the partial separation of the pure diastereomers, which were obtained in a combined yield of 75%. Removal of the protecting groups with trimethylsilyl triflate,[19] *N*-acylation with octanoyl chloride[20] and final chromatography afforded *erythro*-**1** in 14% overall yield from pentadecyne.

erythro-**1**: $[\alpha]_D = +3.0$ ($c = 0.8$ in $CHCl_3$); IR (NaCl): $\tilde{\nu} = 1550, 1644, 3010, 3287\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, 6H, $J = 6.2$ Hz), 1.01 (s, 2H), 1.25 (s, 28H), 1.60 (m, 4H), 2.24 (t, 2H, $J = 7.2$ Hz), 2.45 (dt, 2H, $J = 7.6$, $J' = 1.2$ Hz), 3.02 (brs, 1H), 3.37 (brs, 1H), 3.71 (dd, 1H, $J = 11.4$, $J' = 3.4$ Hz), 3.87 (dd, 1H, $J = 11.2$, $J' = 4$ Hz), 4.18 (m, 1H), 4.85 (s, 1H), 6.37 (brd, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 8.36$, 14.04, 14.10, 22.58, 22.66, 25.70, 25.82, 27.27, 28.99, 29.19, 29.33, 29.37, 29.44, 29.57, 29.63, 29.64, 29.64, 29.67, 31.65, 31.89, 36.77, 53.74, 63.12, 70.52, 107.52, 115.40, 174.00. HR-MS calcd for $C_{27}H_{51}NO_3$: 437.386895; found: 437.387000.

The dihydroceramide desaturase inhibition assay was performed by using rat liver microsomes, which were prepared as reported.[5] The activity of dihydroceramide desaturase was determined in phosphate buffer (0.1 M, pH 7.4), with D-*erythro*-*N*-octanoylsphingosine as substrate. The inhibitor (at the indicated concentrations) and the substrate (15 nmol) were solubilized (15 nmol of BSA in phosphate buffer/ethanol 9:1 v/v, 100 µL), combined with the microsome suspension (1 mg of protein) and NADH (30 µL, 1 µM in phosphate buffer), and made up to a final volume of 300 µL with phosphate buffer. The suspension was incubated for 30 min at 37 °C, and the reactions were terminated by the addition of $CHCl_3$ (0.5 mL) containing D-*erythro*-*N*-hexanoylsphingosine (1 nmol) as an internal standard for quantification. The lipids were extracted with $CHCl_3$ (2 × 250 µL), the combined organic layers were evaporated under a stream of nitrogen, and the residue was derivatized with bistrimethylsilyltrifluoroacetamide (50 µL, 25 °C, 60 min). After derivatization, $CHCl_3$ (50 µL) was added and the samples were stored at −80 °C. Instrumental analyses were carried out by gas chromatography coupled to electron impact (70 eV) mass spectrometry using a Fisons gas chromatograph (8000 series) coupled to a Fisons MD-800 mass-selective detector. The system was equipped with a nonpolar Hewlett-Packard HP-1 capillary column (30 m × 0.20 mm i.d.), which was programmed from 100 °C to 340 °C at 7 °C min^{-1}. Analyses were carried out in the selected ion monitoring mode. Selected ions were m/z = 311, 313, 230, and 258. Dwell (time for which a given mass is monitored) was set at 0.02 s and the mass span at 0.5.

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[1] T. Kolter, K. Sandhoff, *Angew. Chem.* **1999**, *111*, 1632–1670; *Angew. Chem. Int. Ed.* **1999**, *38*, 1532–1568.

[2] T. Kolter, K. Sandhoff, *Chem. Soc. Rev.* **1996**, *25*, 371–381.

[3] C. Arenz, A. Giannis, *Angew. Chem.* **2000**, *112*, 1498–1500; *Angew. Chem. Int. Ed.* **2000**, *39*, 1440–1442.

[4] The synthesis of two fluorinated dihydroceramide analogues that have a marginal activity as inhibitors of dihydroceramide desaturase has been reported recently: S. De Jonghe, I. Van Overmeire, S. Van Calenbergh, C. Hendrix, R. Busson, D. De Keukeleire, P. Herdewijn, *Eur. J. Org. Chem.* **2000**, 3177–3183.

[5] C. Michel, G. van Echten-Deckert, J. Rother, K. Sandhoff, E. Wang, A. H. Merrill, Jr., *J. Biol. Chem.* **1997**, *272*, 22432–22437.

[6] C. Michel, G. van Echten-Deckert, *FEBS Lett.* **1997**, *416*, 153–155.

[7] J. W. Kok, M. Nikolova-Karakashian, K. Klappe, C. Alexander, A. H. Merrill, Jr., *J. Biol. Chem.* **1997**, *272*, 21128–21136.

[8] L. Geeraert, G. P. Mannaerts, P. P. van Veldhoven, *Biochem. J.* **1997**, *327*, 125–132.

