Synthesis of Poly(aryl propargyl ether) (PAPE) Stars and Evaluation of Their Cytotoxic Properties

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Abstract: The synthesis of a series of low generation poly(aryl propargyl ether) (PAPE) stars **1** and **2** from the corresponding linear branches is described. The first generation branches **3** were readily constructed in a three-step sequence based on Grignard addition, Williamson propargylation, and then Sonogashira–Linstrumelle (S–L) coupling reaction. The use of iodinated compound **4** in an S–L key step allows rapid synthesis of higher linear branches. Their subsequent attachment to benzenoid core **6** via an alkylation step efficiently afforded PAPE stars up to two generations **2** containing methoxycarbonyl ester groups at their peripheries. Transesterification of methyl esters under titanium catalysis proved to be effective and gave several functionalized PAPE stars **2**. These amino esters and polyhydroxy amide terminated PAPE stars **2** were evaluated for their cytocompatibility. No significant toxicity was detected in a concentration range of 0.1 to 1000 μg/mL.

Key words: poly(aryl propargyl ether), PAPE stars, transesterification, palladium, alkynes, Sonogashira coupling

Dendrimers are unique synthetic macromolecules, which have attracted much interest due to their unique properties since their introduction in the mid-1980s.[1] In contrast to linear polymers, these macromolecules prepared by an iterative synthetic methodology are characterized by highly branched and well-defined structures, globular shape, numerous surface functionalities, and internal cavities. These characteristics, along with water solubility, are some of the features that make them attractive for drug-delivery applications.[2] Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure[3] or by attaching it to terminal functional groups via electrostatic or covalent bonds (prodrug).[4] The covalent linkage of a drug to a dendrimer provides a stable system.

An ideal drug carrier must be biochemically inert and nontoxic while protecting the drug until it reaches the desired site of action, where the drug could be released. Over the past years, many drug-delivery systems (e.g., liposomes, synthetic and natural polymers) have been explored for this purpose.[5] By contrast, the use of dendrimers, which possess many of the above-mentioned properties for an ideal drug carrier system, has not been highlighted. At present, probably the most investigated family of dendrimers for drug-delivery is the polyamidoamine (PAMAM) dendrimers due to their commercial availability.[6] Results from these studies proved to be disappointing because of lack of biocompatibility, toxicity, and/or analytical difficulties.[7] Another well-known dendritic system is based on polyether dendrimers, including poly(ether ketone or sulfone),[8] poly(aryl ether phenylquinoxaline),[9] fluorinated poly(benzyl ether),[10] and poly(hydroxy ether).[11] Although poly(aryl ether) dendrimers were demonstrated to be suitable candidates for drug delivery,[12] it is of interest to develop and evaluate novel, biocompatible, dendritic systems.

As part of our research[13] towards novel dendrimers for drug-delivery we have initiated a program on the synthesis of low generation poly(aryl propargyl ether) stars **1** and **2**[14] from linear poly(aryl propargyl ether) branches **3** possessing a phenolic anchor (Figure 1). As this functionality showed increased reactivity compared to aliphatic hydroxyl group, we expect to link **3** to various cores, such as 1,3,5-benzenetricarbonyl chloride (**5**) or 1,3,5-tris(bromomethyl)benzene (**6**) by an acylation or an alkylation step, respectively. We chose to introduce as repeating group an aryl propargyl ether moiety in which the triple bond of the nonconjugated heteroatom-containing flexible linkage provides a focal point for further structural manipulation (e.g., partial[15] or total[16] reduction, hydrometalation,[17] followed by a coupling reaction). Furthermore, ramification materialized by the introduction of a 4-substituted phenyl group, may potentiate the interaction with an active drug depending on the nature of the functionalities. A further particularity of star macromolecules **1** and **2** is the ease of ^{1}H NMR analysis due to the absence of complicated multiplicity. Herein we describe the synthesis and characterization of a series of low generation poly(aryl propargyl ether) (PAPE) stars **1** and **2** as well as comment on their preliminary cytotoxic activities for further applications in biological studies.

In order to avoid the formation of structural defects during macromolecule construction, a convergent approach was chosen. Thus, the synthesis of functionalized PAPE stars **1** and **2** required a rapid and flexible method to prepare low generation linear branches **3** bearing a phenol substituent, which will be used as the focal point functionality (Figure 1). To this end, the synthesis of the first generation branches **3** (n = 1) will involve an iterative three-step sequence based on Grignard addition, Williamson alkyla-

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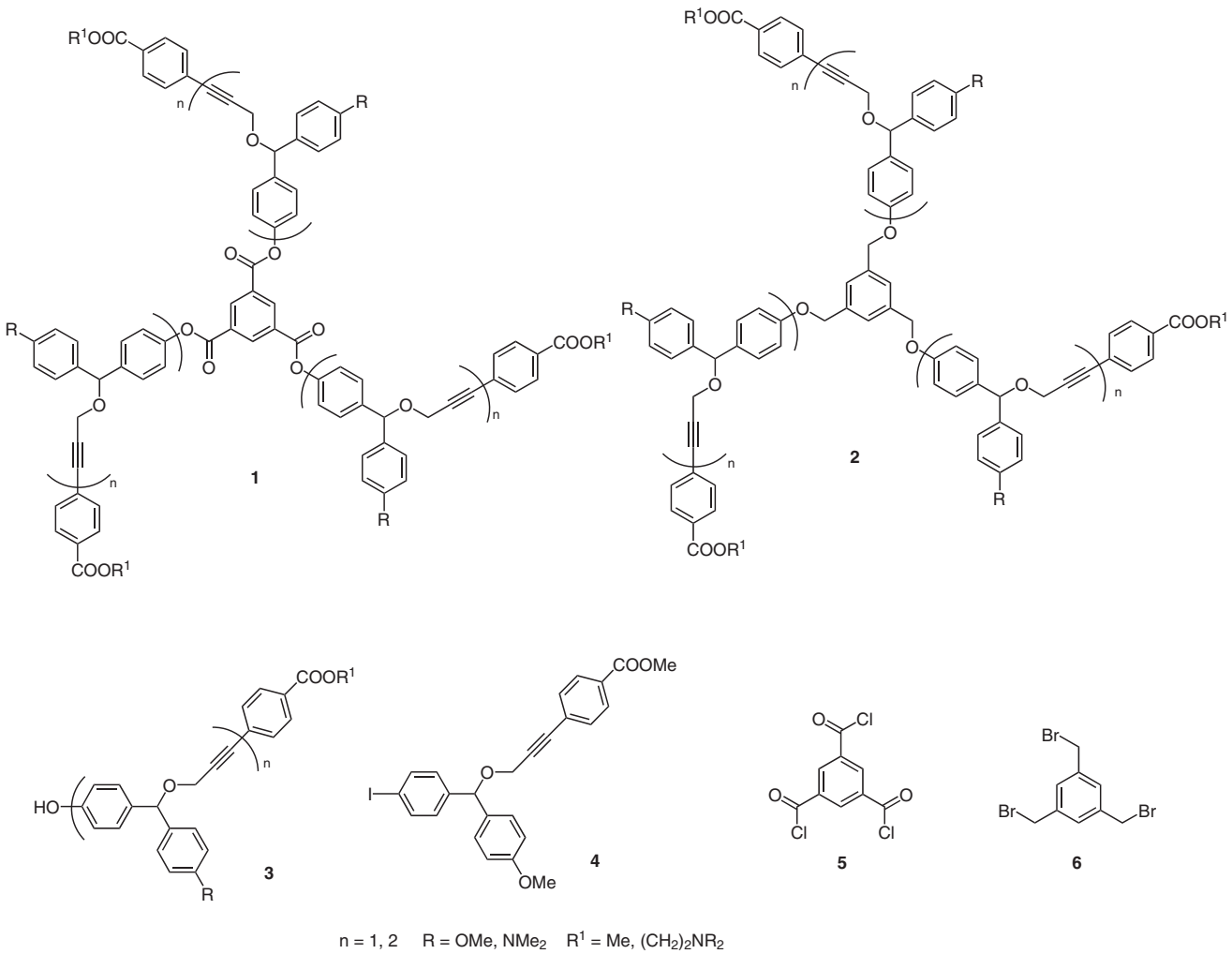
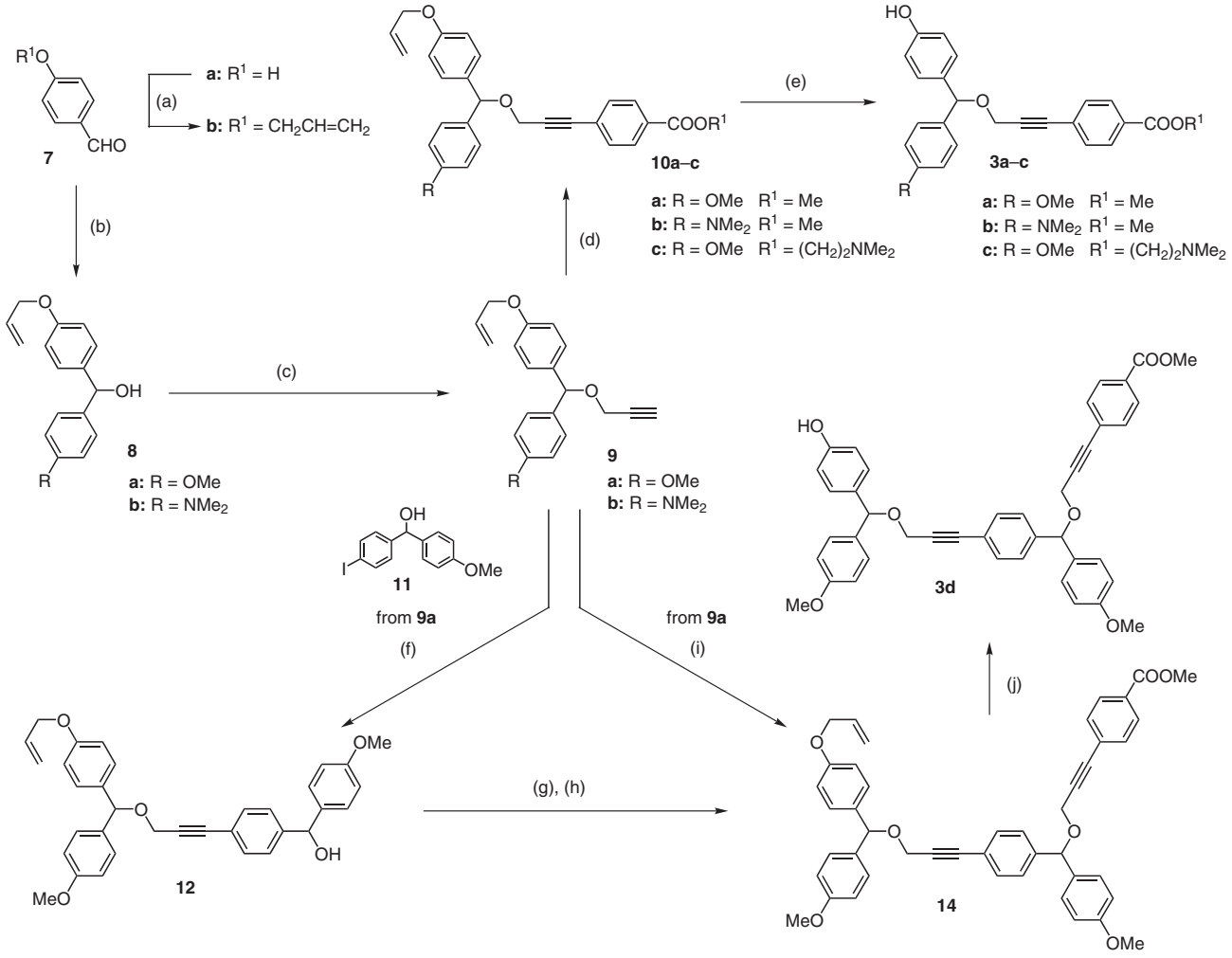


