A divergent synthesis of modular dendrimers *via* sequential C–C bond fragmentation thio-Michael addition†

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The C–C bond fragmentation of carbocycles has been developed as a new method for the divergent synthesis of dendrimers. The scope of this reaction was examined with the preparation of six first generation dendrimers from structurally diverse and readily available fragmentation precursors. By pairing the fragmentation with a thio-Michael reaction, the preparation of a [G4]-ene$_{24}$ dendrimer has been achieved.

The success of hyperbranched monodisperse macromolecules in fields spanning nanotechnology[1a–e] to medicine[1f,g, 3] has driven the development of efficient strategies for the synthesis and functionalisation of dendrimers.[2] Recent synthetic highlights include the development of methods for internal functionalisation,[2d,e,g,j,n] accelerated growth,[2h–j] degradability,[2k,m] and bifunctionality.[2f] Remarkably, these discoveries have been achieved using only a handful of powerful organic reactions. Herein, we report the first example of a divergent dendrimer synthesis using the C–C bond fragmentation of carbocyclic β-ketoesters.

Recently, we commenced studies aimed at tackling the preparation of dendrimers with tuneable physical properties and the prediction of those properties.[3,4] Inspired by the broad utility of C=C ring opening in ROMP polymerisation[5] we decided to explore a strategy based around the C–C bond fragmentation[6,7] of cycloalkanones. The strength of this approach lies in the ubiquity of the substrates, providing a broad, and untapped resource for polymer synthesis.

While Grob-fragmentations are known, simple cycloalkanones require ring strain and/or forcing conditions to be viable (eqn (1)).[6a] To overcome this lack of reactivity we identified the fragmentation of β-ketoesters as worth investigating (*i.e.* **3**). It was postulated that the ester group would weaken the C–C bond thereby favouring fragmentation, a hypothesis supported by the observation that related materials undergo ring opening as a minor side reaction.[8] Alternately, **3** can be viewed as a substrate that can open by a retro-Dieckmann[9]/elimination sequence to provide the same product.[10]

In addition to facilitating C–C bond fragmentation the ester group in starting material **3** provides an α,β-unsaturated ester motif in product **4**. This functionality was considered useful for either chain extension, as developed herein, or as a malleable chemical handle for the attachment of materials to the interior of the dendrimer.[11]

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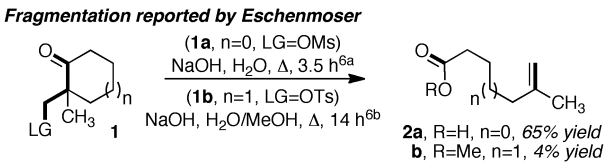
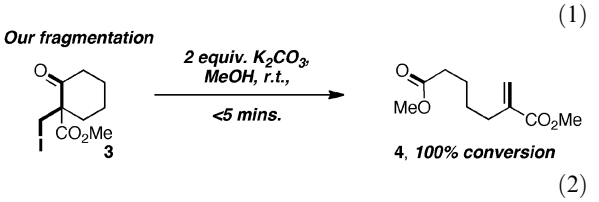
To explore these ideas β-ketoester **3** was exposed to methanol and K_2CO_3 at room temperature in a trial reaction. Remarkably, complete C–C bond cleavage occurred in less than 5 minutes, providing α,β-unsaturated ester **4** quantitatively (eqn (2)). The facile nature of this test reaction, ready availability of the starting material (ESI†), and the range of carbocycles potentially suited to this reaction proved ample incentive for further investigation. In this communication the use of a Grob/Eschenmoser fragmentation to prepare a range of first generation alkenes, and the fourth generation dendrimer **11a**, is reported.