[9] T. Mikami, M. Kashiwagi, K. Tsuchihashi, T. Akino, S. Gasa, *J. Biochem. Tokyo* **1998**, *123*, 906–911.

[10] C. Causeret, L. Geeraert, G. Van der Hoeven, G. P. Mannaerts, P. P. Van Veldhoven, *Lipids* **2000**, *35*, 1117–1125.

[11] A. R. Johnson, J. A. Pearson, F. S. Shenstone, A. C. Fogerty, *Nature* **1967**, *214*, 1244–1245.

[12] J. Quintana, M. Barrot, G. Fabrias, F. Camps, *Tetrahedron* **1998**, *54*, 10187–10198, and references therein.

[13] A. R. Johnson, A. C. Fogerty, J. A. Pearson, F. S. Shenstone, A. M. Bersten, *Lipids* **1968**, *4*, 265–269.

[14] A. C. Fogerty, A. R. Johnson, J. A. Pearson, *Lipids* **1972**, *7*, 335–338.

[15] J. R. Clark, H. W. Kircher, *Lipids* **1972**, *7*, 769–772.

[16] R. J. Aldulayymi, M. S. Baird, M. J. Simpson, S. Nyman, G. R. Port, *Tetrahedron* **1996**, *52*, 12509–12520.

[17] P. Herold, *Helv. Chim. Acta* **1988**, *71*, 354–362.

[18] G. Niel, F. Roux, Y. Maisonnasse, I. Maugras, J. Poncet, P. Jouin, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1275–1280.

[19] M. Sakaitani, Y. Ohfune, *J. Org. Chem.* **1990**, *55*, 870–876.

[20] P. De Ceuster, G. P. Mannaerts, P. P. Van Veldhoven, *Biochem. J.* **1995**, *311*, 139–146.

[21] K. Raith, J. Darius, R. H. Neubert, *J. Chromatogr. A* **2000**, *876*, 229–233.

[22] The activities of dihydroceramide desaturase were 1.4 ± 0.3 nmol h^{-1} mg^{-1} in microsomes incubated with *threo*-**1** and 1.3 ± 0.2 nmol h^{-1} mg^{-1} in control microsomes (average ± standard deviation, $n = 3$).

[23] R. H. Unger, L. Orci, *Int. J. Obes.* **2000**, *24*(Suppl. 4), S28–S32.

Synthesis of Cored Dendrimers with Internal Cross-Links**

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Steven C. Zimmerman*

The physical properties of a dendrimer may be manipulated by post-synthetic modification of its periphery, core, or interior. Such alterations can tune the bulk properties of the dendritic system and frequently convert simple dendrimers into functional macromolecules. For example, incorporation of molecular recognition elements on the periphery of a dendrimer produces multivalent receptors capable of ligand binding or supramolecular assembly.[1] Organometallic functional groups can also be added to the periphery, thus creating macromolecular catalysts.[1–3] In contrast to the many reports of end-group functionalization, there are only a few examples of covalent modification of the interior of the dendrimer.[4] We recently reported[5] the "coring" of dendrimer **1** by ring-closing metathesis (RCM) of the peripheral homoallyl ether groups[6] using ruthenium benzylidene catalyst **2**[7] followed by hydrolytic removal of the core. In some respects, "cored" dendrimers resemble hollow, polymeric nanospheres or core-shell nanoparticles.[8] Consequently, the potential of "cored" dendrimers to encapsulate or complex substances makes them outstanding candidates for delivery agents or molecular sensors.

Our reported synthesis of cored dendrimers[5] is limited in its scalability by the requirement of high dilution (about

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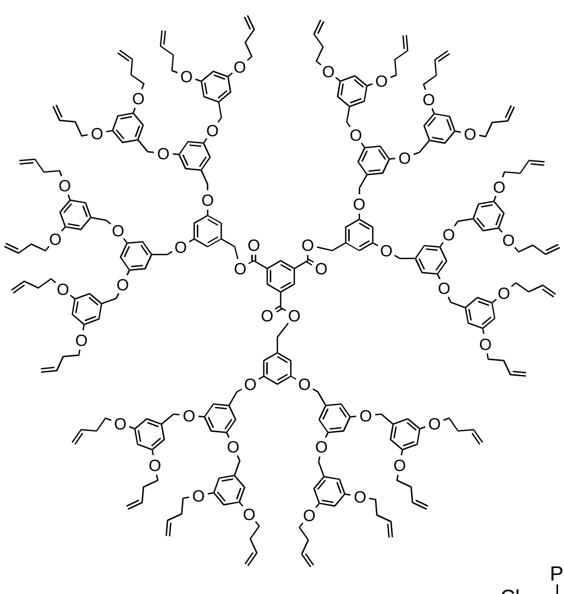

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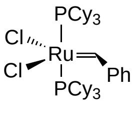

