JOC Note

Cross-Linking Dendrimers with Allyl Ether End-Groups Using the Ring-Closing Metathesis Reaction

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Abstract: A third generation Fréchet-type dendrimer containing 24 allyl ether end-groups was synthesized, cross-linked using the ring-closing metathesis (RCM) reaction, and the core was removed hydrolytically without significant fragmentation. The results are analogous to those previously reported for homoallyl ether dendrimers (Wendland, M. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1999**, *121*, 1389−1390) suggesting that the less readily available homoallyl ether dendrimers can be replaced by their allyl ethers analogues in a range of applications.

Introduction

We recently reported the synthesis of dendrimers whose cores are removed. For example, the end-groups of dendrimer **1** were extensively cross-linked with **2** to give **3** whose trimesic acid core (**4**) was removed hydrolytically giving "cored" dendrimer **5** (Scheme 1).[1,2] There are a number of potential applications for the resultant nanoparticles, for example, as higher capacity drug delivery agents and as molecularly imprinted dendrimers (MIDs).[3] The dendrimer cross-linking chemistry alone or in combination with coring can also be used to form a stable shell around metallic nanoparticles,[4] to rigidify the binding sites in molecularly imprinted polymers,[5] and to create organic nanotubes by a "molding" process.[6] Most commonly, the cross-linking of dendrimers has involved the ring-closing metathesis (RCM) reaction[7] of homoallyl ether end-groups.[1,3,6] There are a few notable exceptions wherein other types of alkenes are cross-linked via the RCM reaction[4,5,8] and entirely different cross-linking chemistries employed.[9]

The choice of the homoallyl ether over the allyl ether group was motivated by the concern that the latter might undergo undesired side reactions. In particular, the possibility for isomerization to a vinyl ether group that would deactivate the catalyst by forming an unreactive ruthenium carbene[10] was a compelling reason to choose the homoallyl group. Despite these concerns, and since our report on cored dendrimers appeared,[1] numerous examples of metathesis reactions of allyl ethers were reported.[11] Furthermore, there was considerable interest in pursuing dendrimers with allyl ether end-groups both to increase the structural diversity of host molecules that could be used for MIDs and because of the obvious cost advantages of the allyl-based starting materials. For these reasons, we prepared allyl and homoallyl ether-based dendrimers as macromolecular hosts[12] and herein report the synthesis of **6**, the **6** → **7** → **8** interconversion, and a direct comparison to our previously reported chemistry.[1] The results suggest that the allyl ether group is an excellent replacement for the homoallyl ether-based end group.

Results and Discussion

The synthesis of dendrimer **6** is outlined in Schemes 2−4. The reported synthesis of **1**[1] used the Mitsunobu etherification reaction,[13] following literature precedent.[14,15] The Williamson etherification approach was explored for the allyl ether-based dendrimer **6**. Thus, treatment of **9** with allyl bromide and base afforded **10** in near quantitative yield (Scheme 2). However, as **10** was carried forward in the synthesis, increasingly an inseparable impurity revealed itself in the ^{1}H NMR. Careful analysis of **10** showed it to contain ca. 2−3% of over-alkylated product **11** whose presence becomes am-