Figure 1 Compounds **1**–**6**

tion, and then Sonogashira–Linstrumelle (S–L) coupling reaction (Scheme 1). Repetition of this iterative three-step reaction sequence would generate the higher generation linear branches. For the accelerated preparation of the second generation linear branches **3** (n = 2), it was planned to use iodinated compound **4** in an S–L coupling reaction. In order to achieve the synthesis of phenol-substituted branches **3**, it was necessary to differentiate the two hydroxy groups of **8** as the alkylation step could induce selectivity issues. Among various protective groups examined[18] (MOM, MEM, TBDMS, TBDPS, or TIPS), the allylic group appeared as the protecting group of choice because of its stability under basic medium and its facility to be removed under mild conditions.

According to the synthetic Scheme 1, the commercially available compound **7a** was first transformed to the allylic ether **7b** and then reacted with 4-substituted aryl Grignard reagents to afford in excellent yields the corresponding dibenzylic alcohols **8a**,**b**. Williamson propargylation of **8a**,**b** yielded the propargyl ethers **9a**,**b** on treatment with propargyl bromide and NaH in a mixture of DMF–THF (1:1). To achieve the synthesis of **10**, the terminal alkyne function was reacted with 4-iodobenzoic acid methyl or *N*,*N*-2-dimethylaminoethyl ester in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) in Et_3N. Under these conditions, the *O*-allyl protected compounds **10a**–**c** were obtained in good yields (**10a**: 98%, **10b**: 67%, **10c**: 96%). The final step to form **3** was the deprotection of the phenolic group. As well known, the *O*-allyl group can be selectively deprotected in the presence of $NaBH_4$ and a catalytic amount of $Pd(PPh_3)_4$.[19] Under these conditions, attempts to remove the *O*-allyl group of **10a** in THF or DMF at 0 °C afforded low yields of **3a** (<15%) contaminated with small amounts of unidentified compounds. Running the reactions for longer times (4 h) and at higher temperatures (50 °C) had no significant improvement on the yield. However, we found that the use of a combination of THF–MeOH (2:8) as solvent at 0 °C gave the best results of **3a**–**c** bearing a free phenol substituent (**3a**: 84%, **3b**: 77%, **3c**: 82%). It should be noted that this four-step sequence was scaled up to the degree that **3a**–**c** are now available in multigram quantities in similar yields.

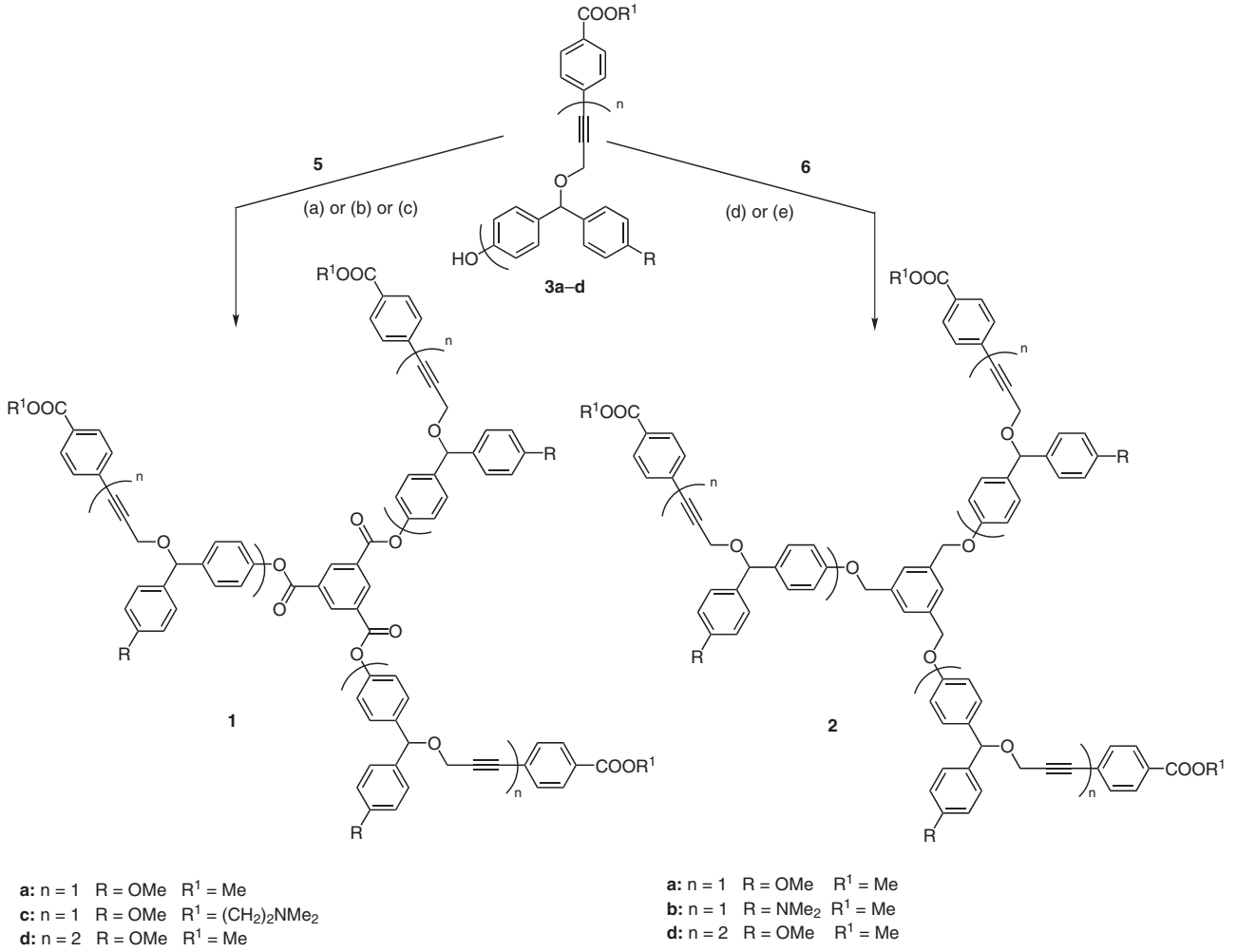
The synthesis of the second generation linear branch **3d** was initially attempted by coupling of alkyne **9a** with the previously described iodinated dibenzylic alcohol intermediate **11**.[13] Thus, the coupling product **12** was obtained in good yield (77%) in the presence of a catalytic amount



Scheme 1 *Reagents and conditions*: (a) $H_2C{=}CHCH_2Br$, K_2CO_3 (2 equiv), KI (10 mol%), acetone, reflux (**7b**: 98%); (b) 4-$MeOC_6H_4MgBr$ or 4-$Me_2NC_6H_4MgBr$ (2 equiv), THF, 40 °C (**8a**: 92%, **8b**: 85%); (c) NaH 60% (2 equiv), $BrCH_2C{\equiv}CH$ (2 equiv), THF–DMF (1:1), 20 °C (**9a**: 91%, **9b**: 84%); (d) 4-$IC_6H_4CO_2R$ [R = Me, $(CH_2)_2NMe_2$] (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, 60 °C (**10a**: 98%, **10b**: 67%, **10c**: 96%); (e) $NaBH_4$ (6 equiv), $Pd(PPh_3)_4$ (5 mol%), THF–MeOH (2:8), 0 °C (**3a**: 84%, **3b**: 77%, **3c**: 82%); (f) **11** (1.5 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, 60 °C (**12**: 77%); (g) NaH 60% (2 equiv), $BrCH_2C{\equiv}CH$ (2 equiv), THF–DMF (1:1), 20 °C (**13**: 99%); (h) 4-$IC_6H_4CO_2Me$ (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, 60 °C (**14**: 58%); (i) **4** (1.5 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, 60 °C (**14**: 74%); (j) $NaBH_4$ (6 equiv), $Pd(PPh_3)_4$ (5 mol%), THF–MeOH (2:8), 30 to 10 °C (**3d**: 80%).

of $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) in triethylamine. Further propargylation of the hydroxyl group of **12** (**13**: 99%, not shown in Scheme 1) followed by an S–L coupling reaction afforded the *O*-allylic protected compound **14** (58%). To speed up the synthesis of **14**, an alternate approach based on the use of iodinated compound **4**[13] was explored. Accordingly, we were pleased to find that the S–L coupling reaction of **4** with alkyne **9a** efficiently afforded the second generation branch **14** in a 74% isolated yield in one-step. Finally, the deprotection step of the *O*-allyl ether of **14** occurred under the same conditions as for the conversion of **10** to **3**. It was noticed that the temperature should be maintained in that case under –10 °C to avoid degradation. Thus, we have developed a synthetic scheme to the first and second generation linear branches **3a–d** in five steps and in good overall yields (overall yields of **3** from **7b**, **3a**: 68%, **3b**: 32%, **3c**: 65%, **3d**: 49%).