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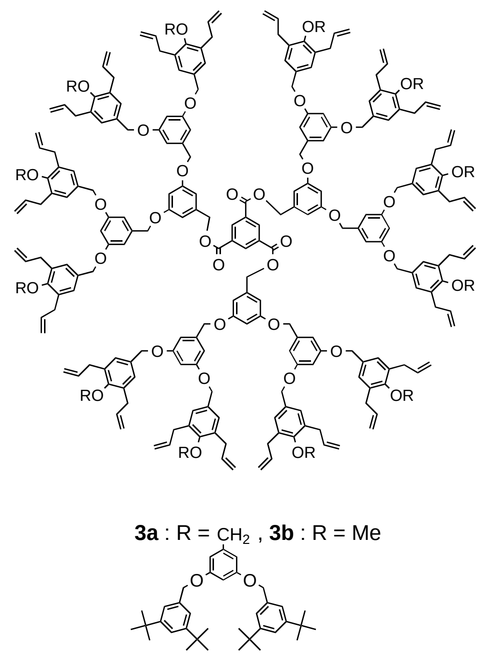
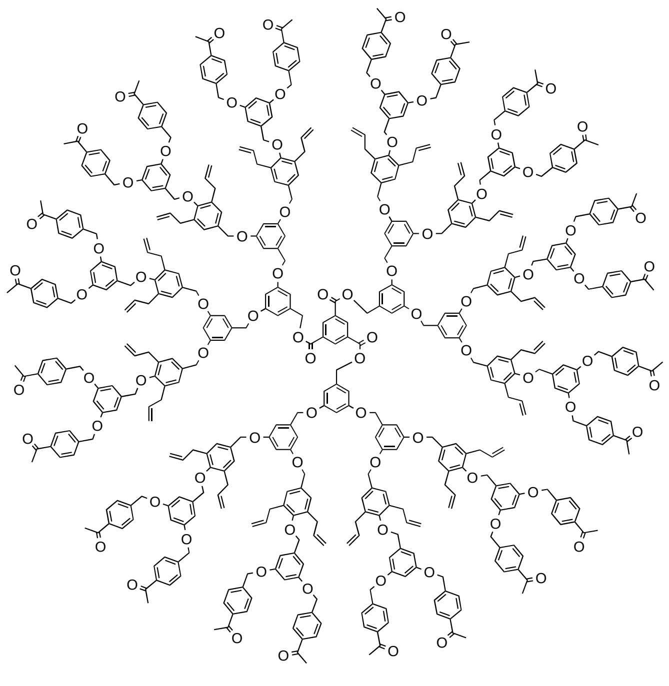


3a : R = CH$_2$, **3b** : R = Me

10^{-5} M) to effect intramolecular cross-linking. By internalizing the alkenes there is a possibility that intermolecular cross-linking will be disfavored, as one dendrimer would need to interpenetrate another. Armes and co-workers used a similar strategy in the synthesis of shell-cross-linked knedel (SCK) micelles.[9] To test the idea that internalizing the cross-linking groups would favor RCM reactions at higher concentration three new dendrimers (**3a**, **3b**, and **4**) were designed and synthesized. Dendrimers **3a** and **3b** are identical except that the latter, a control compound, lacks the additional dendritic layer so the allyl groups reside on the surface. In both cases, the dendrimer contains labile ester linkages to the core.



