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Bis(1,3-dihydroxy-isopropyl)amine (BDI) as an AB_4 dendritic building block: rapid synthesis of a second generation dendrimer

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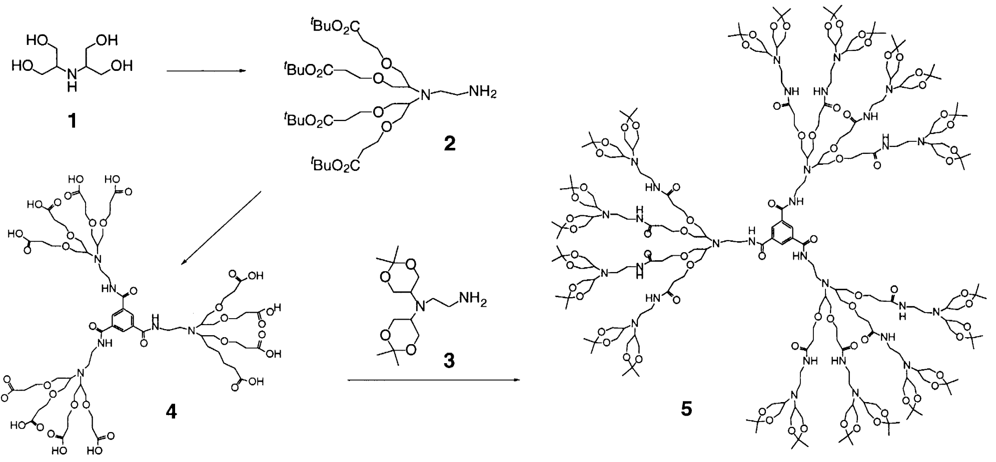
Abstract

Bis(1,3-dihydroxy-isopropyl)amine (BDI) **1**, a symmetrical AB_4 dendritic building block, is developed into two diamine linkers in which the nitrogen is more nucleophilic. The four primary alcohols in BDI undergo Michael reactions with *t*-butyl acrylate. Branch cells of this rare multiplicity allow the rapid construction of a second generation dendrimer **5** with 48 protected peripheral primary alcohol groups. © 2000 Elsevier Science Ltd. All rights reserved.

The polyhydroxylated amine, bis(1,3-dihydroxy-isopropyl)amine (BDI) **1**, is readily accessible via reductive amination of dihydroxyacetone.[1] The inherent symmetry of BDI makes it an attractive unit as an AB_4 dendritic building block for the preparation of highly branched structures, although the nucleophilicity of the nitrogen in BDI is low. This paper reports the synthesis from BDI of two more nucleophilic amine linkers **2** and **3** together with their use in rapid construction of a second generation dendrimer **5**.



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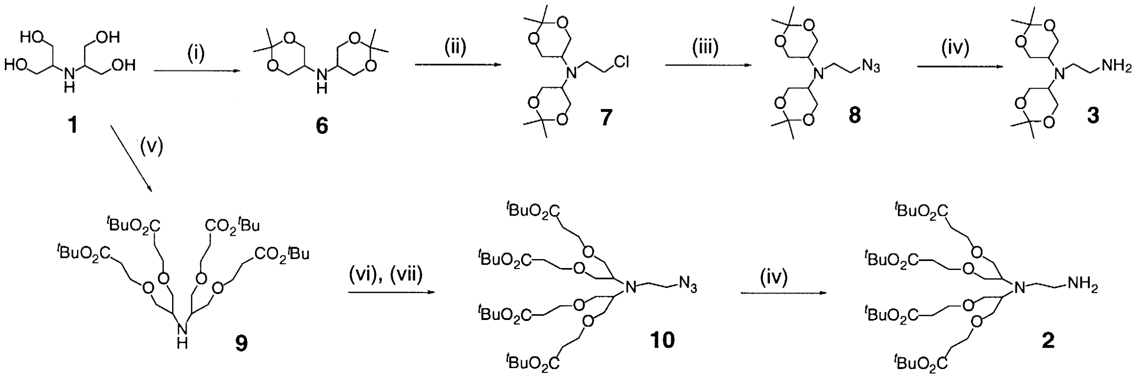
There are numerous elegant and efficient strategies for the construction of dendrimers.[2] The vast majority of these, however, involve branch cells with two- or threefold multiplicity, and therefore the number of peripheral groups doubles or triples with each generation. Various strategies for accelerated dendrimer synthesis have been reported, including the use of hyperbranched monomers.[3] AB_4 or AB_8 dendrons which are second or third generation wedges derived from AB_2 monomers, allow the addition of more than one layer at a time. Schlüter constructed several AB_4 building blocks, with peripheral amino or hydroxy functionality,[4] and prepared a fourth generation wedge with sixteen terminal groups.[5] Mitchell constructed first generation ester terminated dendrimers using an AB_4 dendron prepared from the reaction of 1,3-diaminopropan-2-ol and acrylate esters.[6] Müllen prepared a second generation polyphenylene dendrimer via Diels–Alder reactions with two tetravalent cyclopentadienones.[7] There is one reported example of a dendrimer with AB_5 multiplicity, based upon hexachlorotriphosphazene branch cells linked by diaminohexane.[8]