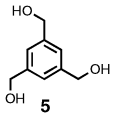
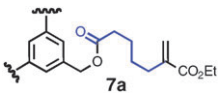
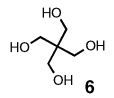
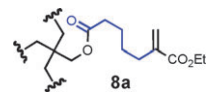
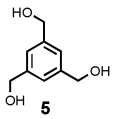
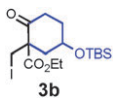
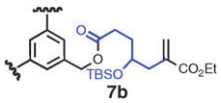
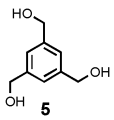
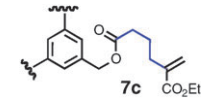
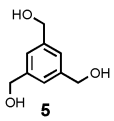
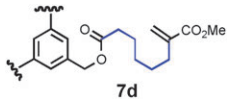
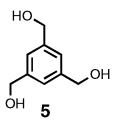
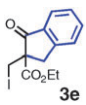
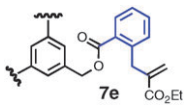




Studies commenced with the assembly of a number of first generation dendrimers from polyol cores and β-ketoesters **3a–e** (Table 1). Fragmentation precursors **3a–e** were chosen to examine the scope of the reaction, while modulating physical properties (*vide infra*). In addition, these substrates are readily prepared in one or two steps, from known or commercial materials.

During initial experiments, triol **5** was reacted with 3 equivalents of β-ketoester **3a**, under conditions analogous to those in eqn (2). Unfortunately, triol **5** was sparingly miscible with β-ketoester **3a**, and little conversion was achieved after 24 hours. Various solvents increased miscibility, however they did not provide a serviceable yield of [G1]-ene$_3$ **7a**. In contrast increasing the stoichiometry of monomer **3a** (2 equiv. per alcohol group) and raising the temperature to 70 °C allowed [G1]-ene$_3$ **7a** to be prepared in 93% isolated yield after 72 hours (Table 1, entry 1). In an attempt to accelerate the reaction, microwave irradiation at 70 °C was trialled. Using these conditions 92% conversion of triol **5** was achieved after 60 minutes, while extended heating introduced decomposition products (Table 1, entry 1b). Although the reaction time is long under conventional heating, the high purity of the product meant that these conditions were used. Next the tetrol core **6** was subjected to four fold fragmentation with β-ketoesters **3a**, providing [G1]-ene$_4$ **8a** in 87% isolated yield (Table 1, entry 2). The use of fragmentation precursor **3b** met

Table 1 Scope of modified Grob/Eschenmoser fragmentation

Entry	Core	β-Ketoester	Product[a]	% Yield[b]
1a				93
1b	5	3a	7a	92[c]
2				87
	6	3a	8a	
3				87
	5	3b	7b	
4				98
	5	3c	7c	
5				91
	5	3d	7d	
6				88
	5	3e	7e	

[a] 2 equiv. **3a–e** and K_2CO_3/alcohol, 70 °C, 72 h. [b] Isolated yield following flash column chromatography. [c] Conversion judged by ^{1}H NMR.

with similar success, providing [G1]-ene$_3$ **7b** in 87% yield (Table 1, entry 3). This product contains key functionality, useful for internal modification, or switchable dendrimer decomposition.[12] Monomer length was explored with pentanone **3c** and heptanone **3d** providing chain-contracted, and -extended, first generation dendrimers **7c** and **7d** (Table 1, entries 4 and 5). The latter example demonstrates that while the reaction reported by Eschenmoser is highly sensitive to ring size,[6a] our substrates are far less so. Finally the introduction of forced turns was explored using indanone **3e** and providing [G1]-ene$_3$ **7e**, in 88% isolated yield (Table 1, entry 6). In all cases the outcome of the reaction was determined using conventional means (ESI†), while with [G1]-ene$_3$ **7a**, in addition, GPC analysis was used to confirm the outcome of the reaction (Fig. 1B).