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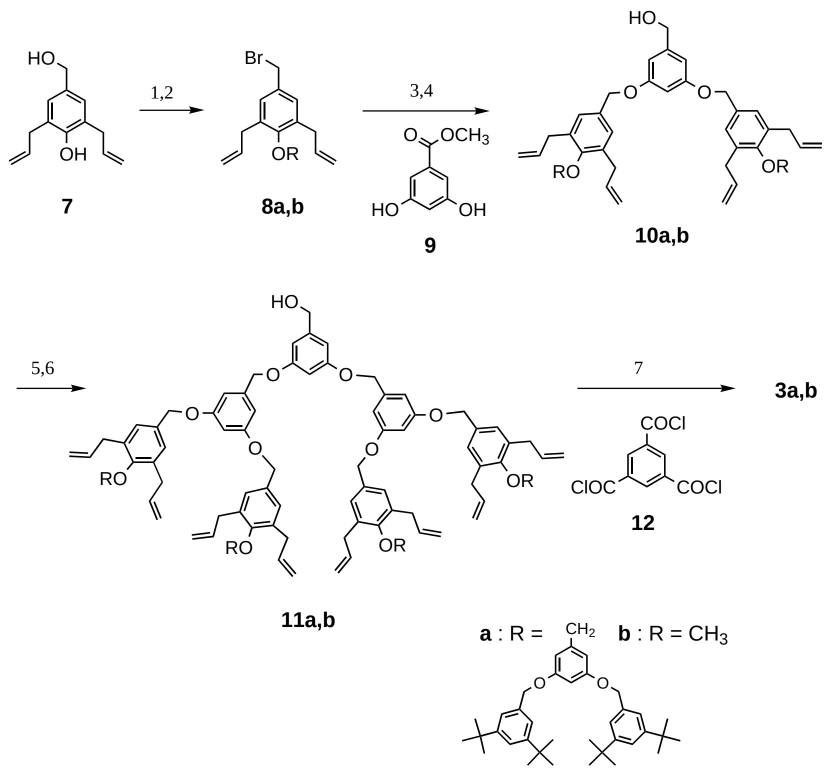
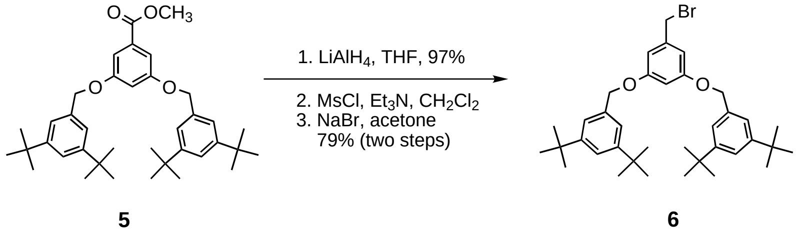
Dendrimers **3a** and **3b** were synthesized using the convergent approach[10] employing either the Mitsunobu etherification[11] or phenol–bromide coupling[10] as shown by Scheme 1. The synthesis of **6**, required for the synthesis of **3a**, is shown in Equation (1) (Ms = mesyl = methanesulfanyl).[12] Bromide **6** was then coupled with phenol **7** and converted into bromide **8a**. Phenol **7** was obtained by reduction of the corresponding aldehyde, a compound first reported by Claisen and Eisleb.[13] The coupling of bromide **8a** with commercially available ester **9** afforded the second generation ester which was reduced to alcohol **10a**. Mitsunobu coupling of **10a** with **9** followed by reduction yielded third generation alcohol **11a**. Treatment of **12** with alcohol **11a** under Dean–Stark conditions afforded dendrimer **3a**.[14, 15] Dendrimer **3b** was synthesized in an analogous manner (Scheme 1).

With the desired dendrimers in hand, attention was turned to the cross-linking experiments. The critical question was whether cross-linking would occur, and, if so, to what extent (both intra- and intermolecularly). Although **1** can be cross-linked completely,[5] the alkenes are more hindered in **3b** and especially congested in **3a**. The sensitivity of some RCM catalysts to steric hindrance is well documented.[16] All the dendrimers were cross-linked by ring-closing metathesis using Grubb's catalyst **2** in benzene (Scheme 2).[7, 16] The catalyst was removed after the RCM reactions using a modification of a reported protocol in which the metathesis solution was treated with tris(hydroxymethyl)phosphane and then silica.[17] Subsequent purification of all compounds by preparative size-exclusion chromatography (SEC) in toluene afforded almost quantitative recovery of the cross-linked products.

Dendrimers **1** and **3b** were cross-linked using 7 mol% of catalyst per alkene at three concentrations (1×10^{-5}, 1×10^{-4},



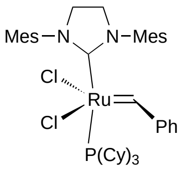
Scheme 1. Syntheses of dendrimers **3a** and **3b**. Reaction conditions: 1) a. **6**, K_2CO_3, 2-butanone (79%); b. CH_3I, K_2CO_3, acetone (71%); 2) CBr_4, PPh_3, THF (**a**: 75%, **b**: 82%); 3) a. **9**, K_2CO_3, acetone, [18]crown-6 (77%); b. **9**, K_2CO_3, acetone (81%); 4) $LiAlH_4$, THF (**a**: 96%, **b**: 81%); 5) PPh_3, DEAD, THF, **9** (**a**: 70%, **b**: 79%); 6) $LiAlH_4$, THF (**a**: 94%, **b**: 93%); 7) **12**, DMAP, benzene (**a**: 34%, **b**: 71%). DEAD = diethylazodicarboxylate, DMAP = 4-dimethylaminopyridine.



(1)

and 1×10^{-3} M). Both ^1H NMR and mass spectrometric analysis clearly indicated that cross-linking of the allyl groups in **3b** had occurred. Thus, the ^1H NMR signals broadened significantly and the alkene methine signal shifted upfield from $\delta = 5.98$ to 5.73, which is consistent with the conversion of monosubstituted into disubstituted alkenes. Matrix-assisted laser-desorption/ionization time-of-flight spectrometry (MALDI-TOF) analysis showed the average loss of 11 molecules of ethylene, thus indicating the formation of 11 out of 12 possible cross-links.[18] Similar results were seen in the cross-linking of dendrimer **1**.