For the synthesis of diamine linker **3**, BDI diacetonide **6** was treated with a solution of chloroacetaldehyde in dichloroethane in the presence of $NaBH(OAc)_3$[9] to give chloride **7**. Some displacement of the chloride by acetate ions derived from the reducing agent was observed, and the yield for this step was 77% based upon recovered starting material; reproducible yields of 55% of **7** could be isolated. Short reaction times limited the amount of acetate formation to less than 5%. Treatment of the chloride with sodium azide in DMF gave azide **8** in 89% yield. The recovery and recycling of unreacted BDI diacetonide **6** was usually performed after the azide displacement step, to reduce the amount of chromatography required. Reduction of azide **8** with Pd black in an atmosphere of hydrogen gave diamine **3**[10] (Scheme 1).

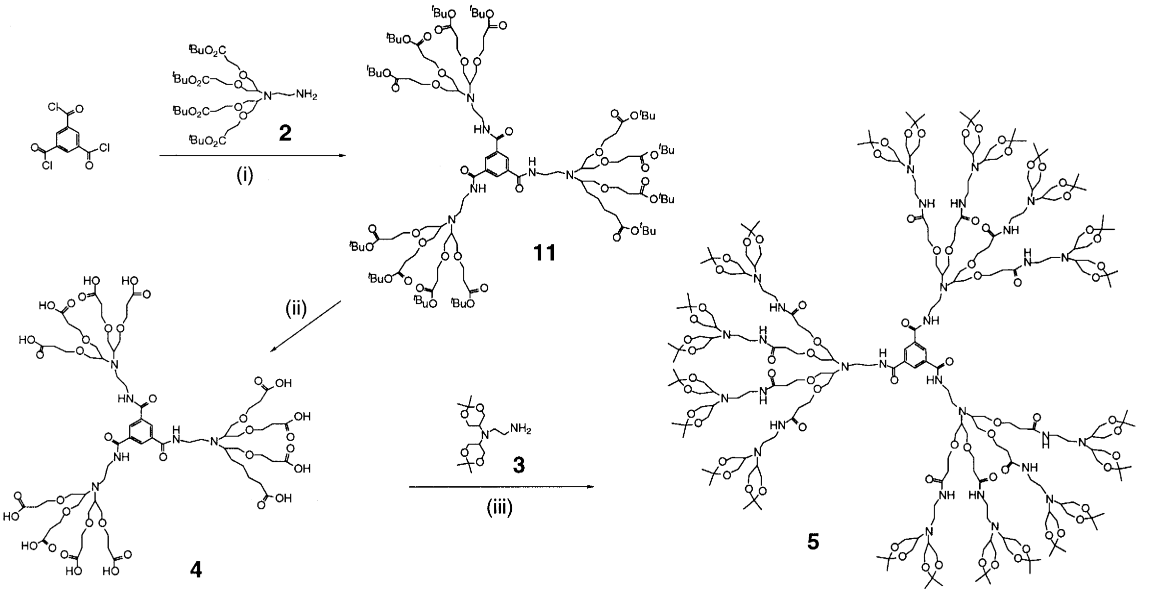


Scheme 1. Synthesis of diamine building blocks **2** and **3**. (i) DMF, Me_2CO, $Me_2C(OMe)_2$, c. H_2SO_4, 74%; (ii) $ClCH_2CHO$, $NaBH(OAc)_3$, DCE, 77%; (iii) NaN_3, DMF, 60°C, 89%; (iv) H_2, Pd black, EtOAc, quant; (v) $CH_2{=}CHCO_2{}^tBu$, 50% NaOH (aq.), $^nBu_4NHSO_4$, 33%; (vi) $ClCH_2CHO$, $NaBH(OAc)_3$, DCE; (vii) NaN_3, DMF, 76%

