The synthesis of precisely structured polyurethanes. Part 2. Chain building methodology

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The development of methodology to construct polyurethanes of precise structure is described. A linker, 4-hydroxymethylphenol, is attached to the Merrifield resin and monomers OCN-M^x-OTBDPS (where M^x = aryl or diarylmethane core; TBDPS = Bu^{t}Ph$_2$Si) are coupled sequentially *via* a dibutyltin dilaurate catalysed process. At each stage, chain cleavage and product distribution analysis allows optimisation of oligomer synthesis.

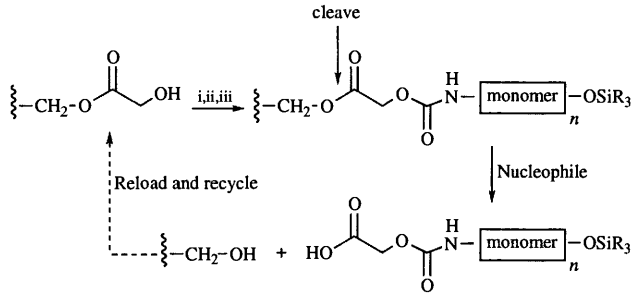
One of the major goals in polymer synthesis is to create known sequences of monomeric units in polymers that also have very narrow molecular weight distribution.[1,2] In a previous paper we described the synthesis of monomers and outlined a solid phase Merrifield strategy to be used to generate precisely structured polyurethanes.[3] The approach outlined was to add the monomers in a predetermined sequence to a solid support that contains a linking group present to facilitate chain removal. Subsequent cleavage of the assembled sequence of monomers from the solid support would complete a simple oligourethane synthesis. The method would also allow the coupling of an oligomeric soft polyether block to the urethane and thus the synthesis of defined elastomeric 1,1- (or higher order) copolymers. We report here the achievement of the first of these goals, the synthesis of defined oligomeric urethanes of single and mixed monomer constitution.

Results and discussions

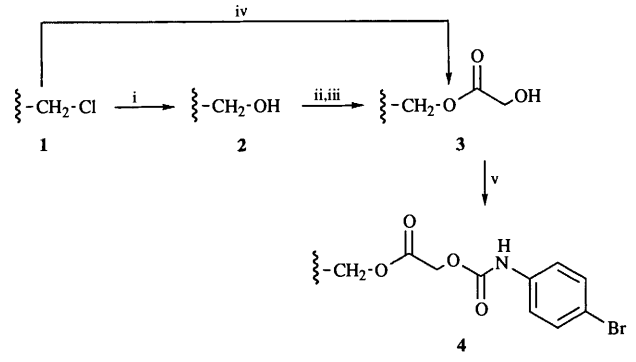
The coupled resins produced throughout this work were analysed by transmission IR (which was particularly useful in the early stages), microanalysis and, if sufficient material was available, by ^{13}C NMR spectroscopy.[4] Mass balance was also a useful indicator as to the success of the reaction. As the project developed it became critical to determine the degree of loading at each step and this was accurately assessed by detachment of the *n*-mers and subsequent analysis by HPLC and NMR spectroscopy. At each stage a solution chemistry analogue of the process was run for comparison.

The first task was the selection of a linker group which would allow cleavage of the chain without disruption of the urethane bonds. A glycolate group[5] was chosen initially to be attached to the resin through the acid functionality. Monomer could then be coupled *via* the hydroxy terminus and after the stepwise addition of the requisite number of monomers the ester link was to be selectively cleaved in preference to the carbamate bonds (Scheme 1).

Conversion of the chloromethyl resin **1** into the hydroxymethyl analogue **2** was achieved *via* reaction with acetate, under phase-transfer conditions, and subsequent hydrolysis (Scheme 2).[5] Reaction of **2** with *tert*-butyldiphenylsiloxyacetic acid[6] under dicyclohexyl carbodiimide (DCC)–4-(dimethylamino)-pyridine (DMAP) coupling conditions gave the protected glycolate attached to the resin. Subsequent deprotection gave **3**, the solid support with the glycolate residue attached (confirmed by ^{13}C NMR and transmission IR). Reaction with 4-bromophenyl isocyanate, as a model isocyanate, using dibutyltin dilaurate[7] as the coupling catalyst, gave a resin containing 1.2% N, (66% theoretical maximum loading based on the initial chlorine



Scheme 1 *Reagents:* i, OCN-monomer-OSiR$_3$; ii, F$^-$; iii, Repeat i and ii



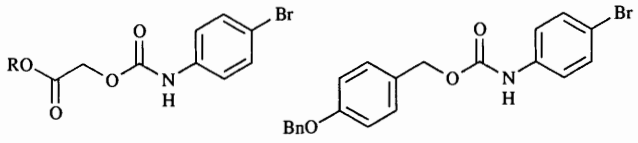
Scheme 2 *Reagents:* i, KOAc, Bu_4NOH, KOH, 2 days; ii, *tert*-butyldiphenylsiloxyacetic acid, DDC, DMAP; iii, TBAF; iv, NaO_2CCH_2OH, Adogen 464; v, 4-bromophenyl isocyanate, dibutyltin dilaurate

content). A higher loading of the linker was sought and therefore an alternative route was investigated. This involved the reaction of sodium glycolate with the chloromethyl support **1** under phase transfer conditions. This gave directly the derivatised resin with ^{13}C NMR indicating the complete loss of chloromethyl groups but 3% chlorine remaining by microanalysis. The degree of loading was not increased by the use of alternative glycolate salts. Upon coupling resin **3** to 4-bromophenyl isocyanate 1.6% N (85% theoretical loading) was incorporated. The recycling of the solid supports was investigated by the conversion of the hydroxymethyl resin **2** into the chloromethyl material **1** upon reaction with thionyl chloride. Reloading with glycolate and coupling to 4-bromophenyl isocyanate gave 1.3% N, suggesting that some loading capacity was reduced upon recycling.