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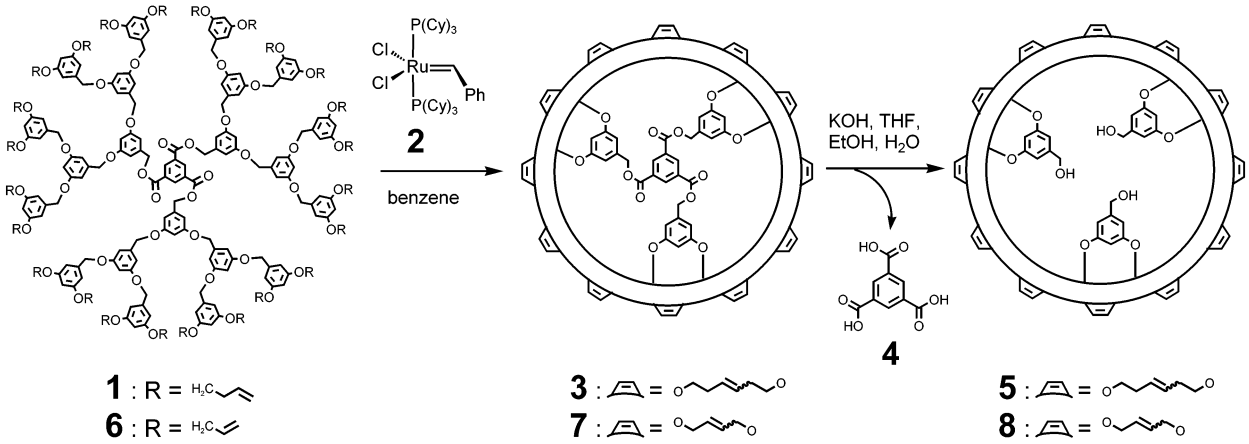
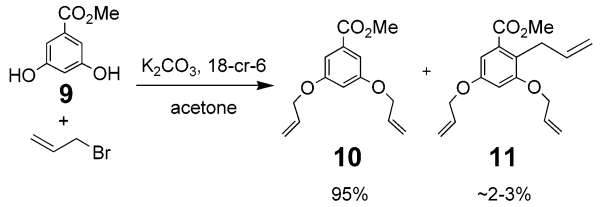
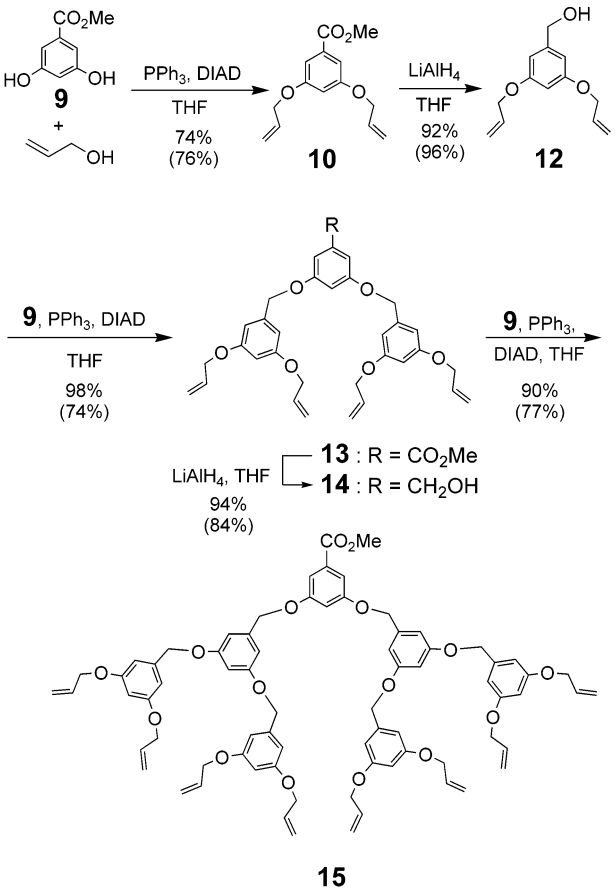
SCHEME 1



SCHEME 2



SCHEME 3. Synthesis of Dendron 14 via Mitsunobu Approach[a]



[a] Yields shown in parentheses are those obtained for analogous reaction in homoallyl series (see ref 1).

plified as the dendrimer surface grows. A similar problem with over-alkylation using the Williamson etherification has been noted previously.[16,17] Careful purification of **10** by silica chromatography removed **11** and afforded pure **10** in 95% yield.

