$ (454,18): calcd. C 76.63, H 5.77; found C 74.60, H 5.90.

    Compound **2d**: IR 3476, 2999–2850, 2360, 1720, 1607, 1585, 1509 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.77 (s, 3H), 3.78 (s, 3H), 3.91 (s, 3H), 4.33 (s, 2H), 4.36 (s, 2H), 4.46 (s, 2H), 5.65 (s, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.31 (m, 12H), 7.48 (d, $J = 8.8$ Hz, 2H), 7.98 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 51.6, 52.2, 55.2, 56.5, 81.0, 81.3, 85.1, 85.5, 85.7, 86.4, 87.2, 88.2, 113.9, 121.6, 121.8, 127.0, 127.3, 128.8, 129.4, 129.8, 131.7, 131.8, 132.8, 132.9, 142.1, 142.2, 159.4, 166.4; MS (ESI): *m*/*z* (%) = 708 (100) [M+NH$_4$]$^+$; $C_{45}H_{38}O_7$ (690,26): calcd. C 78.24, H 5.54; found C 76.50, H 5.68.

    Compound **2e**: IR 3500, 3000–2800, 1720, 1608, 1510 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.59 (t, $J = 6.2$ Hz, 2H), 3.70 (m, 8H), 3.83 (s, 3H), 4.26 (s, 2H), 4.29 (s, 2H), 5.57 (s, 2H), 6.78 (d, $J = 8.6$ Hz, 2H), 6.79 (d, $J = 8.6$ Hz, 2H), 7.31 (m, 14H), 7.90 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 29.5, 52.0, 55.0, 56.3, 60.9, 80.9, 81.1, 81.9, 85.1, 85.5, 86.2, 86.5, 88.1, 113.7, 113.8, 121.7, 122.4, 126.8, 127.1, 128.6, 129.3, 129.6, 131.5, 131.6, 132.6, 132.8, 141.4, 141.9, 159.1, 159.2, 166.2; MS (ESI): *m*/*z* (%) = 727 (100) [M+Na]$^+$.

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12. Compound **1a**: IR 2953, 2360, 1720, 1606, 1509 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.86 (t, $J = 6.8$ Hz, 6H), 3.76 (s, 9H), 3.90 (s, 9H), 4.35 (s, 6H), 4.52 (t, $J = 6.8$ Hz, 6H), 5.62 (s, 3H), 6.85 (d, $J = 8.8$ Hz, 6H), 7.25 (d, $J = 8.8$ Hz, 6H), 7.33 (d, $J = 8.8$ Hz, 6H), 7.38 (d, $J = 8.8$ Hz, 6H), 7.46 (d, $J = 8.4$ Hz, 6H), 7.96 (d, $J = 8.4$ Hz, 6H), 8.9 (s, 3H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 20.0, 52.2, 55.2, 56.4, 63.4, 81.3, 82.2, 85.0, 85.6, 88.2, 113.9, 122.4, 127.0, 127.3, 128.7, 129.4, 129.7, 131.2, 131.6, 132.8, 134.8, 141.5, 159.3, 164.6, 166.4; MS (ESI): *m*/*z* (%) = 1537 (25) [M+NH$_4{}^+$]$^+$, 275 (100).