For the synthesis of the diamine linker **2**, the hydroxylated arms of BDI **1** were extended through Michael reactions with *t*-butyl acrylate in 50% NaOH solution to give tetraester **9** in 33% yield, in accordance with a literature procedure for the preparation of polyether esters.[11] A two carbon linker was installed by reductive alkylation of **9** with chloroacetaldehyde and subsequent azide displacement of the crude chloride to give azidotetraester **10** in 52% yield, (76% based upon recovered starting material **9**). The azide **10** was reduced with Pd black in an atmosphere of hydrogen to give diamine **2**[12] in quantitative yield.

Reaction of **2** with 1,3,5-benzenetricarbonyl chloride gave the first generation dendrimer **11**[13] with 12 peripheral ester groups, which were hydrolysed with a 1:1 solution of TFA:DCM. Treatment of dodeca-acid **4** with an excess of diamine **3** and TBTU[14] in DMF achieved the twelve coupling reactions necessary to prepare the second generation dendrimer **5**, which was purified by size exclusion chromatography (Scheme 2).[15]

Dendrimer **5** with 48 peripheral protected primary hydroxyl groups was thus prepared from BDI **1**



Scheme 2. Construction of second generation dendrimer **5**. (i) **2**, CH_2Cl_2, $EtNPr^i_2$, 0°C, 38%; (ii) TFA:DCM, 1:1; (iii) **3**, TBTU, DMF, EtN^iPr_2

in seven linear steps, with the purification of intermediates by chromatography required on only three occasions. The ^{1}H NMR spectrum of **5** gave several broad peaks, but the ratio of signals corresponding to the methyl groups and the signal at 2.39 ppm from the twelve sets of CH_2CONH protons suggested a successful synthesis. Conclusive evidence was provided by a MALDI-TOF experiment, with a signal at 4914 corresponding to $(M+Na)^+$. Further investigation of the utility of the compounds described for the preparation of highly branched dendritic structures with an extensive array of primary alcohols at the periphery is underway.

Acknowledgements

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References

1. Scott, D. A.; Krülle, T. M.; Finn, M.; Nash, R. J.; Winters, A. L.; Asano, N.; Butters T. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 7581.
2. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Syntheses, Perspectives*; VCH: Weinheim, 1996. (b) Fischer, M. and Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884.
3. (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 82. (b) L'abbé, G.; Forier B.; Dehaen. W. *Chem. Commun.* **1996**, 2143.
4. (a) Klopsch, R.; Koch, S.; Schlüter, A.-D. *Eur. J. Org. Chem.* **1998**, 1275. (b) Ingerl, A.; Neubert, I.; Klopsch, R.; Schlüter, A.-D. *Eur. J. Org. Chem.* **1998**, 2551.
5. Klopsch, R.; Franke, P.; Schlüter, A.-D. *Chem. Eur. J.* **1996**, *2*, 1330.
6. Twyman, L. J.; Beezer, A. E.; Mitchell, J. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 407.
7. Morgenroth, F.; Berresheim, A. J.; Wagner, M.; Müllen, K. *Chem. Commun.* **1998**, 1139.
8. Sournies, F.; Crasnier, F.; Graffeuil, M.; Faucher, J.-P.; Lahana, R.; Labarre, M.-C.; Labarre, J.-F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 578.
9. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