After the synthesis of derivatives **3a–d**, their attachment to different cores was carried out (Scheme 2). First, the acylation of **3** with the 1,3,5-benzenetricarbonyl chloride (**5**) core was investigated under various conditions[20] including Et_3N, pyridine, or DMAP in CH_2Cl_2, THF, or toluene. Best results were obtained when the acylation reaction was conducted from **3a** in the presence of triethylamine and DMAP in dichloromethane at 0 °C. Under these conditions, 40% of first generation acylated PAPE stars **1a** were isolated. As shown in Scheme 2, performing the acylation reaction with **3c** and **3d** afforded the corresponding PAPE stars **1c** and **1d**, but in moderate yields (20 and 24%, respectively). Surprisingly, starting from **3b** the above mentioned reaction conditions did not yield the desired PAPE stars **1b** and a complex mixture of inseparable products was obtained. It seems that the presence of the 4-dimethylaminoaryl group within the structure of **3b** interferes with the outcome of the acylation reaction with 1,3,5-benzenetricarbonyl chloride (**5**) core.



Scheme 2 *Reagents and conditions*: (a) **3a** (3.3 equiv), Et_3N (30 equiv), DMAP (6 equiv), CH_2Cl_2, 0–20 °C (**1a**: 40%); (b) **3c** (3.3 equiv), pyridine (30 equiv), DMAP (6 equiv), THF, 0 °C (**1c**: 20%); (c) (**3d**: 3.3 equiv), TEA (10 equiv), DMAP (10 mol%), CH_2Cl_2, 0 to 20 °C (**1d**: 24%); (d) **3a** or **3d** (3.6 equiv), K_2CO_3 (6 equiv), KI (2.7 equiv), Aliquat 336 (cat.), acetone, reflux (**2a**: 80%, **2d**: 90%); (e) **3b** (3 equiv), NaH 60% (3.3 equiv), THF–DMF (1:1), 20 °C (**2b**: 22%).

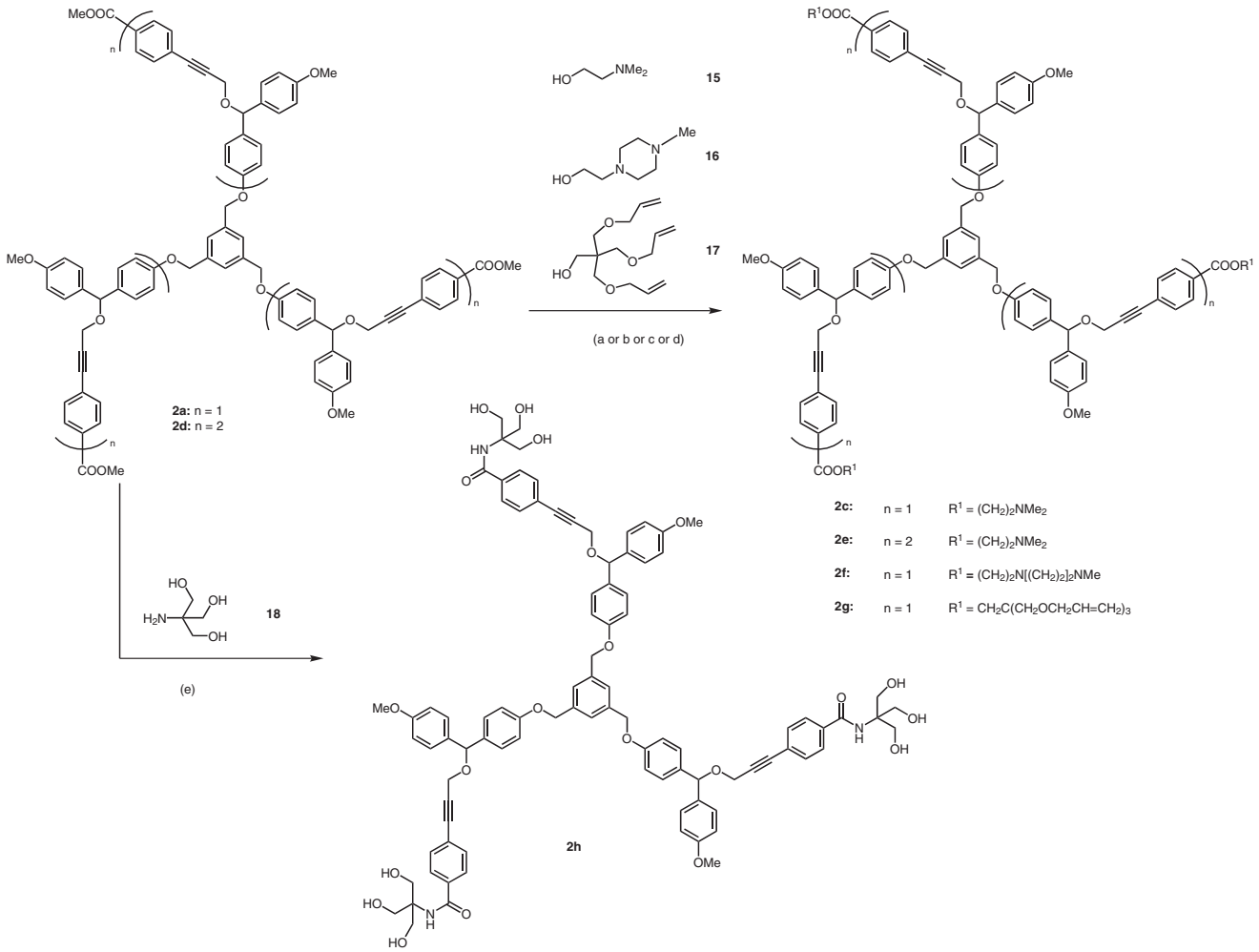
Next, we explored the preparation of PAPE stars **2** using an alkylation step with 1,3,5-tris(bromomethyl)benzene (**6**) as anchoring linkage (Scheme 2). Various experimental conditions were studied using several combinations of base/solvent/additive mixtures (e.g., NaH, Cs_2CO_3, K_2CO_3/THF, DMF, acetone /KI, crown-ether, and Bu_4NI). It was found that the reaction of the first **3a** and second **3d** generation branches with **6** in refluxing acetone in the presence of potassium carbonate, potassium iodide, and Aliquat 336 afforded the stars PAPE **2a** and **2d** in excellent isolated yields (80 and 90%, respectively). Under the same conditions, the reaction of **6** with **3b** having a 4-dimethylaminoaryl group within the structure of linear branch afforded, however, the corresponding star **2b** in very low yield (<5%). This yield was enhanced to 22% by changing the nature of the base (NaH) and solvent (THF–DMF, 1:1). Extended reaction times and higher temperature led to decomposition and decreased the yield. It should be noted that all our attempts to prepare **2c** from **3c** having an *N*,*N*-2-dimethylaminoethoxy carbonyl group resulted unfortunately in unsatisfactory yields. In most cases, all starting material were consumed and a complex mixture of inseparable products was obtained.

Difficulties encountered in the linkage of **3c** to the core **6** led us to examine an alternative route to form the PAPE star **2c** having on the surface functionalized polar groups (e.g., *N*,*N*-2-dimethylaminoethoxy carbonyl group). The presence of these latter on **2c** would improve its water solubility for further biological studies. As the synthesis of PAPE stars **2a** and **2d** was efficiently accomplished in multigrams quantities, this prompted us to examine a convergent approach to introduce polar groups by transesterification of methyl esters on the surface of PAPE stars **2** leading to the corresponding analogues with higher alcohol moieties. If this transformation proves to be effective, it should represent a straightforward route to a variety of PAPE stars **2** carrying different functional groups on the surface.