The cleavage of the coupled resin **4** was investigated. Numerous conditions were used to achieve quantitative

removal of the chain selectively at the ester position, leaving the carbamate moiety intact.[8,9] When using LiCl–dimethylformamide (DMF), NaOH–tetrahydrofuran (THF)–H_2O, trifluoroacetic acid (TFA), or K_2CO_3–MeOH, either no reaction occurred, or both the ester and carbamate were cleaved, or an intramolecular cleavage took place with nitrogen attack on the ester moiety. LiBr–1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to cleave the ester link selectively but the process was incomplete.

In order to resolve this problem, soluble analogues were examined. Methyl glycolate and glycolic acid were coupled[7] to 4-bromophenyl isocyanate to give the resin mimics **5** and **6**

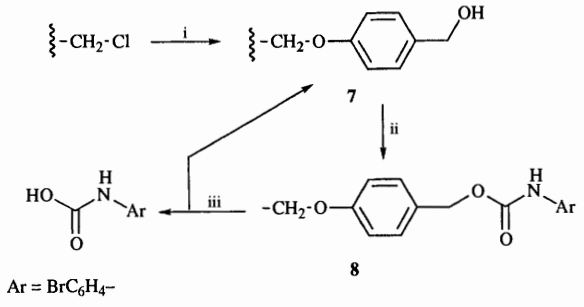


5 R = H
6 R = Me

9

respectively, which were then subjected to the above cleavage conditions. Again poor selectivity was observed, with the carbamate bond cleavage competing with ester cleavage.

The use of an alternative linker was therefore sought that would achieve more selective and efficient cleavage of the assembled oligomers. An electron-donating linker was chosen rather than the electron-withdrawing glycolate. Accordingly 4-(hydroxymethyl)phenol, a linkage which has been successfully used in peptide synthesis,[10] was reacted with the Merrifield chloromethyl resin **1** to generate **7** (Scheme 3). When coupled



Ar = BrC_6H_4–

Scheme 3 *Reagents:* i, 4-hydroxymethylphenol, NaOMe, DMA; ii, ArNCO; iii, 50% TFA in CH_2Cl_2

under the catalytic conditions with 4-bromophenyl isocyanate, urethane **8** was formed (82% loading). A solution chemistry analogue **9** was also prepared from 4-benzyloxybenzyl alcohol and 4-bromophenyl isocyanate in 98% yield.

The solution product **9** and the solid supported coupled material **8** were subjected to the cleavage conditions of 50% trifluoroacetic acid in dichloromethane. The urethane bond was cleaved highly selectively yielding 4-bromoaniline and either 4-benzyloxybenzyl alcohol or the hydroxymethyl phenol support **7**. Thus it was now possible to efficiently load and remove material from the solid support. The other main advantage in using the electron donating linker was that the resin was immediately available for reloading and recycling of the resin.

With the methodology established for linker coupling/cleavage the next phase of this work involved the assembly of the prepared monomers[3] in a sequential manner.

For the initial work the MDI analogue, OCN-M^1-OTBDPS[3] (see Fig. 1), was used together with the solid support **7** and 4-benzyloxybenzyl alcohol as the resin-linker mimic. The solution chemistry coupling proceeded in 81% yield, and the solid support in up to 75% of the theoretical loading of the resin. Optimum conditions for the reaction involved the immediate use of freshly prepared monomer, OCN-M^1-OTBDPS, which was used in excess.

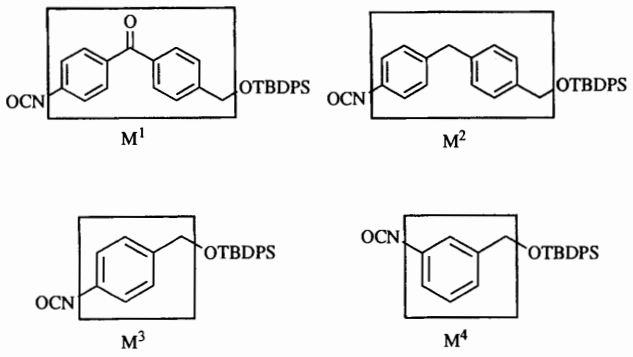
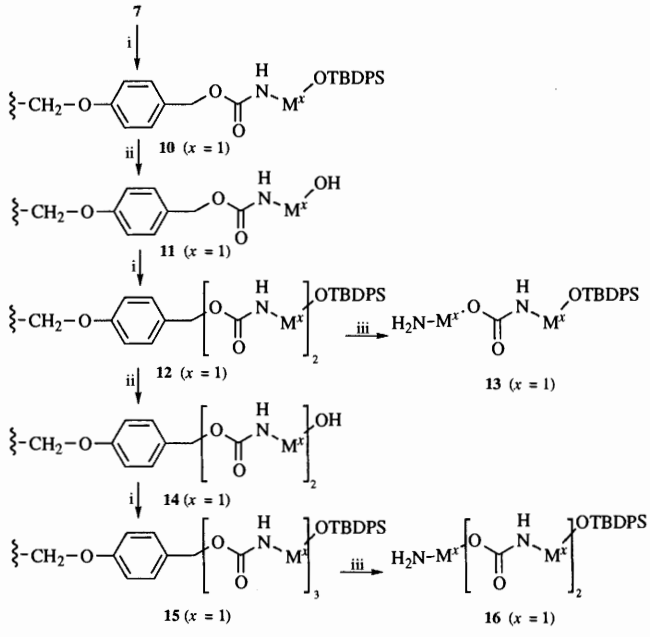


Fig. 1

Removal of the attached monomer from the solid support was again successfully performed under acidic (TFA–CH_2Cl_2) conditions in quantitative yield. The attachment of monomers to the resin was then attempted in a sequential fashion to form resin-dimers and trimers from OCN-M^1-OTBDPS (Scheme 4).