In the synthesis of **1**, the Mitsunobu approach was found to give only trace amounts of the C-alkylation byproducts. As shown in Scheme 3, ester **10** could also be produced by Mitsunobu coupling of **9** with homoallyl alcohol with only a trace of C-alkylation; however, the yield was only 74%. The yield was only 74%. The Mitsunobu protocol proved superior for subsequent steps (vide supra), but for this first step, the procedure in Scheme 2 was utilized on a large scale with the careful chromatographic purification. Reduction of **10** with lithium aluminum hydride afforded alcohol **12** in 92% yield. Mitsunobu coupling of **12** with **9** afforded the second generation methyl ester **13** in 98% yield. The third generation methyl ester **15** was produced by lithium aluminum hydride reduction of **13** to afford **14** in 94% yield followed by Mitsunobu coupling with **9** (90% yield). Dendron **15**, a key intermediate in the synthesis of MIDs,[3] was readily prepared on >10 g scale. As seen in Schemes 2 and 3 preparation of **15** requires 5 steps from **9** and allyl bromide with an overall yield of 72%, whereas the analogous homoallyl dendron was prepared in a lower overall yield (35%) from **9** and the more expensive homoallyl alcohol.[1]

To examine whether the allyl ether end-groups would undergo RCM-mediated cross-linking, dendron **15** was reduced with lithium aluminum hydride (100% yield of **16**) and reacted with trimesic acid (**4**) under Mitsunobu esterification conditions to give dendrimer **6** in 76% yield (Scheme 4). The ring-closing metathesis reaction of dendrimer **6** with three additions of 2 mol % Grubbs ruthenium alkylidene catalyst **2** per alkene over 72 h gave exclusively the intramolecular product **7** in 95% yield when performed at a concentration of 10^{-5} M in benzene. The progress of the RCM reaction could be monitored by matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF-MS) and additional portions of catalyst were added to the reaction following the apparent loss of efficacy of the catalyst.

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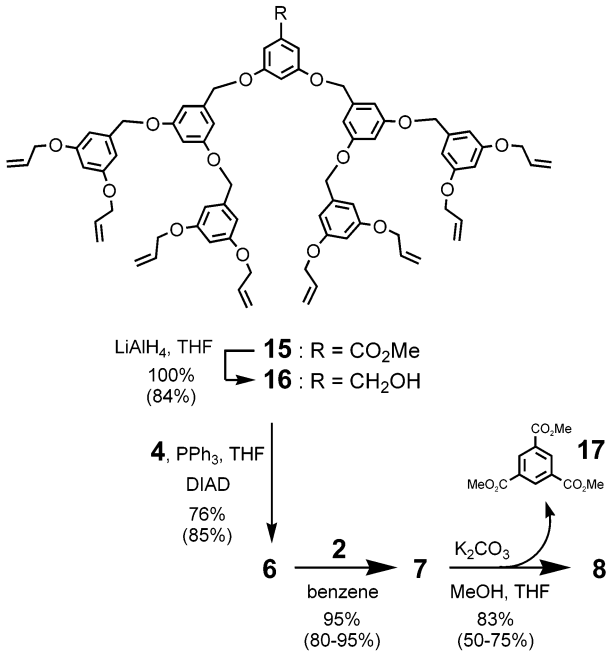
SCHEME 4. Synthesis of Dendrimer 6[a]



[a] Yields shown in parentheses are those obtained for analogous reaction in homoallyl series (see ref 1). The coring of the homoallyl series was carried out using the reagents shown in Scheme 1

TABLE 1. Comparison of Theoretical to SEC and MALDI-TOF-MS Determined Experimental Molecular Weights

	molecular weight			
compd	theoret[a]	SEC[b]	MALDI[c]	peak assignment
6	3756.5	3750	3753.0	$M + Na^+$
7	3420.2	1530	3420.7	$M + Na^+ - 12C_2H_4$
	3448.2		3449.8	$M + Na^+ - 11C_2H_4$
8	3264.2	1570	3266.5	$M + Na^+ - 12C_2H_4 - C_9O_3$
	3292.2		3292.0	$M + Na^+ - 11C_2H_4 - C_9O_3$

[a] Calculated for indicated peak assignment. [b] THF eluent with polystyrene calibration. [c] $M + K^+$ peaks are present but not shown.

Product **7** contained primarily 12 out of 12 possible cross-links with a trace peak intensity corresponding to the product with 11 cross-links (see Table 1 and the Supporting Information).