Dendrimer **3a** was cross-linked at two concentrations (1×10^{-5} and 1×10^{-3} M) using 4 mol% of **2** per alkene. Indeed, cross-linking did occur at the concentrations examined which indicated that the catalyst could access the internal alkenes. The same ^1H NMR and MALDI analyses used for **1** and **3b** showed the cross-linking of **3a** to be less advanced. In particular, the MALDI-TOF peak assignments indicate the average formation of 8–9 out of 12 possible cross-links at 10^{-3} M and 10 out of 12 cross-links at 10^{-5} M.[18] The degree of cross-linking did not increase when higher catalyst loadings were used. Grubbs and co-workers recently reported the development of a new ruthenium benzylideneimidazol-2-ylidene catalyst **17** (mes = mesityl) capable of cross-linking sterically hindered olefins.[19] Gratifyingly, metathesis of



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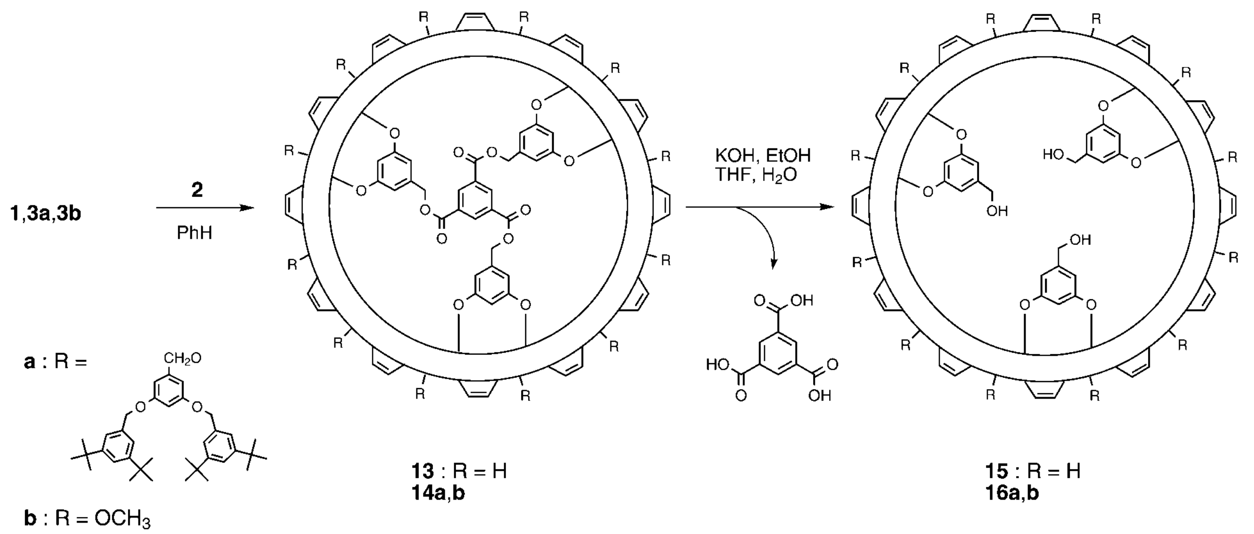

Scheme 2. Synthesis of cored dendrimers.

3a with **17** at both 10^{-3} M and 10^{-5} M resulted in greater than 95 % cross-linking based on ^{1}H NMR analysis.

The extent of intermolecular cross-linking, namely, oligomer formation, was determined by both MALDI-TOF analysis and size-exclusion chromatography (SEC) using toluene as eluent. Each SEC trace consisted of two signals corresponding to formation of the monomer and oligomer (Figure 1). The relative areas of these two signals were used to calculate the percentage of oligomer formation (Table 1). The molecular weights of dendrimers, pre- and post-cross-linking, were determined using both MALDI-TOF and SEC analyses.[18] No oligomer formation was evident in either the MALDI-TOF spectra or SEC traces of dendrimers **1**, **3a**, and **3b** cross-linked at 10^{-5} M, thus indicating that complete intramolecular metathesis had occurred. As the concentration of the RCM reaction was increased to 1×10^{-4} M, an additional peak evident in the SEC traces of **1** and **3b** (Figure 1 a and 1 b) revealed the formation of small amounts of oligomer, which MALDI-TOF analysis showed to be dimer. Substantial oligomer formation occurred with both **1** and **3b** at a RCM reaction concentration of 10^{-3} M. However, dendrimer **3a** underwent more than 95% intramolecular cross-linking at 10^{-3} M ([alkene] = 0.024 M) with both catalysts **2** and **17**, the latter giving greater than 95 % cross-linking based on ^{1}H NMR analysis. This result is consistent with a model wherein the alkene groups are sterically blocked from intermolecular metathesis.