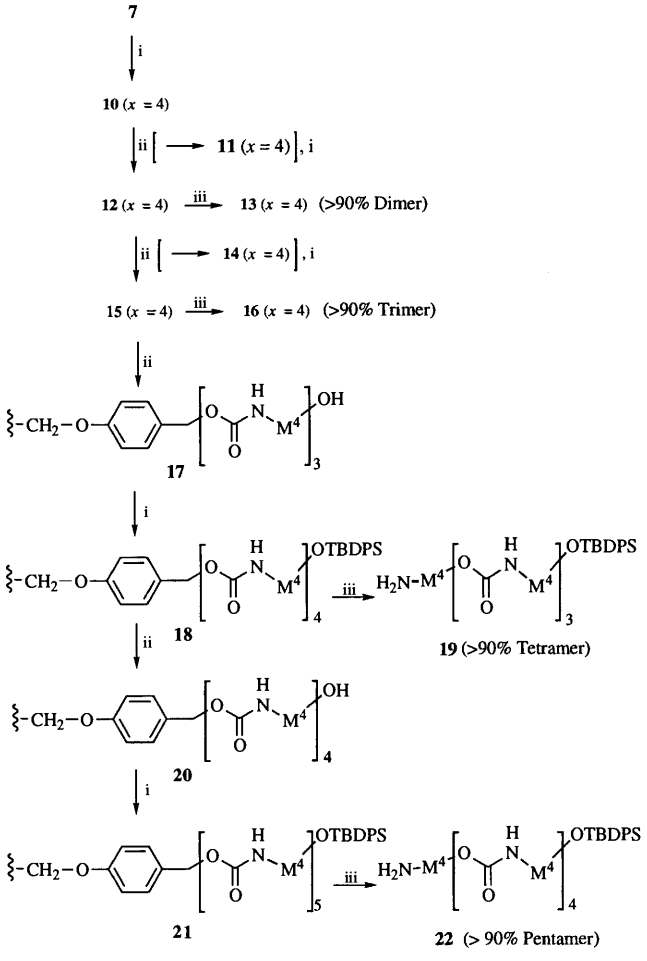
Scheme 4 *Reagents:* i, OCN-M^1-OTBDPS, dibutyltin dilaurate, DCM; ii, TBAF, THF; iii, 50% TFA in CH_2Cl_2

Microanalyses of the resins at each stage indicated that the OCN-M^1-OTBDPS monomer loaded onto the resin in high yield. However, HPLC analysis of the cleaved trimer **16** (x = 1), showed that both trimer **16** (x = 1) and dimer **13** (x = 1) were present in a ratio of 7:2. The cause could have been any one or more of: inefficient monomer addition, incomplete deprotection or non-specific chain removal. The use of 1.5–2 equivalents of tetrabutylammonium fluoride (TBAF)[9] ensured complete removal of the protecting group but detailed investigation indicated that the coupling efficiency with OCN-M^1-OTBDPS was still variable and reproducibility was a problem. The problem was finally identified as the high water sensitivity of the OCN-M^1-OTBDPS monomer, and hence the use of alternative monomers was explored.

The methylene derivative OCN-M^2-OTBDPS was less water sensitive, and so more reproducible additions were achieved in the synthesis of **10** (x = 2) and **11** (x = 2). However, due to the greater synthetic accessibility of the monomers OCN-M^3-OTBDPS and OCN-M^4-OTBDPS, the use of these was explored for the preparation of larger n-mers. In addition, mixed n-mers were prepared in order to reveal whether incomplete sequences resulted from incomplete coupling cycles or chain degradation during linker cleavage.

Initially OCN-M^3-OTBDPS was studied in both solution (4-benzyloxybenzyl alcohol starter) and solid phase (**7** starter). The coupling occurred readily (solution phase 91%, solid phase 92%); however, when subjected to the cleavage conditions to remove the assembled mixed dimer **13** (x = 3, 1) and trimer **16** (x = 3, 1, 1) from the solid support only the monomer H_2N-M^1-OTBDPS and the dimer **13** (x = 1) respectively were isolated. This was because the in-chain monomer unit –CONH-M^3-O– was too similar in reactivity to the linker, hydroxymethyl phenol, and the urethane bond was cleaved at a comparable rate to the ester link. OCN-M^3-OTBDPS was therefore discarded.

The more stable *meta* analogue, OCN-M^4-OTBDPS, was found to couple to the resin in high yield (92% loading for the first coupling) and was altogether a more efficient and suitable monomer. Chain building was carried out with this compound as depicted in Scheme 5 and extended to the pentamer. For each



Scheme 5 *Reagents:* i, OCN-M^4-OTBDPS, dibutyltin dilaurate, CH_2Cl_2; ii, TBAF, THF; iii, 50% TFA in CH_2Cl_2

of the coupling and deprotection procedures, a twofold excess of TBAF and the isocyanate were used and chain building proceeded without problems. This time the resin *n*-mers readily cleaved to give free *n*-mers using the acidic detachment procedure.

Analysis of the products after cleavage from the resin was achieved using HPLC, although at the pentamer stage, solubility problems were encountered. GPC analysis, the method of choice for molecular mass confirmation for the higher *n*-mers, was performed on the monomer to tetramer samples and confirmed their degree of polymerisation. Mass balance, IR and NMR of the loaded resins, by this stage, were not useful.

Thus cleavage of the resin–tetramer **18** gave the free tetramer **19** containing lower homologues in a ratio of 91:8:1 (tetramer):(trimer):(monomer) and cleavage of the resin–pentamer **21** gave a product **22** of ratio 92:7:1 for (pentamer):(tetramer):(monomer).

In conclusion, using the methodology developed here, we have been able to prepare up to 5-mers of known molecular weight distribution and the technique is now ready for application to the synthesis of specific homo- and co-polymers and block co-polymers with polyether blocks.

Experimental

For general details, see Paper 1.[3] All reactions involving isocyanate monomers were carried out under strictly anhydrous conditions. Unless otherwise stated, HPLC analysis of oligomers was carried out using 20% ethyl acetate–dichloromethane as eluent on a 15 cm normal phase Microsorb column.

Chloromethyl resin 1

Chloromethylpolystyrene–1% divinylbenzene, supplier: Novachem, 1.6 mequiv. g^{-1}. Microanalytical data for comparative purposes (Found, 6.35% Cl) (1.8 mequiv.) g^{-1}. ν_{max}(Nujol)/cm^{-1} 1920w, 1850w, 1780w, 1600s and 1580m; δ_C(63 MHz; $CDCl_3$) 40.76, 44.40, 46.35, 128.16 and 145.54.