Consistent with previous studies of cross-linked dendrimers,[1,3] the cross-linked dendrimer **7** eluted later than the uncross-linked **6** on an analytical size-exclusion chromatography (SEC) column. The SEC determined MW of **7** was 1530 Da, 55% below the MALDI-TOF-MS measured and the theoretical MW (Table 1). This underestimation in the molecular weight of **7** indicates that the cross-linked structure adopts a much more compact shape with a smaller hydrodynamic radius. Additionally, the ^{1}H NMR spectra of **7** showed significant broadening of signals due to the isomeric mixture formed during the metathesis reaction. Despite broadening of the peaks, the ^{1}H NMR spectra clearly indicated the formation of cross-linked allyl ether groups in the 6.10 to 5.60 ppm range and the disappearance of the terminal alkene proton peaks at 5.37 and 5.24 ppm.

The cross-linked dendrimer **7** was cored using a trans-esterification reaction with potassium carbonate and methanol in THF (Scheme 4). The cored dendrimer **8** was isolated in 83% yield indicating that the dendrimer underwent significant intra-dendron cross-linking to hold the macromolecular structure together after core removal. Only a trace amount of fragmentation was observed in the MALDI-TOF spectrum. The mass spectra indicated that coring was quantitative with the primary peak corresponding to the cored product with 12 of 12 cross-links and a very minor peak corresponding to the product with 11 cross-links. The ^{1}H NMR spectra clearly showed the core removal with the disappearance of the broad peak in the 9.20 to 8.80 ppm range corresponding to the aromatic protons of the core. The SEC determined M_w of **8** was 1570 Da, 52% below the MALDI-TOF-MS measured actual MW. The SEC results indicated that coring the dendrimer did not cause a significant change in size.

Conclusion

In conclusion, we synthesized a dendrimer containing allyl ether end-groups that underwent complete cross-linking and coring. Synthesis of this dendrimer proceeded in a manner similar to the iterative Mitsunobu etherification-lithium aluminum hydride reduction protocol employed with the analogous homoallyl ether end-group dendrimer.[1] Given that the yields were similar to and in many cases higher than those obtained for the homoallyl system and the allyl bromide starting material is considerably less expensive, the allyl ether-based dendrons and dendrimers are the clear choice of future applications.

Experimental Section

3,5-Bis(2-propen-1-oxy)benzoic acid methyl ester ([G-1]-CO_2Me) (10). A solution of 25.0 g (149 mmol) of dihydroxybenzoic acid methyl ester (**9**), 51 mL (595 mmol) of allyl bromide, 82.2 g (595 mmol) of K_2CO_3 and 3.90 g (15 mmol) of 18-crown-6 in 295 mL acetone was refluxed at 75 °C for 24 h. Acetone was removed under reduced pressure. To the resultant solid was added 200 mL of water. The aqueous layer was extracted with Et_2O (2 × 200 mL). The organic layers were combined and washed with 200 mL of 15% (w/v) aqueous NaOH and an equal volume of water. The organic layer was dried over sodium sulfate, filtered, and evaporated. Purification by column chromatography (silica gel, 19:1 PE/EtOAc) afforded **10** as clear crystals weighing 36.9 g (95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (d, 2H, $J = 2.5$), 6.69 (t, 1H, $J = 2.5$), 6.04 (ddt, 2H, $J = 17.5, 11.0, 5.0$), 5.42 (ddt, 2H, $J = 17.3, 1.6, 1.0$), 5.23 (ddt, 2H, $J = 10.5, 1.5, 1.0$), 4.55 (ddd, 4H, $J = 5.5, 1.8, 1.5$), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.0, 159.8, 133.0, 132.2, 118.2, 108.3, 107.3, 69.2, 52.4; MS (FD) m/z 248.1 (MH^+). Anal. Calc'd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.68; H, 6.46.

General Procedure for LAH Reduction. To a suspension of lithium aluminum hydride (LAH) in THF cooled to 0 °C was added dropwise a solution of the appropriate ester in THF. After addition, the solution was allowed to warm to room temperature and stirred for 24 h. Excess LAH was quenched by slow addition of water followed by neutralization with 3 M aqueous HCl. The THF was removed under reduced pressure. The resultant aqueous solution was extracted with Et_2O and each organic layer was washed with an equal volume of water. The combined organic layers were dried over sodium sulfate, filtered and evaporated.