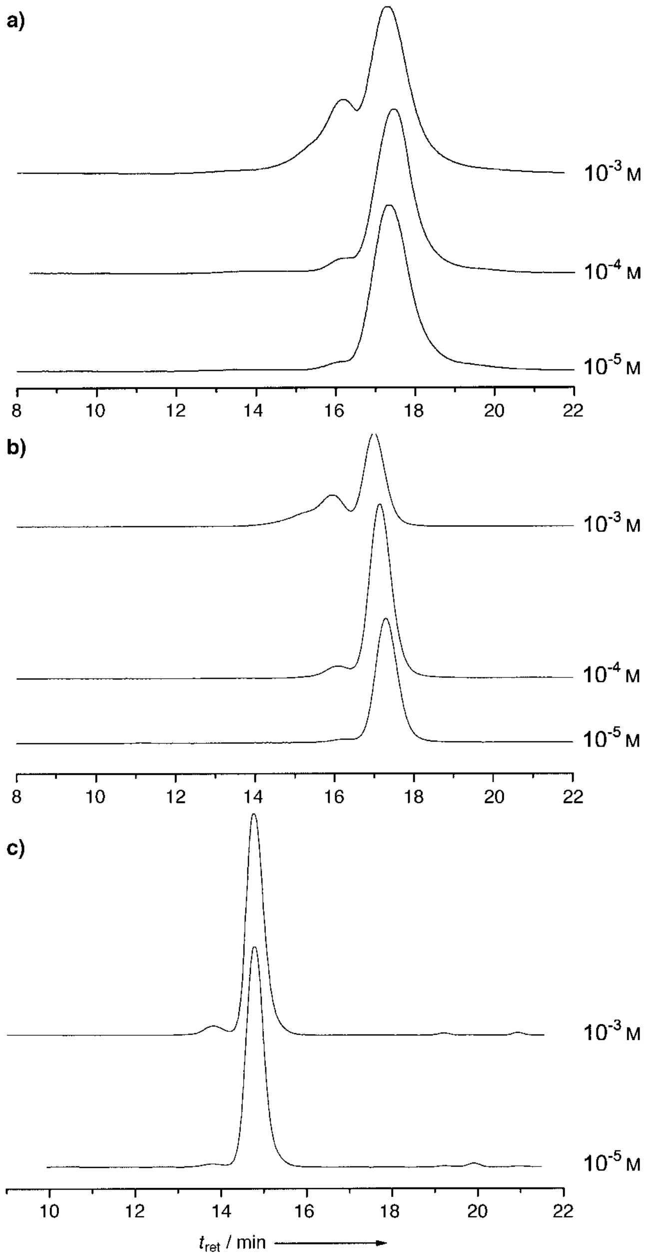

Figure 1. Comparison of cross-linked dendrimers by SEC. a) **3b**; b) **1**; c) **3a**.

Table 1. A comparative SEC analysis of intermolecular cross-linking in **1**, **3a**, and **3b** with **2**.

Conc. of RCM [M]	Relative amount of oligomer formed [%] **1**	**3a**	**3b**
1×10^{-5}	0	0	0
1×10^{-4}	7	–	7
1×10^{-3}	38	<5	29

For these dendritic systems to be useful, the cross-linked dendrimer must remain intact when the core is removed. Scheme 2 also depicts the "coring" procedure. Hydrolysis of **14a** and **14b** led to complete core removal as evidenced by the loss of the aromatic signal at $\delta = 8.95$ in the ^{1}H NMR spectrum and a reduction of m/z 159 ($C_9H_3O_3$) in the MALDI-TOF spectrum.[18] Whereas dendrimer **14b** produced **16b** fully intact, the MALDI-TOF and SEC data for **16a** revealed a minor amount of cross-linked mono- and didendron formed in the hydrolysis of **14a**.[18]

The ability to fully cross-link dendrimer **3a** intramolecularly at 10^{-3} M makes this cross-linking-coring approach suitable for further development. It was considered to be particularly important to develop a system wherein the end groups could ultimately be conjugated with targeting or reporter groups or converted into groups that provide water solubility. For these reasons, a synthesis of **4** was developed (Scheme 3). Bromide **18**, prepared by bromination of 4-methylacetophenone with *N*-bromosuccinimide (NBS), was coupled with alcohol **19** to afford **20**, which was purified as its 3,5-dinitrobenzoate derivative. Conversion of **20** into the bromide, coupling with **7**, and treatment with mesyl chloride/sodium bromide afforded **21**. Coupling of **21** with *t*BDPS-protected **22**[20] yielded **23**, which was treated with acid chloride **12** to afford dendrimer **4**. Preliminary cross-linking studies of dendrimer **4** indicated the formation of 11 of 12 cross-links at 10^{-3} M in dichloromethane using 4 mol% of catalyst **2** per alkene.

The previously reported synthesis of cored dendrimers was limited by the high-dilution conditions required for intramolecular metathesis. The current work solves this problem. Thus, larger quantities of cored dendrimers can now be produced, thus making it possible to develop a range of applications. Efforts in this direction have been successful and will be reported in due course.