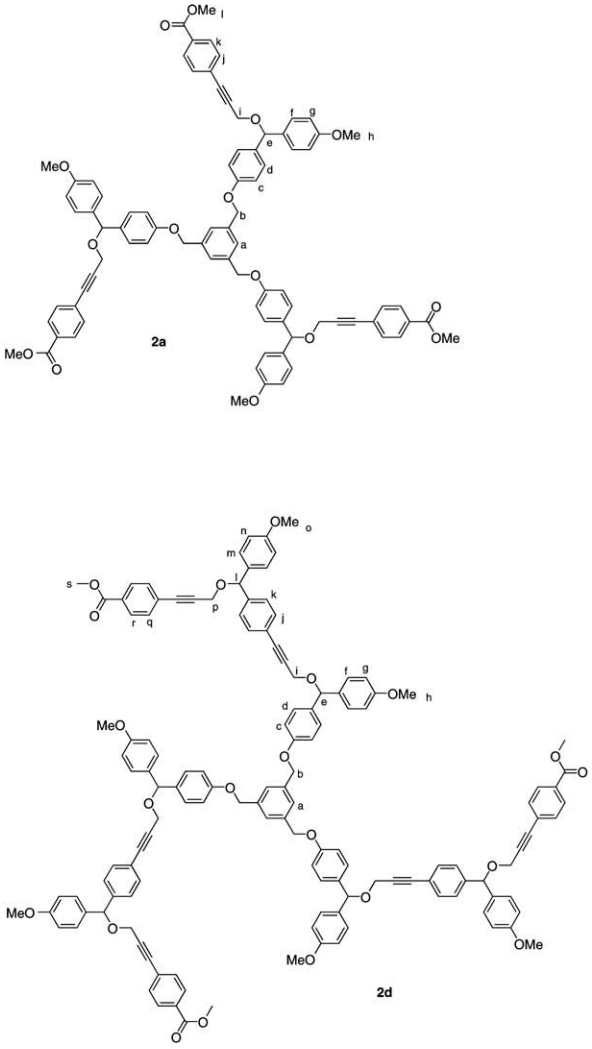
Initial attempts to introduce the *N*,*N*-2-dimethylaminoethyl esters by transesterification of first-generation star **2a** with *N*,*N*-2-dimethylaminoethanol (**15**) under various basic conditions[21] (K_2CO_3/Aliquat 336/toluene, DBU/LiBr,

NaOH, or DABCO) afforded low yields of **2c** contaminated by inseparable starting material, the methyl ester **2a**. Extended reaction times led to decomposition and decreased yields. It should be noted that similar results were obtained when using strong nonionic bases such as triaminophosphane,[22] while under neutral iodine catalysis[23] the transesterification was effective and afforded **2c** in moderate yield (40%). Finally, we turned our attention towards Seebach's[24] transesterification conditions based on titanium catalysis. When the first **2a** and second **2d** generation stars were heated with the amino alcohol **15** at 130 °C in the presence of a catalytic amount of titanium(IV) isopropoxide (15 mol%), an almost quantitative yield of PAPE stars **2c** and **2e** was obtained (89 and 95%, respectively) (Scheme 3). To the best of our knowledge, this is the first report on the use of Seebach's conditions to perform functionalization of dendrimer surface. On the basis of these promising results, the transesterification reaction of **2a** was tested with diamino alcohol **16** and afforded the corresponding functionalized PAPE star **2f** in 54% yield. The scope of this reaction was also expanded to introduce polyallylic ethers. Thus under similar conditions, reaction of **2a** with alcohol **17**[25] gave the desired PAPE star **2g** in 84% isolated yield. Newkome had previously described how the TRIS [tris(hydroxymethyl)aminomethane] (**18**) group can be used to convert terminal esters into terminal hydroxyls. This method could potentially increase in a final and single step the number of polar terminal groups. This TRIS group has the advantage of being neutral but polar, increasing solubility without being charged, which can cause sometimes toxicology issues. When the methyl ester terminated first generation star **2a** was reacted in DMSO with an excess of TRIS (**18**) in the presence of potassium carbonate, the star **2h** having nine terminal hydroxyl groups was obtained in a 71% isolated yield.

All these macromolecules were completely characterized by routine physical methods including ^{1}H, ^{13}C NMR, IR, elemental analysis, and MS. However, one of the reasons why we particularly chose to develop PAPE stars is the ease of ^{1}H NMR analysis because of the absence of complicated multiplicity induced. Careful analysis of ^{1}H NMR spectra allowed to characterize easily our stars. As shown for the first and second generation stars **2a** and **2d** (Figure 2), the resonance signals in ^{1}H NMR are all sharp and distinct so as they can be easily assigned according to the chemical shifts and integrations. Analyzing the ^{1}H NMR spectrum of the first generation star **2a**, the appear-



Scheme 3 *Reagents and conditions*: (a) **2a** or **2d** (1 equiv), Ti(O-*i*Pr)$_4$ (15 mol%), **15**, **16** or **17** (0.15 M), 130 °C, (**2c**: 89%, **2e**: 95%, **2f**: 54%, **2g**: 84%); (b) **2a** (1 equiv), **18** (3.3 equiv), K_2CO_3 (3.3 equiv), DMSO, 60 °C (**2h**: 71%).



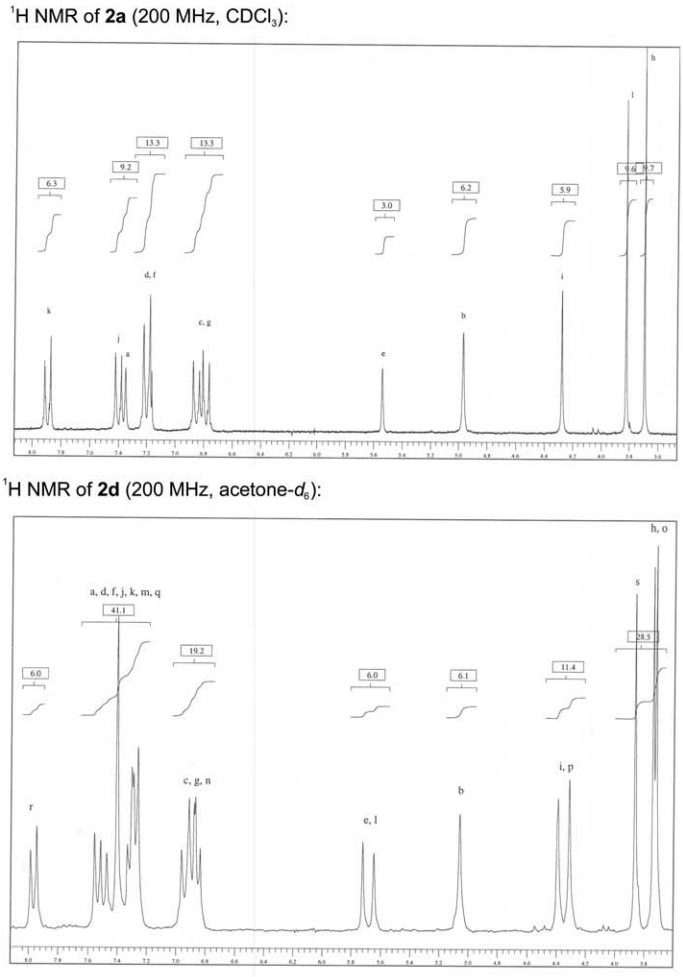


Figure 2 ^{1}H NMR spectra of **2a** and **2d**

ance of core signals around 5.0 and 7.42 ppm, corresponding respectively to CH_2 linkage to branches and aromatic CH signals from the core, proved the formation of the star. The ^{1}H NMR spectrum of the second generation star **2d** showed distinct resonance signals for each generation even using a 200 MHz apparatus. Different signals can indeed be observed for the two different OMe and the two different CH_2 of the PAPE iterative unit. In most cases simple electrospray ionization techniques were sufficient to characterize the stars, but some needed MALDI-TOF analysis to detect the molecular mass ions.

Cytocompatibility has been evaluated by in vitro MTT cell proliferation assays.[26] This test is a colorimetric assay based on the enzymatic reduction of a tetrazolium salt into purple colored formazan in metabolically active cells. The enzymatic activity is quantified in cells surviving after treatment with antineoplastic agents and is directly proportional to the cellular proliferation response and the cytotoxicity of the product. No significant toxicity was detected associated with the products tested **2c**, **2e**, **2f**, and **2h** (Figure 3) in a concentration range of 0.1 to 1000 µg/mL.

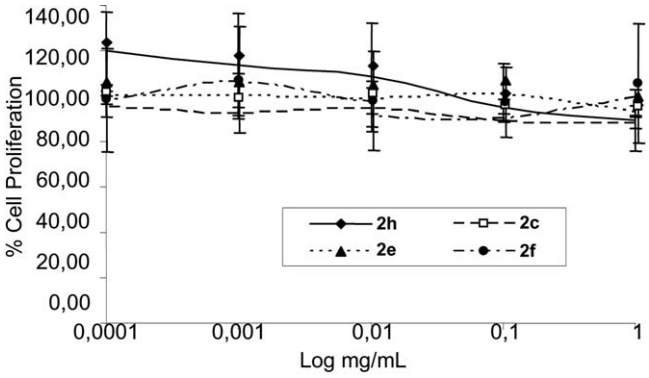


Figure 3 MTT Cell proliferation assay results (RAW 264.7 cells)

In conclusion, we have succeeded in developing a convenient route to low generation PAPE stars **1** and **2**. First generation branches **3a–c** were obtained according a three-step sequence developed previously. The second generation branch **3d** was readily obtained using iodinated compound **4**. Acylated PAPE **1** stars have been isolated in moderate yields in comparison with alkylated PAPE stars **2**, which were obtained in good to excellent yields.

Surprisingly the presence of amino chains within compound **3b** interfered with star synthesis. These results led us to explore another way of introduction of polar groups, essential for biological studies. Transesterification proved to be an effective way of access to stars bearing polar moieties. Reaction of TRIS group with the methyl esters of **2a** and **2d** afforded another polar, but neutral kind of star. Preliminary evaluation of the cytotoxicity of some of the synthesized PAPE stars showed that these macromolecules are biocompatible making them suitable for further in vitro biological studies. Additional developments concerning functionalization of the C≡C bonds on these star macromolecules are currently in progress and will be reported in due course.

All glassware were oven-dried at 140 °C and all reactions were conducted under argon. THF was distilled from sodium/benzophenone ketyl. Et_3N was distilled from KOH under argon prior to use. The compounds were all identified by usual physical methods: ^1H NMR, ^{13}C NMR, IR, and elemental analysis. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 or Bruker ARX 400 spectrometer. ^1H chemical shifts are reported in ppm from an internal standard TMS or of residual $CHCl_3$ (7.27 ppm). ^{13}C chemical shifts are reported in ppm from the central peak of $CDCl_3$ (77.14 ppm). IR spectra were recorded on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a PerkinElmer 240 analyzer. Mass spectra were obtained with a LCT Micromass spectrometer. Analytical TLC analyses were performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected.