3,5-Bis(2-propen-1-oxy)benzyl alcohol ([G-1]-OH) (12). Prepared according to the general reduction procedure using 11.4 g (301 mmol) of LAH in 239 mL of THF and 36.9 g (149 mmol) of ester **10** dissolved in 150 mL of THF to afford 31.9 g (92%) of

12 as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.55 (d, 2H, J = 2.4), 6.43 (t, 1H, J = 1.8), 6.05 (ddt, 2H, J = 17.2, 10.4, 5.6), 5.41 (ddt, 2H, J = 17.2, 1.6, 1.6), 5.28 (ddt, 2H, J = 10.4, 1.6, 1.2), 4.62 (s, 2H), 4.52 (ddd, 4H, J = 5.2, 1.6, 1.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 143.5, 133.3, 118.0, 105.8, 101.4, 69.1, 65.4; MS (FD) m/z 220.2 (MH^+).

General Procedure for Mitsunobu Coupling. To a mixture at 0 °C of the appropriate alcohol, the appropriate ester or acid and triphenylphosphine (PPh_3) in THF was added dropwise a solution of diisopropyl azodicarboxylate (DIAD) in THF. The reaction warmed to room temperature and stirred for 24 h. The reaction was stopped by adding water and evaporated to remove THF. The aqueous layer was extracted with Et_2O and each organic layer was washed with 2.5 M aqueous KOH and an equal volume of water. The combined organic layers were dried over sodium sulfate, filtered and evaporated.

3,5-Bis[3,5-bis(2-propen-1-oxy)benzyloxy)benzoic acid methyl ester ([G-2]-CO_2Me) (13). Prepared according to the general Mitsunobu procedure using 10.9 g (50 mmol) of alcohol **12**, 13.8 g (23 mmol) of ester **9**, 14.8 g (56 mmol) of PPh_3 in 50 mL of THF and 11.1 mL (56 mmol) of DIAD in 200 mL of THF. Column chromatography (silica gel, 19:1 to 4:1 PE/EtOAc) afforded 12.6 g (98%) of **13** as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, 2H, J = 1.6), 6.77 (t, 1H, J = 1.8), 6.59 (d, 4H, J = 1.6), 6.45 (t, 2H, J = 2.0), 6.04 (ddt, 4H, J = 13.6, 9.2, 3.6), 5.41 (ddt, 4H, J = 13.8, 1.6, 1.2), 5.28 (ddt, 4H, J = 8.4, 1.2, 1.2), 5.00 (s, 4H), 4.52 (ddd, 8H, J = 4.0, 1.6, 1.2), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.0, 160.2, 159.9, 139.0, 133.3, 132.3, 118.0, 108.6, 107.5, 106.4, 101.7, 70.3, 69.1, 52.5; MS (FD) 572.0 (MH^+). Anal. Calc'd for $C_{39}H_{36}O_8$: C, 71.31; H, 6.34. Found: C, 71.17; H, 6.34.

3,5-Bis[3,5-bis(2-propen-1-oxy)benzyloxy]benzyl alcohol ([G-2]-OH) (14). Prepared according to the general reduction procedure using 650 mg (17 mmol) of LAH in 25 mL of THF and 6.14 g (11 mmol) of ester **13** in 90 mL of THF to afford 5.5 g (94%) of **14** as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.61 (d, 2H, J = 2.4), 6.59 (d, 4H, J = 2.4), 6.52 (t, 1H, J = 2.2), 6.45 (t, 2H, J = 2.2), 6.04 (ddt, 4H, J = 17.2, 10.8, 5.2), 5.41 (ddt, 4H, J = 17.2, 2.0, 1.2), 5.28 (ddt, 4H, J = 10.4, 1.6, 1.4), 4.96 (s, 4H), 4.63 (s, 2H), 4.52 (ddt, 8H, J = 5.2, 1.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 160.1, 143.7, 139.4, 133.3, 118.0, 106.3, 106.0, 101.6, 101.5, 70.2, 69.1, 65.5; MS (FD) m/z 544.3 (MH^+).