Hydroxymethyl resin 2

Tetrabutylammonium hydroxide (0.3 g, 40% aqueous solution), potassium acetate (3 g, 36.1 mmol), and potassium hydroxide (2.0 g in 6 ml water) were added to the Merrifield chloromethyl resin (1.13 g, *ca.* 1.8 mmol) suspended in chlorobenzene (10 ml). The mixture was stirred at 85 °C for 2 days. After filtration the polymer was washed repeatedly with methanol, water, acetone, dichloromethane and finally hexane. After drying under vacuum the polymer weighed 1.16 g; ν_{max}(Nujol)/cm^{-1} 3350br, 1920w, 1850w, 1780w and 1580m (Found: Cl, 0%).

Hydroxyacetoxymethyl resin 3 *via* direct coupling

Adogen 464 (1.5 g), and sodium glycolate (1.50 g, 15.3 mmol) in water (25 ml) were added to the Merrifield chloromethyl resin **1** (5.01 g, *ca.* 8.0 mmol) suspended in chlorobenzene (40 ml). The mixture was stirred at 100 °C for 4 days. After filtration the polymer was washed repeatedly, as described above, and dried under vacuum to yield resin **3** (5.30 g). Microanalysis indicated there to be 0.19% Cl remaining, ≡3% of the chlorine sites. This is equivalent to 1.55 mequiv. g^{-1} of glycolate having been added; ν_{max}(Nujol)/cm^{-1} 3280br, 1920w, 1850w, 1780w, 1730s, 1600s, 1580m and 1500s; δ_C(63 MHz; $CDCl_3$) 40.73, 44.30br, 60.84, 67.23, 128.14br, 145.61 and 173.10.

Hydroxyacetoxymethyl resin 3 *via* protected glycolate

tert-Butyldiphenylsiloxyacetic acid[6] (380 mg, 1.21 mmol), DCC (363 mg, 1.76 mmol), and DMAP (13 mg, 0.11 mmol) were added to the hydroxymethyl resin **2** (0.680 g, *ca.* 1.1 mmol) in dichloromethane (20 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *tert-butyldiphenylsiloxyacetoxy resin* (0.965 g); ν_{max}(Nujol)/cm^{-1} 3260w, 1920w, 1850w, 1780w, 1730w and 1600s.

Tetrabutylammonium fluoride (0.48 ml, 0.48 mmol; 1 mol l^{-1} solution in THF) was added to the siloxyacetoxy resin (300 mg, *ca.* 0.48 mmol) in THF (5 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *title resin* **3** (0.220 g). Analytical data was consistent with that for **3** prepared by the direct route.

N-(4-Bromophenyl)carbamoyloxyacetoxymethyl resin 4

4-Bromophenyl isocyanate (69 mg, 0.35 mmol) and dibutyltin dilaurate (2 drops) were added to the hydroxymethyl resin **2** (200 mg, *ca.* 0.32 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described

above to yield the *title resin* (260 mg); ν_{max}(Nujol)/cm^{-1} 3280br, 1920w, 1850w, 1780w, 1740s, 1600s, 1580m and 1500s; δ_C(63 MHz; $CDCl_3$) 40.72, 44.13, 61.47, 67.18, 116.40, 120.54, 128.04br, 132.07, 137.22, 145.60, 153.75 and 168.10 (Found: C, 76.8; H, 6.4; N, 1.6%. Maximum theoretical loading: N, 1.8%).

Regeneration of chloromethyl resin 1

Thionyl chloride (0.04 ml, 0.516 mmol) was added to the hydroxymethyl resin **2** (215 mg, *ca.* 0.34 mmol) in chlorobenzene (10 ml) and the resulting mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *title resin* **1** (225 mg); ν_{max}(Nujol)/cm^{-1} 1920w, 1850w, 1780w, 1600s and 1580m.

***N*-(4-Bromophenyl)carbamoyloxyacetic acid 5**

4-Bromophenyl isocyanate (200 mg, 1.01 mmol) and dibutyltin dilaurate (1 drop) were added to glycolic acid (77 mg, 1.01 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 18 h, water (10 ml) was added and the product extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried, evaporated and purified by flash chromatography [light petroleum (bp 40–60 °C)–ethyl acetate, 1:1] to give the *title compound* **5** as colourless crystals (192 mg, 69%), mp 285 °C (decomp.) (from hexane–ethyl acetate, 1:1); ν_{max}(Nujol)/cm^{-1} 3357m, 3327m, 2930s, 1747s, 1709s, 1594m and 1492m; δ_H(270 MHz; $CDCl_3$) 4.72 (2 H, s, CH_2O), 7.00 (1 H, br s, NH), 7.30 (2 H, d, *J* 8.1 Hz, 2′-H) and 7.42 (2 H, d, *J* 8.1 Hz, 3′-H); *m*/*z* (EI) 275 (M^+, 1%), 273 (M^+, 1), 199 ($M^+ - HO_2CCH_2OH$, 95), 197 ($M^+ - HO_2CCH_2OH$, 100); and 90 ($MeOCOCH_2OH^+$, 81) (Found: C, 39.5; H, 2.8; N, 4.9. $C_9H_8O_4NBr$ requires: C, 39.44; H, 2.94; N, 5.11%).

Methyl *N*-(4-bromophenyl)carbamoyloxyacetate 6

4-Bromophenyl isocyanate (440 mg, 2.22 mmol), and dibutyltin dilaurate (2 drops) were added to methyl glycolate (0.17 ml, 2.22 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 18 h, water (20 ml) was added and the product extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried and evaporated to yield a white solid which was purified by recrystallisation (ethyl acetate–hexane, 1:1) to give the *title compound* **6** as colourless crystals (423 mg, 65%); ν_{max}(Nujol)/cm^{-1} 3364s, 2930s, 1756s, 1731s, 1596m, 1500m and 1400s; δ_H(270 MHz; $CDCl_3$) 3.80 (3 H, s, OCH_3), 4.68 (2 H, s, CH_2O), 6.85 (1 H, br s, NH), 7.26 (2 H, d, *J* 8.6 Hz, 2′-H) and 7.40 (2 H, d, *J* 8.6 Hz, 3′-H); *m*/*z* (EI) 289 (M^+, 7%), 287 (M^+, 9), 199 ($M^+ - MeOCOCH_2OH$, 96), 197 ($M^+ - MeOCOCH_2OH$, 100) and 90 ($MeOCOCH_2OH^+$, 32).