Having established the viability of the Grob/Eschenmoser fragmentation, a phosphine catalysed thio-Michael addition was investigated to introduce a branching diol.[2l] We found that the threefold reaction of [G1]-ene$_3$ **7a** with thiol **9** proceeded rapidly, either solvent free or more conveniently, in acetonitrile, to afford [G1]-ol$_6$ **10a** in full conversion. Repeating the Grob/Eschenmoser fragmentation and thio-Michael reactions furnished [G4]-ene$_{24}$ **11a** in five subsequent steps (Scheme 1). Each step reached greater than 95% completion as judged by ^{1}H NMR analysis. Trituration of the crude reaction mixtures gave high yields with few impurities, although for analytical purposes flash column chromatography was performed, giving lower isolated yields but greater

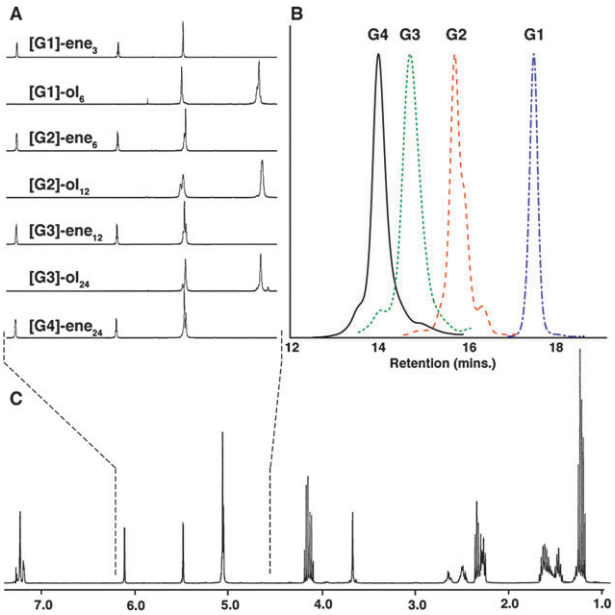


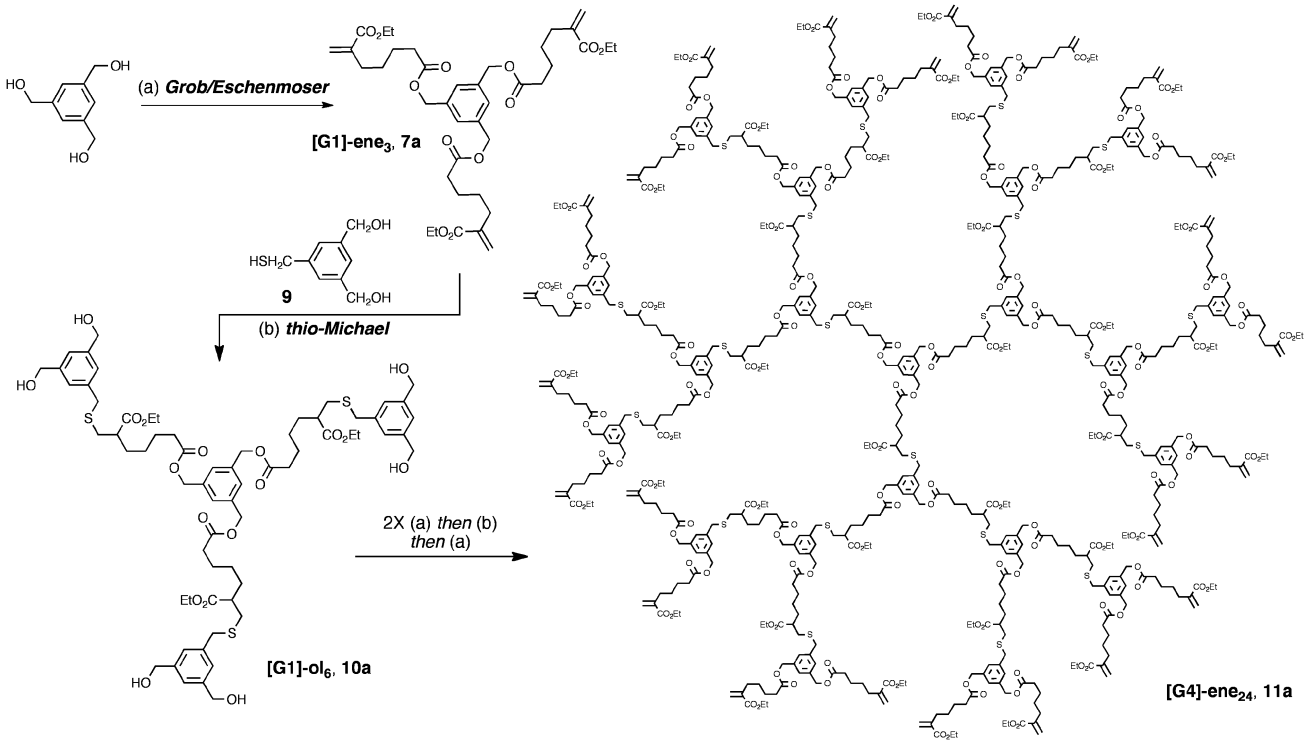
Fig. 1 (A) ^{1}H NMR Expansion of **[G1]-ene$_3$** to **[G4]-ene$_{24}$** between δ 6.2 and 4.5 ppm. (B) GPC trace of alkenes **[G1]-ene$_3$** to **[G4]-ene$_{24}$**. (C) ^{1}H NMR of **[G4]-ene$_{24}$**.