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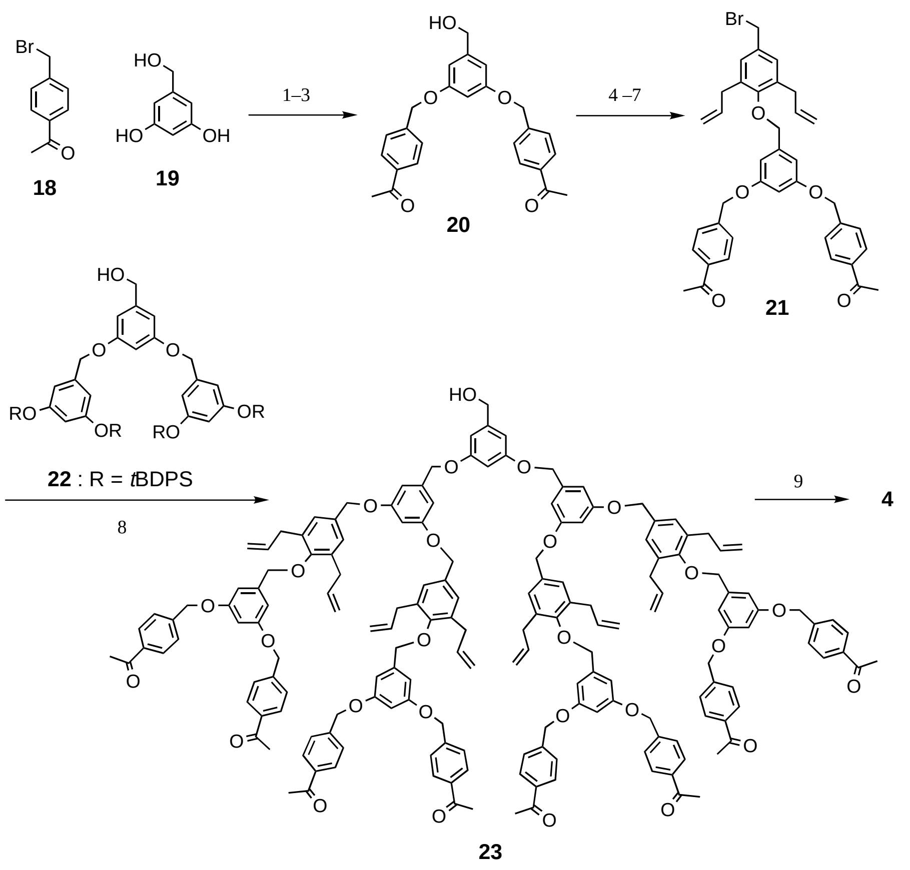

Scheme 3. Synthesis of dendrimer **4**. Reaction conditions: 1) K$_2$CO$_3$, 2-butanone (76%); 2) 3,5-dinitrobenzoyl chloride, pyridine, DMAP (53%); 3) K$_2$CO$_3$, MeOH (62%); 4) MsCl, Et$_3$N, CH$_2$Cl$_2$; 5) NaBr, acetone (92%); 6) **7**, K$_2$CO$_3$, 2-butanone (85%); 7) MsCl, Et$_3$N, CH$_2$Cl$_2$; NaBr, acetone (80%); 8) **22**, KF, [18]crown-6, 2-butanone (57%); 9) **12**, DMAP, benzene (52%). Ms = mesyl = methanesulfonyl.

[1] Selected recent reviews: K. Inoue, *Prog. Polym. Sci.* **2000**, *25*, 453–571; D. K. Smith, F. Diederich, *Top. Curr. Chem.* **2000**, *210*, 183–227; M. W. P. L. Baars, E. W. Meijer, *Top. Curr. Chem.* **2000**, *210*, 131–182; S. C. Zimmerman, *Curr. Opin. Coll. Interf. Sci.* **1997**, *2*, 89–99; F. W. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1687–1712; G. R. Newkome, E. He, C. N. Moorefield, *Chem. Rev.* **1999**, *99*, 1681–1746; V. Balzani, S. Campagna, G. Denti, A. Juris, S. Serroni, M. Venturi, *Acc. Chem. Res.* **1998**, *31*, 26–34.

[2] Selected examples: H. Brunner, *J. Organomet. Chem.* **1995**, *500*, 39–46; D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, *4*, 1353–1361; E. de Wolf, G. van Koten, B.-J. Deelman, *Chem. Soc. Rev.* **1999**, *28*, 37–41; R. A. Gossage, L. A. van de Kuil, G. van Koten, *Acc. Chem. Res.* **1998**, *31*, 423–431; O. A. Mathews, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1–56.