4-(Hydroxymethyl)phenoxymethyl resin (= resin-linker) 7

4-(Hydroxymethyl)phenol (2.98 g, 24.0 mmol) was added to the chloromethyl resin **1** (5.00 g, *ca.* 8.0 mmol), suspended in *N*,*N*-dimethylacetamide (25 ml). Sodium methoxide (1.30 g, 24.0 mmol) was then added and the reaction was stirred at 50 °C for 6 h. After filtration the polymer was washed repeatedly as described above to yield the *title resin-linker* **7** (6.16 g); ν_{max}(Nujol)/cm^{-1} 3400br, 1920w, 1850w, 1780w, 1600s and 1500m; δ_C(63 MHz; $CDCl_3$) 41.07, 43.64br, 65.22, 70.56, 115.55, 128.69br, 145.50 and 159.10.

***N*-(4-Bromophenyl)carbamoyl-linker-resin 8**

To the derivatised resin **7** (500 mg, *ca.* 0.8 mmol), suspended in dichloromethane (10 ml), was added 4-bromophenyl isocyanate (178 mg, 0.9 mmol) and dibutyltin dilaurate (2 drops). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *title resin* **8** (601 mg); ν_{max}(Nujol)/cm^{-1} 3300br, 2920s, 1920w, 1850w, 1780w, 1730s and 1600s; δ_C(63 MHz; $CDCl_3$) 40.65, 44.23br, 67.02, 70.21, 115.18, 116.09, 120.49, 125.85, 128.09br, 130.14, 131.98, 137.14, 145.48 and 153.42 (Found: N, 1.4%. Maximum loading: N, 1.7%).

4-Benzyloxybenzyl *N*-(4-bromophenyl)carbamoate 9

4-Bromophenyl isocyanate (370 mg, 1.87 mmol) and dibutyltin dilaurate (2 drops) were added to a solution of 4-benzyloxybenzyl alcohol (373 mg, 1.74 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 18 h. The dichloromethane was removed *in vacuo*, the white solid was redissolved in ethyl acetate (50 ml) and the insoluble material was removed by filtration. The resulting filtrate was evaporated and recrystallised (ethyl acetate–hexane) to yield the *title compound* **9** (708 mg, 98%), mp 144–145 °C; ν_{max}(Nujol)/cm^{-1} 3332s, 2918s, 1706s, 1591s and 1530s; δ_H(270 MHz; $CDCl_3$) 5.07 (2 H, s, CH_2O), 5.13 (2 H, s, CH_2Ph), 6.62 (1 H, br s, NH), 6.97 (2 H, d, *J* 8.8 Hz) and 7.38 (11 H, m, Ar); δ_C(63 MHz; $CDCl_3$) 67.03 (CH_2O), 70.07 (CH_2Ph), 115.01 (C-3, C-5), 115.98, 120.19, 121.56, 127.42, 128.02, 128.21, 128.61, 130.24, 131.99, 136.80, 136.94, 153.14 and 159.03; *m*/*z* (FAB) 412 (M^+, 80%), 369 ($M^+ - CO_2$, 74), 197 ($PhCH_2OC_6H_4CH_2^+$, 100) and 91 ($PHCH_2^+$, 71).

Linker cleavage of resin 8

Trifluoroacetic acid (2.5 ml) was added dropwise to a solution of resin **8** (100 mg, *ca.* 0.10 mmol) in dichloromethane (2.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 20 ml). The combined organic extracts were dried and evaporated to yield 4-bromoaniline (20 mg). The resin was washed and dried using the same procedure as that described above to yield the resin-linker adduct **7** (60 mg) (Found: N, 0%). The IR spectrum indicated the loss of the carbamate linkage.

Resin-linker-monomer-OTBDPS 10 (x = 1)

The resin-linker **7** (137 mg, *ca.*, 0.21 mmol) was added to the isocyanate monomer OCN-M^1-OTBDPS (178 mg, 0.240 mmol) and dibutyltin dilaurate (1 drop) in toluene (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *monomer resin* **10** (x = 1) (170 mg); ν_{max}(Nujol)/cm^{-1} 3300br, 2923s, 1920w, 1850w, 1780w and 1740m (Found: N, 0.9%. Maximum loading: N, 1.2%).

Benzyl 4-(*tert*-butyldiphenylsiloxy-M^1-carbamoyloxymethyl)-phenyl ether

4-Benzyloxybenzyl alcohol (41 mg, 0.19 mmol), in toluene (2 ml) was added to the monomer OCN-M^1-OTBDPS (118 mg, 0.24 mmol) and dibutyltin dilaurate (1 drop) in toluene (15 ml). The reaction mixture was stirred at room temperature for 18 h. The toluene was removed *in vacuo*, and the product purified by flash chromatography [ether–light petroleum (bp 40–60 °C), 2:3] to yield the *title compound* (41 mg, 81%) as a colourless solid, mp 44–45 °C; ν_{max}(Nujol)/cm^{-1} 2921s, 1735m, 1647w, 1589s and 1513s; δ_H(270 MHz; $CDCl_3$) 4.84 (2 H, s), 5.08 (2 H, s), 5.16 (2 H, s), 6.62 (1 H, br s, NH), 6.97 (2 H, d, *J* 8.0 Hz, 3-H, 5-H), 7.25 (6 H, m, Ar), 7.40 (15 H, m, Ar) and 7.75 (4 H, m, Ar); δ_C(63 MHz; $CDCl_3$) 19.35 (CMe_3), 26.88 (CMe_3), 65.24, 67.24, 70.13 (CH_2Ph), 115.10 (C-3, C-5), 117.55, 125.65, 127.43, 127.80, 128.04, 128.13, 128.63, 129.82, 129.98, 130.30, 131.70, 132.65, 133.32, 135.57, 136.63, 136.85, 141.78, 145.62, 152.96, 159.14 and 195.25 (ArCOAr); *m*/*z* (FAB) 706 (MH^+, 25%), 197 ($PhCH_2OC_6H_4CH_2^+$, 64), and 91 ($PHCH_2^+$, 100) (Found: MH^+ 706.2993; $C_{45}H_{44}NO_5Si$ requires: *M* 706.2989).