4-Allyloxybenzaldehyde (7b)

4-Hydroxybenzaldehyde (**7a**; 1.22 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), and KI (166 mg, 1 mmol) were dispersed in anhyd acetone (100 mL) under an inert atmosphere. 3-Bromoprop-1-ene (1.73 mL, 20 mmol) was added and the resulting mixture was refluxed and the reaction progress was monitored by TLC analysis until complete consumption of **7a** (3 h). The solvent was concentrated under vacuum and the resulting residue was partitioned between EtOAc (40 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to afford aldehyde **7b** as a yellow oil; yield: 1.60 g (98%); R_f = 0.51 (cyclohexane–EtOAc, 8:2).

IR (neat): 3076, 2925, 2837, 1686, 1596, 1575, 1507 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.06 (m, 1 H), 5.43 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.31 (dq, *J* = 12.0, 1.5 Hz, 1 H), 4.61 (dt, *J* = 5.2, 1.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 190.6, 163.6, 132.3, 131.9, 130.1, 118.2, 115.0, 69.0.

MS (ESI): *m*/*z* = 185 $(M + Na)^+$.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.95; H, 6.32.

Grignard Addition to 7b; General Procedure

Under an inert atmosphere, **7b** (1 equiv, 10 mmol) was dissolved in anhyd THF (30 mL) to give a 0.3 M solution. This solution was cooled to –40 °C, and a solution of Grignard reagent in THF (2.2 equiv) was added dropwise. The resulting mixture was stirred at this temperature and the progress of the reaction was monitored by TLC analysis until complete consumption of **7b** (2–3 h). The mixture was quenched with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under vacuum.

Compound 8a

Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded **8a** as a colorless oil; yield: 2.5 g (92%); R_f = 0.27 (cyclohexane–EtOAc, 8:2).

IR (neat): 3421, 2933, 2836, 1608, 1584, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.04 (m, 1 H), 5.74 (s, 1 H), 5.39 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.25 (dq, *J* = 9.0, 1.5 Hz, 1 H), 4.51 (dt, *J* = 5.2, 1.5 Hz, 2 H), 3.77 (s, 3 H), 2.20 (br s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 158.0, 136.6, 136.4, 133.3, 127.7, 117.6, 114.6, 113.8, 75.3, 68.8, 55.2.

MS (ESI): *m*/*z* = 563 $(2 M + Na)^+$, 293 $(M + Na)^+$.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.32; H, 6.52.

Compound 8b

Recrystallization from cyclohexane–EtOAc (95:5) afforded **8b** as a blue solid; yield: 10.83 g (85%); mp 81 °C; R_f = 0.31 (cyclohexane–EtOAc, 7:3).

IR (neat): 3273, 3000, 2800, 1612, 1522, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 6.04 (m, 1 H), 5.66 (s, 1 H), 5.39 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.22 (dq, *J* = 10.4, 1.6, Hz, 1 H), 4.53 (dt, *J* = 5.2, 1.6 Hz, 2 H), 4.35 (br s, 1 H, OH), 2.88 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.4, 150.8, 139.4, 134.9, 134.6, 128.4, 117.2, 115.0, 113.1, 75.5, 69.3, 40.8.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47. Found: C, 76.02; H, 7.34.

Propargylation of Alcohols 8a,b; General Procedure

NaH (60%, 2 equiv) was suspended in anhyd THF (0.4 M) and a solution of alcohol **8a**,**b** (1 equiv) in anhyd DMF (40 mL) was added under an inert atmosphere. The mixture was left to stir for 30 min and 3-bromoprop-1-yne (2 equiv) was added. The mixture was stirred at r.t. and the progress of the reaction was monitored by TLC analysis until complete consumption of the starting material (1–3 h) before quenching with H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum.

Compound 9a

Purification by flash chromatography (cyclohexane–EtOAc, 9:1, R_f = 0.39) afforded **9a** as a yellow oil; yield: 4.60 g (91%); R_f = 0.39 (cyclohexane–EtOAc, 9:1).

IR (neat): 3288, 3000, 2800, 1609, 1584, 1508, 1240, 1171, 1067, 1027 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.01 (m, 1 H), 5.57 (s, 1 H), 5.38 (dq, *J* = 18.8, 1.5 Hz, 1 H), 5,25 (dq, *J* = 10.4, 1.5 Hz, 1 H), 4.50 (dt, *J* = 5.2, 1.5 Hz, 2 H), 4.10 (d, *J* = 2.4 Hz, 2 H), 3.77 (s, 3 H), 2.42 (t, *J* = 2.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.1, 159.1, 133.7, 133.5, 133.3, 128.5, 117.6, 114.6, 113.8, 80.8, 79.9, 74.3, 68.8, 55.5, 55.2.

MS (ESI): *m*/*z* = 639 $(2 M + Na)^+$, 331 $(M + Na)^+$.

Compound 9b

Purification by flash chromatography (cyclohexane–EtOAc, 8:2, R_f = 0.48) afforded **9b** as a yellow oil; yield: 10.4 g (91%); R_f = 0.39 (cyclohexane–EtOAc, 8:1).

IR (neat): 3288, 3000, 2800, 1610, 1520, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.68 (d, *J* = 8.6 Hz, 2 H), 5.53 (s, 1 H), 6.02 (m, 1 H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.25 (dq, *J* = 10.4, 1.5 Hz, 1 H), 4.51 (dt, *J* = 5.0, 1.5 Hz, 2 H), 4.10 (d, *J* = 2.4 Hz, 2 H), 2.92 (s, 6 H), 2.41 (t, *J* = 2.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.7, 150.0, 134.2, 133.2, 128.8, 128.2, 117.3, 114.3, 112.2, 80.9, 80.1, 74.1, 68.6, 55.2, 40.4.

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.25; H, 7.32.

Compound 13

Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded **13** as a yellow oil; yield: 3.42 g (99%); R_f = 0.54 (cyclohexane–EtOAc, 7:3).

IR (neat): 3288, 2928, 2850, 1609, 1584, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.2 Hz, 2 H), 7.24 (m, 8 H), 6.85 (d, *J* = 8.8 Hz, 6 H), 6.01 (m, 1 H), 5.62 (s, 1 H), 5.60 (s, 1 H), 5.36 (q, *J* = 17.2, 1.5, 1.6 Hz, 1 H),.5.28 (q, *J* = 10.6, 1.5, 1.6 Hz, 1 H), 4.51 (dt, *J* = 5.2, 1.5 Hz, 2 H), 4.32 (s, 2 H), 4.11 (d, *J* = 2.4 Hz, 2 H), 3.77 (s, 6 H), 2.40 (t, *J* = 2.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 159.1, 158.1, 141.9, 134.0, 133.7, 133.3, 132.7, 131.8, 128.7, 128.5, 127.0, 121.9, 117.6, 114.6, 113.9, 113.8, 88.1, 85.5, 79.6, 80.9, 74.6, 68.8, 56.4, 55.6, 55.2.

MS (ESI): *m*/*z* = 581 $(M + Na)^+$.

Sonogashira–Linstrumelle Coupling Reaction of 9; General Procedure

To a solution of the iodinated compound, 4-iodobenzoic acid methyl or *N*,*N*-2-dimethylaminoethyl ester in freshly distilled Et_3N (20 mL) were added $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%). The resulting mixture was allowed to reach 60 °C and a solution of alkyne **9** in Et_3N (20 mL) was slowly added dropwise. The mixture was further stirred at 60 °C and the progress of the reaction was monitored by TLC analysis until complete consumption of starting material (2–4 h). The mixture was concentrated under vacuum. The residue was dissolved in EtOAc (100 mL) and the EtOAc layer washed successively with aq HCl (0.5 M, 10 mL), H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated under vacuum.

Compound 10a

Obtained from **9a** (1 equiv) and 4-iodobenzoic acid methyl ester (1.2 equiv). Purification by flash chromatography (cyclohexane–EtOAc, 9:1) afforded pure **10a** as a brown oil; yield: 1.7 g (98%); R_f = 0.24 (cyclohexane–EtOAc, 9:1).

IR (neat): 2998, 2838, 1719, 1606, 1584, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.6 Hz, 2 H), 7.48 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.02 (m, 1 H), 5.61 (s, 1 H), 5.38 (dq, *J* = 17.4, 1.5 Hz, 1 H), 5.25 (dq, *J* = 8.4, 1.5 Hz, 1 H), 4.51 (dt, *J* = 5.2, 1.5 Hz, 2 H), 4.36 (s, 2 H), 3.91 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 159.1, 158.1, 133.8, 133.6, 133.3, 131.6, 129.7, 129.4, 128.5, 127.5, 117.6, 114.6, 113.8, 88.6, 85.5, 81.3, 68.8, 56.4, 55.2, 52.2.

MS (ESI): *m*/*z* = 465 $(M + Na)^+$.

Compound 10b

Obtained from **9b** (1.2 equiv) and 4-iodobenzoic acid methyl ester (1 equiv). Purification by flash chromatography (cyclohexane–EtOAc, 9:1) afforded pure **10b** as a yellow oil; yield: 910 mg (67%); R_f = 0.30 (cyclohexane–EtOAc, 8:2).

IR (neat): 3000, 2800, 1719, 1607, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 6.08 (m, 1 H), 5.65 (s, 1 H), 5.44 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.32 (dq, *J* = 10.4, 1.5 Hz, 1 H), 4.57 (dt, *J* = 5.2, 1.5 Hz, 2 H), 4.42 (s, 2 H), 3.97 (s, 3 H), 2.99 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 157.9, 150.2, 134.3, 133.3, 131.6, 129.4, 128.4, 128.9, 127.6, 117.5, 114.5, 112.4, 88.9, 85.3, 81.5, 68.8, 56.2, 52.1, 40.5.

MS (ESI): *m*/*z* = 478 $(M + Na)^+$, 456 $(M + H)^+$.