10. Selected data for diamine **3**: Oil, δ_H (200 MHz, CDCl$_3$) 1.36 (6H, s, C(CH$_3$)$_2$), 1.42 (6H, s, C(CH$_3$)$_2$), 2.68 (2H, t, *J* 5.7, C*H*$_2$NH$_2$), 2.79 (2H, t, *J* 5.7, NCH$_2$), 3.07 (2H, quin, *J* 7.3, 2 NCH), 3.75 (8H, d, *J* 7.3, 4 OCH$_2$); δ_C (50 MHz, CDCl$_3$) 21.6, 25.9 (2 C(*C*H$_3$)$_2$), 39.8 (CH$_2$NH$_2$), 47.2 (NCH$_2$), 52.1 (CH), 62.2 (OCH$_2$), 98.0 (*C*(CH$_3$)$_2$).
11. Dupraz, A.; Guy, P.; Dupuy, C. *Tetrahedron Lett.* **1996**, *37*, 1237.
12. Selected data for aminotetraester **2**: δ_H (200 MHz, CDCl$_3$) 1.40 (36H, s, 4 C(CH$_3$)$_3$), 2.42 (8H, t, *J* 6.4, 4 CH$_2$CO$_2$^{t}Bu), 2.52 (2H, t, *J* 5.1, C*H*$_2$NH$_2$), 2.72 (2H, t, *J* 5.3, NCH$_2$), 3.00 (2H, quin, *J* 6.1, 2 NCH), 3.38 (8H, m, 4 CHC*H*$_2$O), 3.58 (8H, t, *J* 6.4, 4 OC*H*$_2$CH$_2$CO$_2$^{t}Bu); δ_C (50 MHz, DEPT, CDCl$_3$) 27.9 (C(*C*H$_3$)$_3$), 36.2 (*C*H$_2$CO$_2$^{t}Bu), 40.6 (CH$_2$NH$_2$), 49.3 (NCH$_2$), 56.9 (NCH), 66.6 (O*C*H$_2$CH$_2$), 70.8 (CH*C*H$_2$O), 80.4 (*C*(CH$_3$)$_3$), 171.2 (C=O).
13. Selected data for dendrimer **11**: δ_H (400 MHz, CDCl$_3$) 1.41 (108H, s, 12 C(CH$_3$)$_3$), 2.40 (24H, t, *J* 6.4, 12 CH$_2$CO$_2$^{t}Bu), 2.97 (6H, t, *J* 5.4, 3 NCH$_2$), 3.08 (6H, quin, *J* 5.9, 6 NCH), 3.38 (6H, br dt, 3 C*H*$_2$NH), 3.46 (24H, m, 12 CHC*H*$_2$O), 3.63 (24H, t, *J* 6.4, 12 OC*H*$_2$CH$_2$CO$_2$^{t}Bu), 7.68 (3H, t, *J* 4.5, NHCO), 8.41 (3H, s, ArH); δ_C (100 MHz, CDCl$_3$) 28.0 (C(*C*H$_3$)$_3$), 36.2 (*C*H$_2$CO$_2$^{t}Bu), 39.5 (NHCH$_2$), 46.1 (NCH$_2$), 57.2 (NCH), 66.7 (O*C*H$_2$CH$_2$), 70.7 (CH*C*H$_2$O), 80.2 (*C*(CH$_3$)$_3$), 128.2 (ArC), 135.5 (ArC), 170.8 (C=O); *m/z* (ES+): 2318.5 (M+H)$^+$, 1160.3 (M+2H)$^{2+}$, 773.9 (M+3H)$^{3+}$.
14. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.
15. Dendrimer **5** was prepared in essentially quantitative yield from **11**, but trace impurities remained after the size exclusion column (Sephadex LH-20, CH$_2$Cl$_2$). Selected data for dendrimer **5**: δ_C (100 MHz, CDCl$_3$) 21.6, 26.0 (2 C(*C*H$_3$)$_2$), 36.7 (*C*H$_2$CONH), 39.9 (CH$_2$CONH*C*H$_2$CH$_2$N), 41.3 (ArCONH*C*H$_2$CH$_2$N), 46.3 (CH$_2$CONHCH$_2$*C*H$_2$N), 48.7 (ArCONHCH$_2$*C*H$_2$N), 52.4 (*C*HCH$_2$OC(CH$_3$)$_2$), 57.4 (*C*HCH$_2$OCH$_2$), 62.4 (NCH*C*H$_2$OC(CH$_3$)$_2$), 67.0 (O*C*H$_2$CH$_2$), 70.3 (NCH*C*H$_2$OCH$_2$), 98.0 (*C*(CH$_3$)$_2$), 128.7 (ArC), 135.5 (ArC), 171.4 (C=O); *m/z* (MALDI): 4914 (M+Na)$^+$; (ES+): 1631.0 (M+3H) $^{3+}$, 1223.3 (M+4H)$^{4+}$.