Linker cleavage of resin 10 (x = 1)

Trifluoroacetic acid (1.5 ml) was added dropwise to a suspension of resin **10** (x = 1) (70 mg, *ca.* 0.05 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by

filtration. The cleaved product was extracted into ethyl acetate (3 × 15 ml). The combined organic extracts were dried and evaporated to yield *H_2N-M^1-OTBDPS* (20 mg, 100% based upon the microanalysis of the resin); ν_{max}(film)/cm^{-1} 3360s, 3220s, 2931s, 1640s and 1593s; δ_H(270 MHz; $CDCl_3$) 1.12 (9 H, s, C*Me*$_3$), 4.84 (2 H, s, CH_2O), 6.68 (2 H, d, *J* 8.6 Hz, 3′-H, 5′-H), 7.41 (8 H, m, Ar) and 7.72 (8 H, m, Ar); *m/z* (EI) 465 (M^+, 1%), 408 ($M^+ - CMe_3$, 100) and 120 ($NH_2C_6H_4CO^+$, 65). The resin was washed and dried using the same procedure as that described above to yield the cleaved resin (49 mg) (Found: N, 0%).

Resin-linker-monomer-OH 11 (*x* = 1)
Tetrabutylammonium fluoride (0.12 ml, 0.12 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a suspension of resin **10** (*x* = 1) (102 mg, *ca.* 0.09 mmol) in THF (5 ml). The mixture was stirred for 18 h, water (10 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *monomer resin* **11** (83 mg); ν_{max}(Nujol)/cm^{-1} 3250br and 2923s (Found: N, 1.0%. Maximum loading: N, 1.6%).

Resin-linker-dimer-OTBDPS 12 (*x* = 1)
Resin **11** (*x* = 1) (80 mg, *ca.* 0.07 mmol) was added to the isocyanate monomer OCN-M^1-OTBDPS (57 mg, 0.11 mmol) and dibutyltin dilaurate (1 drop) in toluene (8 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration, the polymer was washed repeatedly as described above to yield the *dimer resin* **12** (*x* = 1) (81 mg); ν_{max}(Nujol)/cm^{-1} 3430br and 2923s (Found: N, 1.8%. Maximum loading: N, 2.0%).

Linker cleavage of resin 12 (*x* = 1)
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **12** (*x* = 1) (60 mg, *ca.* 0.08 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *dimer* **13** (*x* = 1) (20 mg), present in a ratio of 2:1, for (dimer):(monomer) by HPLC (normal phase 10% ethyl acetate–dichloromethane, flow rate 0.5 ml min^{-1}). Dimer **13** (*x* = 1) showed: δ_H(270 MHz; $CDCl_3$) 1.09 (6 H, s, C*Me*$_2$), 1.27 (3 H, s, C*Me*), 3.25 (2 H, br s, NH_2), 4.84 (2 H, s, CH_2OSi), 5.30 (2 H, s, CH_2OCO), 6.68 (4 H, m, Ar), 7.42 (10 H, m, Ar) and 7.74 (12 H, m, Ar); *m/z* (FAB) 719 (MH^+, 45%), 661 ($M^+ - CMe_3$, 53) and 57 (CMe_3^+, 100).

Resin-linker-dimer-OH 14 (*x* = 1)
Tetrabutylammonium fluoride (0.25 ml, 0.25 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **12** (*x* = 1) (250 mg, *ca.* 0.16 mmol) in THF (5 ml). The reaction was stirred for 18 h, water (10 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *dimer resin* **14** (*x* = 1) (210 mg) which was used for the subsequent step without further characterisation.

Resin-linker-trimer-OTBDPS 15 (*x* = 1)
Resin **14** (*x* = 1) (210 mg, *ca.* 0.16 mmol of available OH) was added to the isocyanate monomer OCN-M^1-OTBDPS (92 mg, 0.19 mmol) and dibutyltin dilaurate (1 drop) in toluene (15 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *trimer resin* **15** (*x* = 1) (230 mg). This was characterised by cleavage to the free trimer below.

Linker cleavage of resin 15 (*x* = 1)
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **15** (*x* = 1) (31 mg, *ca.* 0.02 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *trimer* **16** (10 mg) in a ratio, determined by HPLC, of 7:2 for (trimer):(dimer). The trimer **16** showed: δ_H(270 MHz; $CDCl_3$) 1.13 (6 H, s, C*Me*$_2$), 1.26 (3 H, s, C*Me*), 3.04 (2 H, br s, NH_2), 4.84 (2 H, s, CH_2OSi), 5.31 (4 H, s, CH_2OCO), 6.65 (4 H, m, Ar), 7.46 (16 H, m, Ar) and 7.75 (14 H, m, Ar); *m/z* (FAB) 972 (MH^+, 1%), 914 ($M^+ - CMe_3$, 1) and 57 (CMe_3^+, 100).

Resin-linker-monomer-OTBDPS 10 (*x* = 2)
The resin-linker **7** (110 mg, *ca.* 0.17 mmol) was added to the isocyanate monomer OCN-M^2-OTBDPS (110 mg, 0.23 mmol) and dibutyltin dilaurate (1 drop) in toluene (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly and dried as described above to yield the *monomer resin* **10** (*x* = 2) (172 mg) (Found: N, 1.1%. Maximum loading: N, 1.5%), which was taken on to the trimer without further characterisation.

Resin-linker-monomer-OH 11 (*x* = 2)
Tetrabutylammonium fluoride (0.27 ml, 0.27 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **10** (*x* = 2) (135 mg, *ca.* 0.14 mmol) in THF (5 ml). The reaction was stirred for 18 h, water (10 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *monomer resin* **11** (*x* = 2) (100 mg, the mass loss indicates *ca.* 95% loading).