Compound 10c

Obtained from **9a** (1.05 equiv) and 4-iodobenzoic acid methyl ester (1.0 equiv). Purification by flash chromatography (EtOAc–Et_3N, 98:2) afforded pure **10c** as a brown oil; yield: 1.91 g (96%); R_f = 0.51 (EtOAc–Et_3N, 98:2).

IR (neat): 3000, 2800, 1716, 1607, 1585, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.2 Hz, 2 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.02 (m, 1 H), 5.61 (s, 1 H), 5.39 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.26 (dq, *J* = 10.4, 1.5 Hz, 1 H), 4.51 (dt, *J* = 5.2, 1.5 Hz, 2 H), 4.42 (t, *J* = 5.8 Hz, 2 H), 4.35 (s, 2 H), 3.77 (s, 3 H), 2.70 (t, *J* = 5.8 Hz, 2 H), 2.32 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 159.1, 158.1, 138.8, 133.5, 133.2, 131.6, 129.7, 129.5, 128.5, 127.4, 117.5, 114.6, 113.8, 88.5, 85.5, 81.3, 68.8, 63.1, 57.8, 56.3, 55.2, 45.8.

Anal. Calcd for $C_{31}H_{33}NO_5$: C, 74.53; H, 6.66. Found: C, 74.15; H, 6.82.

Compound 12

Obtained from **9a** (1 equiv) and **11** (1.5 equiv). Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded pure **12** as a brown oil; yield: 3.21 g (77%); R_f = 0.27 (EtOAc–cyclohexane, 7:3).

IR (neat): 3456, 2999, 2836, 1608, 1584, 1507 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H), 7.25 (m, 6 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 4 H), 6.02 (m, 1 H), 5.78 (s, 1 H), 5.63 (s, 1 H), 5.38 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.26 (dq, *J* = 10.6, 1.6 Hz, 1 H), 4.50 (dt, *J* = 5.2, 1.6 Hz, 2 H), 4.32 (s, 2 H), 3.78 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 159.,0, 158.0, 144.4, 135.8, 133.9, 133.7, 133.3, 131.7, 128.5, 127.9, 126.2, 121.6, 117.5, 114.6, 113.9, 113.7, 86.1, 85.3, 80.9, 75.3, 68.8, 56.4, 55.2.

Anal. Calcd for $C_{34}H_{32}O_5$: C, 78.44; H, 6.20. Found: C, 78.15; H, 6.39.

Compound 14

Obtained from **9a** (1 equiv) and **4** (2 equiv). Purification by flash chromatography (cyclohexane–EtOAc, 9:1) afforded pure **14** as a brown oil; yield: 230 mg (74%); R_f = 0.3 (EtOAc–cyclohexane, 2:8).

IR (neat): 2951, 2837, 1719, 1607, 1584, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 6 H), 6.84 (d, *J* = 8.8 Hz, 4 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.99 (m, 1 H), 5.62 (s, 1 H), 5.60 (s, 1 H), 5.35 (dq,

J = 17.2, 1.5 Hz, 1 H), 5.23 (dq, J = 10.4, 1.5 Hz, 1 H), 4.48 (dt, J = 5.4, 1.5 Hz, 2 H), 4.34 (s, 2 H), 4.30 (s, 2 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 159.3, 159.1, 158.1, 142.0, 133.9, 133.7, 132.8, 133.3, 131.8, 131.6, 129.7, 129.4, 128.7, 128.5, 127.3, 127.0, 122.0, 117.5, 114.6, 113.9, 113.7, 88.2, 86.1, 85.7, 85.5, 81.3, 80.9, 68.8, 56.5, 55.2, 52.1.

MS (ESI): m/z = 715 $(M + Na)^+$.

Deprotection of Phenolic Group in 10a–c and 14; General Procedure

To a suspension of the allylic protected branch **10a–c**, **14** (1 equiv) and $Pd(PPh_3)_4$ (5 mol%) in a mixture of anhyd MeOH (0.06 M/branch) and anhyd THF (0.25 M/branch) was added $NaBH_4$ (6 equiv) at 0 °C (at –10 °C for **3d**). The mixture was further stirred at 0 °C (or –10 °C) and the progress of the reaction was monitored by TLC analysis until complete consumption of the starting material (45 min to 4 h) before workup. The mixture was dissolved in EtOAc (100 mL) and the EtOAc layer was washed with brine (30 mL), dried (Na_2SO_4), and concentrated under vacuum.

Compound 3a

Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded pure **3a** as a yellow oil; yield: 4.27 g (84%); R_f = 0.46 (EtOAc–cyclohexane, 4:6).

IR (neat): 3382, 2975, 2851, 1720, 1607, 1509 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.6 Hz, 2 H), 7.47 (d, J = 8.6 Hz, 2 H), 7.27 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 5.60 (s, 1 H), 5.56 (s, 1 H, OH), 4.35 (s, 2 H), 3.91 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.6, 159.0, 155.3, 133.5, 133.3, 131.6, 129.5, 129.3, 128.7, 128.5, 127.4, 115.1, 113.7, 88.5, 85.4, 81.3, 56.3, 55.1, 52.2.

MS (ESI): m/z = 425 $(M + Na)^+$.

Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.28; H, 5.92.

Compound 3b

Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded pure **3b** as a yellow oil; yield: 650 mg (77%); R_f = 0.27 (EtOAc–cyclohexane, 3:7).

IR (neat): 3381, 3000, 2800, 1719, 1608, 1514 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.12 (d, J = 8.2 Hz, 2 H), 7.10 (d, J = 8.2 Hz, 2 H), 6.64 (d, J = 8.2 Hz, 2 H), 6.60 (d, J = 8.2 Hz, 2 H), 5.47 (s, 1 H), 4.24 (s, 2 H), 3.79 (s, 3 H), 2.78 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.7, 155.4, 150.1, 133.4, 131.6, 129.3, 128.5, 128.3, 127.6, 115.1, 112.7, 88.9, 85.3, 81.7, 56.1, 52.2, 40.6.

MS (ESI): m/z = 438 $(M + Na)^+$, 416 $(M + H)^+$.

Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06. Found: C, 74.78; H, 6.18.

Compound 3c

Purification by flash chromatography (CH_2Cl_2–cyclohexane–EtOAc, 6:3:1) afforded pure **3c** as a brown solid; yield: 920 mg (82%); mp 110–112 °C; R_f = 0.22 (CH_2Cl_2–EtOAc–cyclohexane, 6:1:3).

IR (neat): 2959-2835, 1720, 1609, 1510 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.18 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.4 Hz, 2 H), 6.62 (d, J = 8.4 Hz, 2 H), 5.48 (s, 1 H), 4.37 (t, J = 5.6 Hz, 2 H), 4.23 (s, 2 H), 3.68 (s, 3 H), 2.70 (t, J = 5.6 Hz, 2 H), 2.29 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.0, 159.0, 156.2, 133.7, 132.5, 131.5, 129.5, 128.7, 128.5, 127.5, 115.4, 113.7, 88.7, 85.4, 81.4, 62.3, 57.6, 56.3, 55.2, 45.4.

MS (ESI): m/z = 482 $(M + Na)^+$, 460 $(M + H)^+$.

Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36. Found: C, 72.96; H, 6.52.

Compound 3d

Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded pure **3d** as a yellow oil; yield: 260 mg (80%); R_f = 0.42 (EtOAc–cyclohexane, 4:6).

IR (neat): 3400, 2953, 2838, 1719, 1607 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, J = 8,0 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 8.4 Hz, 4 H), 7.20 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.76 (d, J = 8.4 Hz, 2 H), 6.08 (br s, 1 H, OH), 5.65 (s, 1 H), 5.62 (s, 1 H), 4.37 (s, 2 H), 4.33 (s, 2 H), 3.89 (s, 3 H), 3.75 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.6, 159.2, 158.9, 155.4, 141.9, 133.6, 133.3, 132.7, 131.7, 131.6, 129.6, 129.4, 128.7, 128.5, 127.3, 126.9, 121.9, 115.2, 113.9, 113.7, 88.2, 86.1, 85.7, 85.5, 81.3, 81.0, 56.4, 56.3, 55.2, 52.2.

MS (ESI): m/z = 1322 $(2 M + NH_4)^+$, 670 $(M + NH_4)^+$.

Anal. Calcd for $C_{42}H_{36}O_7$: C, 77.28; H, 5.56. Found: C, 77.02; H, 5.83.

Star 1a

A solution of **3a** (170 mg, 0.42 mmol), DMAP (94 mg, 0.76 mmol), distilled Et_3N (0.53 mL, 3.84 mmol), and **5** (34 mg, 0.12 mmol) in anhyd CH_2Cl_2 (1.2 mL) was stirred at 0 °C under an inert atmosphere for 1 h. The mixture was then stirred at r.t. and the progress of the reaction was monitored by TLC analysis until complete consumption of **5** (3 h) before quenching with aq $NaHCO_3$ (1 mL). The organic layer was washed with brine (0.5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography (CH_2Cl_2–cyclohexane–EtOAc, 60:35:5) afforded pure **1a** as a colorless oil; yield: 70 mg (40%); R_f = 0.69 (CH_2Cl_2–EtOAc–cyclohexane, 6:1:3).

IR (neat): 2951, 2849, 1719, 1607, 1509 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.12 (s, 3 H), 7.91 (d, J = 8.2 Hz, 6 H), 7.42 (d, J = 8.2 Hz, 6 H), 7.39 (d, J = 8.4 Hz, 6 H), 7.23 (d, J = 8.6 Hz, 6 H), 7.16 (d, J = 8.4 Hz, 6 H), 6.82 (d, J = 8.6 Hz, 6 H), 5.63 (s, 3 H), 4.32 (s, 6 H), 3.83 (s, 9 H), 3.72 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.2, 159.4, 149.9, 139.8, 136.0, 132.8, 131.7, 131.2, 129.8, 129.4, 128.8, 128.4, 127.3, 121.4, 114.0, 88.2, 85.7, 81.1, 56.5, 55.3, 52.2.