[3] [Co(salen)] (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion) units for asymmetric ring opening of epoxides: R. Breinbauer, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 3750–3753; *Angew. Chem. Int. Ed.* **2000**, *39*, 3604–3607; Rh$^{\text{I}}$ complexes for hydroformylation: a) S. C. Bourque, F. Maltais, W.-J. Xiao, O. Tardif, H. Alper, P. Arya, L. E. Manzer, *J. Am. Chem. Soc.* **1999**, *121*, 3035–3038; b) A. Gong, Q. Fan, Y. Chen, H. Liu, C. Chen, F. Xi, *J. Mol. Catal. A* **2000**, *159*, 225–232; Sc-poly(amidoamine) (Sc-PAMAM) dendrimers for catalysis of the Diels–Alder and aldol reactions: M. T. Reetz, D. Giebel, *Angew. Chem.* **2000**, *112*, 2614–2617; *Angew. Chem. Int. Ed.* **2000**, *39*, 2498–2501; nickel(II) complexes for Kharasch additions: G. van Koten, J. T. B. H. Jastrzebski, *J. Mol. Catal. A* **1999**, *146*, 317–323; palladium(II) moieties for hydrogenation: T. Mizugaki, M. Ooe, K. Ebitani, K. Kaneda, *J. Mol. Catal.* **1999**, *145*, 329–333.

[4] Selected examples: nitro group reduction: G. R. Newkome, V. V. Narayanan, L. A. Godínez, *J. Org. Chem.* **2000**, *65*, 1643–1649; amine quaternization: a) Y. Pan, W. T. Ford, *Macromolecules* **1999**, *32*, 5468–5470; b) L. J. Twyman, *Tetrahedron Lett.* **2000**, *41*, 6875–6878; intra/interdendrimer cross-linking: M. Zhao, Y. Liu, R. M. Crooks, D. E. Bergbreiter, *J. Am. Chem. Soc.* **1999**, *121*, 923–930; incorporation of hydroxyl groups: c) J. R. McElhanon, M.-J. Wu, M. Escobar, D. V. McGrath, *Macromolecules* **1996**, *29*, 8979–8982; d) A. W. Freeman, L. A. J. Chrisstoffels, J. M. J. Fréchet, *J. Org. Chem.* **2000**, *65*, 7612–7617; polylithiation/addition: L. Lochmann, K. L. Wooley, P. T. Ivanova, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1993**, *115*, 7043–7044; electrophile addition: J.-P. Majoral, C. Larré, R. Laurent, A.-M. Caminade, *Coord. Chem. Rev.* **1999**, *192*, 3–18; metal ion coordination: G. R. Newkome, C. N. Moorefield, J. M. Keith, G. R. Baker, G. H. Escamilla, *Angew. Chem.* **1994**, *106*, 701–703; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 666–668.

[5] M. S. Wendland, S. C. Zimmerman, *J. Am. Chem. Soc.* **1999**, *121*, 1389–1390.

[6] Reports detailing surface-oligomerization methods without coring: C. O. Nobel IV, R. L. McCarley, *J. Am. Chem. Soc.* **2000**, *122*, 6518–6519; J. Wang, X. Jia, H. Zhong, H. Wu, Y. Li, X. Xu, M. Li, Y. Wei, *J. Polym. Sci. Part A* **2000**, *38*, 4147–4153; M. Tominaga, K. Konishi, T. Aida, *Chem. Lett.* **2000**, *4*, 374–375.

[7] E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.

[8] J. Ding, G. Liu, *Chem. Mater.* **1998**, *10*, 537–542; F. Caruso, *Chem. Eur. J.* **2000**, *6*, 413–419; J. Hotz, W. Meier, *Langmuir* **1998**, *14*, 1031–1036; Q. Zhang, E. E. Remsen, K. L. Wooley, *J. Am. Chem. Soc.* **2000**, *122*, 3642–3651; T. K. Mandal, M. S. Fleming, D. R. Walt, *Chem. Mater.* **2000**, *12*, 3481–3487; M. Iijima, Y. Nagasaki, T. Okada, M. Kato, K. Kataoka, *Macromolecules* **1999**, *32*, 1140–1146; V. Bütün, A. B. Lowe, N. C. Billingham, S. P. Armes, *J. Am. Chem. Soc.* **1999**, *121*, 4288–4289.

[9] V. Bütün, X.-S. Wang, M. V. de Páz Bañez, K. L. Robinson, N. C. Billingham, S. P. Armes, Z. Tuzar, *Macromolecules* **2000**, *33*, 1–3.

[10] C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.

[11] F. Zeng, S. C. Zimmerman, *J. Am. Chem. Soc.* **1996**, *118*, 5326–5327; O. Mitsunobu, *Synthesis* **1981**, *1*, 1–28.

[12] S. C. Zimmerman, F. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095–1098.

[13] L. Claisen, O. Eisleb, *Liebigs Ann. Chem.* **1913**, *401*, 107.

[14] H.-T. Chang, C.-T. Chen, T. Kondo, G. Siuzdak, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 202–206; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 182–186.

[15] Dendrimer purity was estimated to be >95% by both ^{1}H NMR and SEC analysis. All compounds had spectroscopic properties in accord with the proposed structures.

[16] T. A. Kirkland, R. H. Grubbs, *J. Org. Chem.* **1997**, *62*, 7310–7318.

[17] H. D. Maynard, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 4137–4140.

[18] Data presented in the Supporting Information.

[19] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

[20] G. L'abbé, B. Forier, W. Dehaen, *Chem. Commun.* **1996**, 2143–2144.