Resin-linker-monomer-OTBDPS 10 (*x* = 3)
The resin-linker **7** (325 mg, *ca.* 0.52 mmol) was added to the isocyanate monomer OCN-M^3-OTBDPS (220 mg, 0.568 mmol) and dibutyltin dilaurate (2 drops) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *monomer resin* **10** (*x* = 3) (450 mg) (Found: N, 1.3%. Maximum loading: N, 1.4%).

Benzyl 4-(*tert*-butyldiphenylsiloxy-M^3-carbamoyloxymethyl)-phenyl ether
4-Benzyloxybenzyl alcohol (35 mg, 0.164 mmol), in toluene (2 ml) was added to the isocyanate monomer OCN-M^3-OTBDPS (80 mg, 0.207 mmol) and dibutyltin dilaurate (1 drop) in toluene (15 ml). The reaction mixture was stirred at room temperature for 18 h. The toluene was removed *in vacuo*, and the product purified by flash chromatography (ethyl acetate–light petroleum (bp 40–60 °C), 1:9) to yield the *title compound* (89 mg, 91%) as a colourless solid, mp 86–87 °C; ν_{max}(Nujol)/cm^{-1} 3319s, 2923s, 1698s and 1615s; δ_H(270 MHz; $CDCl_3$) 4.71 (2 H, s, CH_2OSi), 5.08 (2 H, s, CH_2Ph), 5.14 (2 H, s, CH_2CON), 6.62 (1 H, br s, NH), 6.97 (2 H, d, *J* 8.0 Hz, 3-H, 5-H), 7.25 (6 H, m, Ar), 7.40 (15 H, m, Ar) and 7.75 (4 H, m, Ar); δ_C(63 MHz; $CDCl_3$) 19.31 (*C*Me$_3$), 26.86 (C*Me*$_3$), 65.24 (CH_2OSi), 66.84 (CH_2Ph), 70.10 (CH_2CON), 115.02 (C-3, C-5), 126.91, 127.43, 127.70, 128.00, 128.53, 128.60, 129.67, 130.19, 133.60, 135.59, 136.32, 136.58, 136.89 and 158.89; *m/z* (FAB) 601 (M^+, 1%), 197 ($PhCH_2OC_6H_4CH_2^+$, 81) and 91 ($PHCH_2^+$, 100) (Found: MH^+ 601.2667; $C_{38}H_{39}NO_4Si$ requires: *M*H^+ 601.2650).

Resin-linker-monomer-OH 11 (*x* = 3)
Tetrabutylammonium fluoride (0.25 ml, 0.25 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **10** (*x* = 3) (210 mg, *ca.* 0.20 mmol) in THF (5 ml). The reaction was stirred for 18 h, water (8 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *monomer resin* **11** (*x* = 3) (180 mg) which was used for chain extension without further characterisation.

Resin-linker-dimer-OTBDPS 12 (x = 3, 1)
Resin **11** (x = 3) (180 mg, *ca.* 0.17 mmol) was added to the isocyanate monomer OCN-M^1-OTBDPS (153 mg, 0.31 mmol) and dibutyltin dilaurate (2 drops) in toluene (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *dimer resin* **12** (x = 3, 1) (226 mg) which was used for chain extension without further characterisation.

Linker cleavage of resin 12 (x = 3, 1) to yield H_2N-M^1-OTBDPS
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **12** (x = 3, 1) (25 mg, *ca.* 0.02 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 = 10 ml). The combined organic extracts were dried and evaporated to yield the title compound H_2N-M^1-OTBDPS (13 mg), identified by HPLC, together with a small amount of the mixed dimer (by HPLC).

Resin-linker-dimer-OH 14 (x = 3, 1)
Tetrabutylammonium fluoride (0.20 ml, 0.20 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **12** (x = 3, 1) (180 mg, *ca.* 0.17 mmol) in THF (5 ml). The reaction was stirred for 18 h, water (8 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *dimer resin* **14** (x = 3, 1) (160 mg).

Resin-linker-trimer-OTBDPS 15 (x = 3, 1, 1)
Resin **14** (i = 3, 1) (160 mg, *ca.* 0.17 mmol) was added to the isocyanate monomer OCN-M^1-OTBDMS (105 mg, 0.211 mmol) and dibutyltin dilaurate (2 drops) in toluene (10 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *trimer resin* **15** (x = 3, 1, 1) (143 mg) (Found: N, 2.2%. Maximum loading: N, 2.7%).

Cleavage of resin 15 (x = 3, 1, 1)
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **15** (x = 3, 1, 1) (29 mg, *ca.* 0.02 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *dimer* **13** (x = 1) (12 mg) with no mixed trimer present (by HPLC) but traces of monomer were detectable.

Resin-linker-monomer-OTBDPS 10 (x = 4)
The resin-linker **7** (885 mg, *ca.* 1.30 mmol) was added to the isocyanate monomer OCN-M^4-OTBDPS (600 mg, 1.55 mmol) and dibutyltin dilaurate (3 drops) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *monomer resin* **10** (x = 4) (1.42 g) (Found: N, 1.3%. Maximum loading: N, 1.4%).

Resin-linker-monomer-OH 11 (x = 4)
Tetrabutylammonium fluoride (2.68 ml, 2.68 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **10** (x = 4) (1.34 g, *ca.* 1.3 mmol) in THF (10 ml). The reaction was stirred for 18 h, water (15 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *monomer resin* **11** (x = 4) (1.05 g) (Found: N, 1.4%. Maximum loading: N, 1.7%).

Resin-linker-dimer-OTBDPS 12 (x = 4)
Resin **11** (x = 4) (1.05 g, *ca.* 1.3 mmol) was added to the isocyanate monomer OCN-M^4-OTBDPS (600 mg, 1.60 mmol) and dibutyltin dilaurate (3 drops) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *dimer resin* **12** (x = 4) (1.20 g) (Found: N, 2.2%. Maximum loading: N, 2.3%).