MS (MALDI-TOF-MS): m/z = 1385 $(M + Na)^+$.

Anal. Calcd for $C_{84}H_{66}O_{18}$: C, 74.00; H, 4.88. Found: C, 73.25; H, 5.18.

Star 1c

To a solution of DMAP (78 mg, 0.64 mmol), distilled pyridine (0.25 mL, 3.2 mmol), and **5** (29 mg, 0.108 mmol) in anhyd THF (1.1 mL) was added a solution of **3c** (150 mg, 0.32 mmol) in anhyd THF (1 mL) at 0 °C under an inert atmosphere. The mixture was then stirred at 0 °C and monitored by TLC analysis until complete consumption of **5** (6 h) before quenching with aq $NaHCO_3$ (1 mL). The organic layer was washed with brine (0.5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography

over alumina (eluent: EtOAc) afforded pure **1c** as a colorless oil; yield: 40 mg (24%); R_f = 0.41 (EtOAc–Et_3N–MeOH, 8:1:1).

IR (neat): 2951–2771, 1743, 1716, 1607, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.12 (s, 3 H), 7.92 (d, *J* = 8.2 Hz, 6 H), 7.42 (d, *J* = 8.2 Hz, 6 H), 7.39 (d, *J* = 7.8 Hz, 6 H), 7.23 (d, *J* = 8.6 Hz, 6 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 6 H), 5.63 (s, 3 H), 4.35 (t, *J* = 5.8 Hz, 6 H), 4.32 (s, 6 H), 3.73 (s, 9 H), 2.64 (t, *J* = 5.8 Hz, 6 H), 2.26 (s, 18 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 163.3, 159.4, 149.9, 139.9, 136.0, 132.9, 131.7, 131.2, 129.8, 129.5, 128.8, 128.4, 127.4, 121.4, 114.0, 88.2, 85.7, 81.1, 63.1, 57.8, 56.5, 55.3, 45.8 ppm.

MS (MALDI-TOF-MS): *m*/*z* = 1556.6 [(M + Na)$^+$, 30], 1534.7 [(M + H)$^+$, 40].

Star 1d

To a solution of **3d** (130 mg, 0.19 mmol), DMAP (1 mg, 0.006 mmol), and distilled Et_3N (0.084 mL, 0.60 mmol) in anhyd CH_2Cl_2 (1 mL) was added a solution of **5** (16 mg, 0.06 mmol) in anhyd CH_2Cl_2 (2 mL) at 0 °C under an inert atmosphere. The mixture was stirred at r.t. and the progress of the reaction was monitored by TLC analysis until complete consumption of **5** (6 h) before quenching with aq $NaHCO_3$ (1 mL). The organic layer was washed with brine (0.5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography (CH_2Cl_2–cyclohexane–EtOAc, 60:35:5) afforded pure **1d** as a colorless solid; yield: 30 mg (24%); mp 71 °C; R_f = 0.46 (CH_2Cl_2–cyclohexane–EtOAc, 80:16:4).

IR (neat): 2952, 2837, 1721, 1607, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.18 (s, 3 H), 7.98 (d, *J* = 8.6 Hz, 6 H), 7.48 (d, *J* = 8.6 Hz, 6 H), 7.45 (d, *J* = 8.6 Hz, 6 H), 7.20–7.35 (m, 30 H), 6.88 (d, *J* = 8.6 Hz, 6 H), 6.87 (d, *J* = 8.6 Hz, 6 H), 5.72 (s, 3 H), 5.67 (s, 3 H), 4.37 (s, 12 H), 3.90 (s, 9 H), 3.79 (s, 9 H), 3.78 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 163.2, 159.3, 149.8, 142.1, 140.0, 136.0, 133.0, 132.8, 131.8, 131.6, 131.2, 129.8, 129.4, 128.8, 128.4, 127.0, 127.3, 121.8, 121.3, 114.0, 88.2, 86.4, 85.7, 85.2, 81.3, 80.7, 56.5, 55.2, 52.2.

MS (MALDI-TOF-MS): *m*/*z* = 2152.7 [(M + K)$^+$, 50], 2136.8 (M + Na)$^+$.

Anal. Calcd for $C_{135}H_{108}O_{24}$: C, 76.69; H, 5.15. Found: C, 75.94; H, 5.22.

Stars 2a and 2d; General Procedure

A suspension of **6** (1 equiv), **3a**, or **3d** (3.6 equiv), K_2CO_3 (6 equiv), KI (2.7 equiv), and Aliquat 336 (cat.) in anhyd acetone (0.05 M, 11 mL) was stirred at 60 °C and the progress of the reaction was monitored by TLC analysis until complete consumption of **6** (36 to 48 h). The mixture was then concentrated under vacuum. The resulting residue was dissolved in EtOAc (10 mL), the organic layer was washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum.

Star 2a

Purification by flash chromatography afforded pure **2a** as a colorless solid; yield: 584 mg (80%); mp 40–42 °C; R_f = 0.46 (CH_2Cl_2–cyclohexane–EtOAc, 6:3:1).

IR (neat): 2950, 2837, 1719, 1607, 1585, 1508 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.2 Hz, 6 H), 7.48 (d, *J* = 8.2 Hz, 6 H), 7.42 (s, 3 H), 7.27 (d, *J* = 8.8 Hz, 12 H), 6.92 (d, *J* = 8.8 Hz, 6 H), 6.87 (d, *J* = 8.8 Hz, 6 H), 5.61 (s, 3 H), 5.03 (s, 6 H), 4.35 (s, 6 H), 3.89 (s, 9 H), 3.76 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 159.0, 158.1, 137.8, 134.0, 133.4, 131.6, 129.6, 129.3, 128.5, 127.4, 125.8, 114.7, 113.7, 88.5, 85.4, 81.2, 69.6, 56.3, 55.1, 52.1.

MS (MALDI-TOF-MS): *m*/*z* = 1343 [(M + Na)$^+$, 50].

Anal. Calcd for $C_{84}H_{72}O_{15}$: C, 76.35; H, 5.49. Found: C, 76.12; H, 5.62.

Star 2d

Purification by flash chromatography (CH_2Cl_2–cyclohexane–EtOAc, 4:5:1) afforded pure **2d** as a colorless solid; yield: 335 mg (90%); mp 59–60 °C; R_f = 0.43 (CH_2Cl_2–cyclohexane–EtOAc, 80:16:4).

IR (neat): 2951, 2837, 1720, 1607, 1584, 1509 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 8.01 (d, *J* = 8.5 Hz, 6 H), 7.59 (d, *J* = 8.5 Hz, 6 H), 7.53 (s, 3 H), 7.45 (m, 12 H), 7.36 (d, *J* = 8.8 Hz, 6 H), 7.33 (d, *J* = 8.8 Hz, 12 H), 7.00 (d, *J* = 8.8 Hz, 6 H), 6.94 (d, *J* = 8.8 Hz, 6 H), 6.91 (d, *J* = 8.8 Hz, 6 H), 5.78 (s, 3 H), 5.70 (s, 3 H), 5.13 (s, 6 H), 4.47 (s, 6 H), 4.36 (s, 6 H), 3.91 (s, 9 H), 3.79 (s, 9 H), 3.78 (s, 9 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 166.4, 160.2, 159.9, 158.9, 143.6, 138.8, 135.3, 134.8, 133.9, 132.4, 132.3, 130.7, 130.0, 129.3, 127.9, 129.05, 129.02, 127.7, 126.7, 122.5, 115.3, 114.5, 55.35, 114.3, 89.3, 86.4, 86.3, 85.8, 81.9, 81.6, 70.1, 56.8, 56.6, 55.31, 52.3.

MS (ESI): *m*/*z* = 2091 (M + NH_4)$^+$, 1054 (M/2 + NH_4)$^+$.

Anal. Calcd for $C_{135}H_{114}O_{21}$: C, 78.24; H, 5.54. Found: C, 77.84; H, 5.61.

Star 2b

To a suspension of NaH (60%, 22 mg, 0.55 mmol) in anhyd THF (1.6 mL) was added a solution of **3b** (210 mg, 0.5 mmol) in anhyd DMF (1.6 mL) under an inert atmosphere. After 30 min, a solution of **6** (60 mg, 0.16 mmol) was added. The mixture was stirred at r.t. and the progress of the reaction was monitored by TLC analysis until complete consumption of **6** (16 h) before quenching with H_2O (0.5 mL). The aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography (CH_2Cl_2–cyclohexane–EtOAc, 5:4:1) afforded pure **2b** as a colorless oil; yield: 50 mg (22%); R_f = 0.45 (CH_2Cl_2–cyclohexane–EtOAc, 5:4:1).

IR (neat): 3000, 2800, 1721, 1608, 1522, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 6 H), 7.47 (d, *J* = 8.2 Hz, 6 H), 7.42 (s, 3 H), 7.29 (d, *J* = 8.6 Hz, 6 H), 7.21 (d, *J* = 8.8 Hz, 6 H), 6.92 (d, *J* = 8.6 Hz, 6 H), 6.69 (d, *J* = 8.8 Hz, 6 H), 5.58 (s, 3 H), 5.04 (s, 6 H), 4.35 (s, 6 H), 3.89 (s, 9 H), 2.91 (s, 18 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 158.0, 150.1, 137.9, 134.6, 131.6, 129.4, 128.9, 129.6, 128.4, 127.6, 125.8, 114.6, 112.4, 88.9, 85.2, 81.5, 69.7, 56.2, 52.1, 40.5.

MS (MALDI-TOF): *m*/*z* = 1382.3 (M + Na)$^+$, 1359.4 (M + H)$^+$.