3,5-Bis{3,5-bis[3,5-bis(2-propen-1-oxy)benzyloxy]-benzyloxy}-benzyl alcohol ([G-3]-OH) (16). Prepared according to the general reduction procedure using 530 mg (14 mmol) of LAH in 25 mL of THF and 9.20 g (8 mmol) of ester **15** in 75 mL of THF to afford 8.95 g (100%) of a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (d, 4H, J = 2.2), 6.58 (d, 2H, J = 2.2), 6.58 (d, 8H, J = 2.2), 6.54 (t, 2H, J = 2.2), 6.51 (t, 1H, J = 2.2), 6.44 (t, 4H, J = 2.2), 6.03 (ddt, 8H, J = 17.2, 10.4, 5.2), 5.40 (ddt, 8H, J = 17.2, 1.6, 1.2), 5.27 (ddt, 8H, J = 10.6, 1.6, 1.2), 4.97 (s, 4H), 4.96 (s, 8H), 4.62 (s, 2H), 4.51 (dt, 16H, J = 5.2, 1.6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 160.2, 160.1, 143.7, 139.5, 139.3, 133.3, 118.0, 106.5, 106.4, 106.0, 101.8, 101.6, 101.4, 70.2, 70.1, 69.1, 65.4; MS (MALDI-TOF) m/z 1215.9 ($M + Na^+$), 1231.9 ($M + K^+$).

Cross-Linked [G-3]-Dendrimer (7). To a solution of 91 mg (24 μmol) of **6** in 1.0 L of benzene was added 11 mg (14 μmol) of Grubbs catalyst (**9**). The mixture was stirred for 24 h and an additional 8.5 mg (10 μmol) of Grubbs catalyst (**9**) was added. After stirring for an additional 48 h, the solvent was removed under reduced pressure. The crude mixture was purified with column chromatography (silica gel, 7:3 PE/EtOAc (500 mL) and 19:1 CH_2Cl_2/EtOAc (1.0 L)). Cored dendrimer **7** was isolated from the second solvent system as 79 mg (95%) of a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50−8.20 (bs, 3H), 6.80−6.10 (bs, 63H), 6.10−5.60 (bs, 24H), 5.20−4.60 (bs, 36H), 4.60−4.20 (bs, 48H); MS (MALDI-TOF) m/z 3420.7 ($M + Na^+ - 12C_2H_4$), 3436.7 ($M + K^+ - 12C_2H_4$), 3449.8 ($M + Na^+ - 11C_2H_4$); SEC (THF) Calc'd MW = 1530.

Cored [G-3]-Dendrimer (8). To a solution of 46 mg (14 μmol) of **7** in 1.0 mL of THF was added 31 mg (22 μmol) of K_2CO_3 and 500 μL (12 mmol) of MeOH. The mixture was stirred at 63 °C for 24 h. The THF and MeOH were removed under reduced pressure. To the resultant solution was added 10 mL of CH_2Cl_2 and 10 mL of water. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 10 mL of water, dried over Na_2SO_4, filtered and evaporated. Column chromatography (silica gel, 3:2 PE/EtOAc (200 mL), 19:1 CH_2Cl_2/acetone (200 mL), and 9:1 CH_2Cl_2/acetone (500 mL)) provided 37 mg (83%) of a white powder: ^{1}H NMR δ 6.60−6.20 (bs, 63H), 6.00−5.60 (bs, 24H), 5.15−4.95 (bs, 6H), 4.95−4.70 (bs, 36H), 4.70−4.20 (bs, 48H); MS (MALDI − TOF) m/z 3266.5 ($M + Na^+ - 12C_2H_4 - C_9O_3$), 3282.3 ($M + K^+ - 12C_2H_4 - C_9O_3$), 3292.0 ($M + Na^+ - 11C_2H_4 - C_9O_3$), 3308.0 ($M + K^+ - 11C_2H_4 - C_9O_3$); SEC (THF) Calc'd MW = 1570.

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Supporting Information Available: Experimental details for preparing **6** and **15** and NMR and MALDI spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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