Cleavage of resin 12 (x = 4) to yield H_2N-dimer-OTBDPS 13 (x = 4)
Trifluoroacetic acid (2.5 ml) was added dropwise to a solution of resin **12** (x = 4) (105 mg, *ca.* 0.03 mmol) in dichloromethane (2.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *product* (30 mg) in a ratio of 98:2 [dimer **13** (x = 4)]:[monomer M^4] by HPLC (20% ethyl acetate–dichloromethane, flow rate 1 ml min^{-1}); δ_H(270 MHz; $CDCl_3$) 1.17 (9 H, s, CMe_3), 4.55 (2 H, br s, NH_2), 4.70 (2 H, s, CH_2OSi), 5.08 (2 H, s, CH_2OCO), 7.00 (4 H, m, Ar), 7.40 (10 H, m, Ar) and 7.75 (4 H, m, Ar); m/z (FAB) 511 (MH^+, 1%) and 106 ($H_2NC_6H_4CH_2^+$, 91).

Resin-linker-dimer-OH 14 (x = 4)
Tetrabutylammonium fluoride (1.4 ml, 1.4 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **12** (x = 4) (1.10 g, *ca.* 0.07 mmol) in THF (10 ml). The reaction was stirred for 18 h, water (15 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *dimer resin* **14** (x = 4) (0.95 g) (Found: N, 2.5%. Maximum loading: N, 2.5%).

Resin-linker-trimer-OTBDPS 15 (x = 4)
Resin **14** (x = 4) (0.90 g, *ca.* 0.70 mmol) was added to the isocyanate monomer OCN-M^4-OTBDPS (600 mg, 1.60 mmol) and dibutyltin dilaurate (3 drops) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *trimer resin* **15** (x = 4) (1.28 g) (Found: N, 2.9%. Maximum loading: N, 3.1%).

Cleavage of 15 (x = 4) to yield H_2N-dimer-OTBDPS 16 (x = 4)
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **15** (x = 4) (30 mg, *ca.* 0.02 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *product* (12 mg), in a ratio of 90:5:5 [trimer **16** (x = 4)]:[dimer **13** (x = 4)]:[monomer] by HPLC; δ_H(270 MHz; $CDCl_3$) 1.15 (9 H, s, CMe_3), 4.72 (2 H, s, CH_2OSi), 5.08 (2 H, s, $H_2NC_6H_4CH_2$), 5.16 (2 H, s, CH_2OCON), 6.70 (4 H, m, Ar), 7.40 (14 H, m, Ar) and 7.70 (4 H, m, Ar); m/z (FAB) 660 (MH^+, 1%).

Resin-linker-trimer-OH 17
Tetrabutylammonium fluoride (2.0 ml, 2.0 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **15** (x = 4) (1.23 g, *ca.* 0.70 mmol) in THF (10 ml). The reaction was stirred for 18 h, water (15 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *trimer resin* **17** (0.97 g) (Found: C, 79.6; H, 7.1; N, 3.4%. Maximum loading: N, 3.8%).

Resin-linker-tetramer-OTBDPS 18
Resin **17** (0.95 g, *ca.* 0.60 mmol) was added to the isocyanate monomer OCN-M^4-OTBDPS (400 mg, 1.07 mmol) and dibutyltin dilaurate (3 drops) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *tetramer resin* **18** (1.20 g) (Found: N, 3.5%. Maximum loading: N, 3.8%).

Cleavage of 18 to yield H_2N-tetramer-OTBDPS 19
Trifluoroacetic acid (1.5 ml) was added dropwise to a solution of resin **18** (30 mg, *ca.* 0.02 mmol) in dichloromethane (1.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *product* (14 mg) in a ratio of 91:8:1 [tetramer **19**]:[trimer **16** (x = 4)]:[monomer] by HPLC; δ_H(270 MHz; $CDCl_3$) 1.17 (9 H, s, CMe_3), 4.74 (2 H, s, CH_2OSi), 5.11 (2 H, s, $H_2NC_6H_4CH_2$), 5.17 (2 H, s, CH_2), 5.18 (2 H, s, CH_2), 6.70 (4 H, m, Ar), 7.40 (18 H, m, Ar) and 7.72 (4 H, m, Ar); m/z (FAB) 809 (MH^+, 17%).

Resin-linker-tetramer-OH 20
Tetrabutylammonium fluoride (1.2 ml, 1.2 mmol; 1 mol l^{-1} solution in THF) was added dropwise to a solution of resin **18** (1.20 g, *ca.* 1.20 mmol) in THF (10 ml). The reaction was stirred for 18 h, water (15 ml) was added and the resin was collected by filtration. The resin was washed and dried using the same procedure as that described above to yield the *title resin* **20** (1.00 g) (Found: N, 3.8%. Maximum loading: N, 4.0%).

Resin-linker-pentamer-OTBDPS 21
Resin **20** (0.98 g, *ca.* 0.5 mmol) was added to the isocyanate monomer OCN-M^4-OTBDPS (390 mg, 1.0 mmol) and dibutyltin dilaurate (3 drops) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18 h. After filtration the polymer was washed repeatedly as described above to yield the *title resin* **21** (1.26 g) (Found: N, 3.8%. Maximum loading: N, 4.3%).

Cleavage of resin 21 to yield H_2N-pentamer-OTBDPS 22
Trifluoroacetic acid (2.5 ml) was added dropwise to a solution of resin **21** (50 mg, *ca.* 0.02 mmol) in dichloromethane (2.5 ml). The reaction was stirred for 30 min, water (10 ml) was added and the resin was removed by filtration. The cleaved product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *product* in a ratio of 92:7:1 (pentamer **22**):(tetramer **19**):(monomer) by HPLC; δ_H(270 MHz; $CDCl_3$) 1.09 (9 H, s, CMe_3), 4.73 (2 H, s, CH_2OSi), 5.11 (2 H, s, $H_2NC_6H_4CH_2$), 5.17 (2 H, s, 3 × CH_2), 6.75 (4 H, m, Ar), 7.37 (22 H, m, Ar) and 7.69 (4 H, m, Ar); m/z (FAB) 958 (MH^+, 7%).

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