Anal. Calcd for $C_{87}H_{81}N_3O_{12}$: C, 76.80; H, 6.00; N, 3.09. Found: C, 75.56; H, 6.13; N, 2.76.

Compound 16

To a solution of 2-piperazin-1-ylethanol (9.25 g, 71 mmol) were added at 0 °C formic acid (8.03 mL, 213 mmol), and then slowly formaldehyde (16.85 mL, 213 mmol). After 20 min at 0 °C, the mixture was heated at 80 °C for 2 days before quenching with H_2O (5 mL) and concentration under vacuum. The resulting residue was dissolved in CH_2Cl_2 (6 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography (CH_2Cl_2–MeOH–Et_3N, 8:1:1) afforded the pure alcohol **16** as a col-

orless oil; yield: 5.4 g (53%); bp 55 °C/1.5 mm Hg; R_f = 0.51 (CH_2Cl_2–MeOH–Et_3N, 8:1:1).

IR (neat): 3222, 2937, 2692 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 5.4 Hz, 2 H), 2.53 (t, *J* = 5.4 Hz, 2 H), 2.45 (m, 8 H), 2.27 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 61.6, 59.4, 54.9, 52.8, 45.8.

Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18. Found: C, 58.19; H, 11.31.

Transesterification Reaction of 2a and 2d; General Procedure

A solution of **2a** or **2d** and Ti(O*i*-Pr)$_4$ (15 mol%) in **15**, **16**, or **17** (0.15 M) was heated at 130 °C and the progress of the reaction was monitored by TLC analysis until complete consumption of the starting material (15–30 min to 2 h) before quenching with H_2O (0.2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 0.5 mL). The combined organic layers were washed with brine (3 × 0.2 mL), dried (Na_2SO_4), filtered, concentrated under vacuum, and purified by flash chromatography.

Star 2c

Colorless oil; yield: 60 mg (89%); R_f = 0.32 (EtOAc–Et_3N–MeOH, 8:1:1).

IR (neat): 2947, 2772, 1715, 1607, 1585, 1509 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.4 Hz, 6 H), 7.39 (d, *J* = 8.4 Hz, 6 H), 7.35 (s, 3 H), 7.20 (d, *J* = 8.8 Hz, 12 H), 6.85 (d, *J* = 8.8 Hz, 6 H), 6.79 (d, *J* = 8.8 Hz, 6 H), 5.54 (s, 3 H), 4.97 (s, 6 H), 4.34 (t, *J* = 5.8 Hz, 6 H), 4.27 (s, 6 H), 3.70 (s, 9 H), 2.63 (t, *J* = 5.8 Hz, 6 H), 2.25 (s, 18 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 159.1, 158.2, 137.9, 134.1, 133.5, 131.6, 129.8, 129.5, 128.5, 127.4, 125.9, 114.7, 113.8, 88.5, 85.5, 81.2, 69.7, 63.1, 57.8, 56.4, 55.2, 45.8.

MS (ESI): *m*/*z* = 1491.4 $(M + H)^+$.

Anal. Calcd for $C_{93}H_{93}N_3O_{15}$: C, 74.83; H, 6.28. Found: C, 73.78; H, 5.61.

Star 2e

Colorless oil; 49 mg (95%); R_f = 0.37 (EtOAc–Et_3N–MeOH, 8:1:1).

IR (neat): 2960, 2771, 1717, 1608, 1585, 1510 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.3 Hz, 6 H), 7.39 (d, *J* = 8.3 Hz, 6 H), 7.34 (m, 12 H), 7.26 (s, 3 H), 7.18 (d, *J* = 8.7 Hz, 18 H), 6.84 (d, *J* = 8.7 Hz, 6 H), 6.79 (d, *J* = 8.7 Hz, 6 H), 6.77 (d, *J* = 8.7 Hz, 6 H), 5.55 (s, 6 H), 4.96 (s, 6 H), 4.34 (t, *J* = 5.8 Hz, 6 H), 4.28 (s, 6 H), 4.24 (s, 6 H), 3.69 (s, 9 H), 3.68 (s, 9 H), 2.63 (t, *J* = 5.8 Hz, 6 H), 2.25 (s, 18 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 159.4, 159.1, 158.2, 142.0, 137.9, 134.2, 133.7, 132.8, 131.8, 131.6, 129.8, 129.5, 128.7, 128.6, 127.3, 127.0, 125.9, 122.0, 114.7, 114.0, 113.8, 88.2, 86.1, 85.7, 85.5, 81.3, 80.9, 69.7, 63.1, 57.8, 56.5, 55.2, 45.8.

MS (MALDI-TOF-MS): *m*/*z* = 2280.9 $(M + K)^+$, 2264.9 $(M + Na)^+$.

Anal. Calcd for $C_{144}H_{135}N_3O_{21}$: C, 77.09; H, 6.06. Found: C, 76.28; H, 6.61.

Star 2f

Purification by flash chromatography afforded **2f** as a colorless oil; yield: 20 mg (54%); R_f = 0.25 (EtOAc–Et_3N–MeOH, 8:1:2).

IR (neat): 2935, 2798, 2359, 1717, 1608, 1585, 1509 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.99 (d, *J* = 8.2 Hz, 6 H), 7.55 (d, *J* = 8.2 Hz, 6 H), 7.52 (s, 3 H), 7.31 (d, *J* = 8.6 Hz, 12 H), 7.00 (d, *J* = 8.6 Hz, 6 H), 6.89 (d, *J* = 8.6 Hz, 6 H), 5.68 (s, 3 H), 5.13 (s, 6 H), 4.41 (t, *J* = 5.8 Hz, 6 H), 4.38 (s, 6 H), 3.76 (s, 9 H), 2.74 (t, *J* = 5.8 Hz, 6 H), 2.58 (m, 12 H), 2.44 (m, 12 H), 2.22 (s, 9 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 166.1, 160.2, 159.2, 139.1, 135.5, 135.0, 132.6, 131.1, 130.3, 129.30, 129.27, 128.3, 126.9, 115.6, 114.6, 89.8, 85.9, 82.2, 70.4, 63.4, 57.3, 56.9, 55.7, 55.6, 53.7, 45.9.

MS (MALDI-TOF-MS): *m*/*z* = 1695.7 $(M + K)^+$, 1680.7 $(M + Na)^+$, 1657.7 $(M + H)^+$.

Anal. Calcd for $C_{102}H_{108}N_6O_{15}$: C, 73.89; H, 6.57. Found: C, 73.08; H, 6.81.

Star 2g

Colorless oil; yield: 30 mg (84%); R_f = 0.21 (CH_2Cl_2–cyclohexane–EtOAc, 3:6:1).

IR (neat): 3000, 2853, 1719, 1607, 1509 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 8.02 (d, *J* = 8.2 Hz, 6 H), 7.57 (d, *J* = 8.2 Hz, 6 H), 7.53 (s, 3 H), 7.32 (d, *J* = 8.6 Hz, 12 H), 6.99 (d, *J* = 8.6 Hz, 6 H), 6.90 (d, *J* = 8.6 Hz, 6 H), 5.80 (m, 9 H), 5.68 (s, 3 H), 5.25 (dd, *J* = 17.3, 1.6 Hz, 9 H), 5.13 (s, 6 H), 5.09 (dd, *J* = 10.5, 1.6 Hz, 9 H), 4.38 (s, 12 H), 3.96 (d, *J* = 5.2 Hz, 18 H), 3.76 (s, 9 H), 3.57 (s, 18 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 166.0, 160.1, 159.2, 139.0, 136.1, 135.4, 134.9, 132.5, 131.1, 130.3, 129.2, 128.1, 126.9, 116.4, 115.5, 114.5, 89.7, 85.8, 82.1, 72.8, 70.3, 70.0, 65.3, 56.8, 55.5, 45.5.

MS (MALDI-TOF-MS): *m*/*z* = 2032 $(M + K)^+$, 2016 $(M + Na)^+$.

Anal. Calcd for $C_{123}H_{132}O_{24}$: C, 74.08; H, 6.67. Found: C, 73.58; H, 6.89.

Star 2h

A suspension of **2a** (28 mg, 0.021 mmol), K_2CO_3 (10 mg, 0.0069 mmol), and **18** (8 mg, 0.07 mmol) in anhyd DMSO (0.2 mL) was stirred at 60 °C and the progress of the reaction was monitored by TLC analysis until complete consumption of **2a** (16 h). The mixture was filtered and the filtrate concentrated under vacuum. The resulting residue was suspended in MeOH (1 mL) and filtered. The resulting solid was suspended in acetone (1 mL), filtered, and the filtrate was concentrated under vacuum to afford **2h** as a colorless oil; yield: 25 mg (71%).

IR (neat): 3385, 3000, 2800, 1642, 1607, 1585, 1529, 1508 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 7.84 (d, *J* = 8.4 Hz, 6 H), 7.53 (d, *J* = 8.4 Hz, 6 H), 7.51 (s, 3 H), 7.40 (br s, 1 H, NH), 7.31 (d, *J* = 8.6 Hz, 12 H), 6.98 (d, *J* = 8.6 Hz, 6 H), 6.89 (d, *J* = 8.6 Hz, 6 H), 5.67 (s, 3 H), 5.12 (s, 6 H), 4.50 (br s, 1 H, OH), 4.37 (s, 6 H), 3.81 (s, 18 H), 3.76 (s, 9 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 168.2, 166.0, 160.1, 160.1, 159.1, 139.0, 135.6, 135.4, 134.9, 132.4, 129.2, 128.2, 126.9, 126.7, 115.5, 114.5, 88.9, 85.8, 82.1, 70.3, 63.5, 63.2, 56.8, 55.5.

MS (MALDI-TOF-MS): *m*/*z* = 1625.8 $(M + K)^+$, 1609.9 $(M + Na)^+$.

Anal. Calcd for $C_{93}H_{93}N_3O_{21}$: C, 70.31; H, 5.90. Found: C, 69.88; H, 6.21.

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