purity (ESI†). Diagnostic signals in the ^{1}H NMR for consumption of the alkene in the thio-Michael, and the benzylic alcohol in the fragmentation allowed the reaction progress to be analysed (Fig. 1A and C).

GPC analysis of the olefin terminating materials, [G1]-ene$_3$ **7a** to [G4]-ene$_{24}$ **11a**, was also conducted demonstrating narrow dispersion (PDI $<$ 1.2, see ESI†), and a predictable increase in molecular size (Fig. 1B). ESI HRMS was possible on all compounds up to [G2]-ene$_6$, providing the expected results, while at higher generations the materials were analysed by MALDI-TOF. The alkene terminating materials failed to ionize using various matrices and methods, while [G3]-ol$_{24}$ provided a positive analysis within the expected mass range.

Access to a range of macromolecules allowed us to test theories for the prediction of dendrimer size. When Random Branching Theory (RBT) was used to reproduce the hydrodynamic radii of [G1]-ene$_3$ **7a** to [G4]-ene$_{24}$ **11a**, as obtained from GPC analysis, the predictions were qualitatively correct, however they failed to reproduce the sharp increase in size relative to mass (ESI†). These studies highlight the need for improved theoretical models[13] for modelling dendrimer size. Ongoing investigations aim to address this topic, using small angle scattering data of the dendrimers presented herein.

In summary, we have developed a divergent synthesis of [G4]-ene$_{24}$ **11a** using the fragmentation of readily available carbocycles. This reaction proceeds in excellent yields, using a range of β-ketoesters, prepared in either one or two steps from commercial materials. The use of C–C bond fragmentation reactions in dendrimer synthesis is new. While the Grob/Eschenmoser fragmentation explored in these studies performed exceptionally well, we believe that a host of related fragmentation reactions are equally well suited to applications in dendrimer and polymer synthesis. These are the subjects of ongoing studies. In addition, we are developing improved models to predict the physical properties of dendrimers bearing internal branching.



Scheme 1 Synthesis of [G4]-ene$_{24}$ **11a**: (a) 2 equiv. **3a** and K_2CO_3/alcohol, 70 °C, 72 h; (b) 10 mol% Me_2PPh, 1 equiv. **9**/alkene, CH_3CN, rt, 1 h.

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Notes and references

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12 Deprotection of TBS alcohols in compounds related to [G1]-ene$_3$**7b** results in lactonisation, a reaction that could provide a switch for removal of the outer generation of a dendrimer.

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