## Dendroids: a building block for the synthesis of polymodal dendritic structures

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Differentially substituted 1,8-naphthalene and 1,2,3-trihydroxybenzene derivatives are synthesised and termed 'dendroids'; these may be differentially derivatised with mimetics of amino acid side chains.

Dendritic polymers are synthetic polymers that are characterised by a non-linear array of monomeric species. They are self-organising moieties that have unique physico-chemical properties with respect to their linear counterparts and have a range of potentially novel industrial applications.<sup>1–5</sup>

The topographical features of starburst dendrimers have been compared with those found in globular proteins.<sup>1</sup> However, proteins display heterogeneous functional moieties on their surfaces, such as the constituent amino acid side-chains or the peptide backbone.

We describe here the synthesis of simple aromatic compounds with low molecular weight (<1000 Daltons) which can serve as a structural motif that is able to display *different* functional groups which correspond to the side-chains of amino acids. Such polymodal 'dendritic wedges'<sup>2</sup> we term 'dendroids' (**1**, Fig. 1). The dendroid motif is anticipated to facilitate *intramolecular* self-organisation (*cf. intermolecular* self-assembly associated with nanostructures<sup>6,7</sup>) by choice of suitable spacer groups B and C, which may non-covalently interact with each other by steric crowding, hydrophobic collapse and stereoelectronic attractive or repulsive effects. For example,



Fig. 1 Dendroid motif 1 exemplified by 1,2,3-trialkoxybenzenes 2 and 1,8-disubstituted naphthalenes 3



Scheme 1 Reagents and conditions: i, CH(OEt)<sub>3</sub>, Amberlyst-IR-120(plus), reflux, 28 h, 92%; ii, K<sub>2</sub>CO<sub>3</sub>, 18-crown-6, room temp., 18 h, 92%; iii, TsOH, room temp., 20 h, 90%; iv, K<sub>2</sub>CO<sub>3</sub>, 18-crown-6, room temp., 21 h, 32%; v, K<sub>2</sub>CO<sub>3</sub>, 18-crown-6, room temp., 21 h, 46%

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**b**  $R^1 = R^3 = H, R^2 = OBn, R^4 = R^5 = Me$ 

**c**  $R^1 = R^3 = H, R^2 = OBn, R^4 = Pr^i, R^5 = (R, S)CHMe-(indol-3-yl)$ 

**d**  $R^1 = R^3 = H, R^2 = OBn, R^4 = Bn, R^5 = CH_2C_6H_4OMe-p$ 

**e**  $R^1 = R^3 = H$ ,  $R^2 = OBn$ ,  $R^4 = Bn$ ,  $R^5 = CH_2CH_2$ -(indol-3-yl) **f**  $R^1 = R^3 = H$ ,  $R^2 = OBn$ ,  $R^4 = CH_2C_6H_4OMe$ -*p*,  $R^5 = CH_2CH_2$ -(indol-3-yl)

 $\mathbf{g} = \mathbf{R}^3 = \mathbf{H}, \mathbf{R}^2 = \mathbf{OBn}, \mathbf{R}^4 = \mathbf{CH}_2\mathbf{CH}_2\mathbf{C}_6\mathbf{H}_4\mathbf{OMe}$ ,  $\mathbf{R}^5 = \mathbf{CH}_2\text{-(indol-3-yl)}$ 

Scheme 2 Reagents and conditions: i,  $PPh_3$  (1 equiv.), diisopropyl azodicarboxylate (1 equiv.), THF, 0 °C to room temp., 4 h

1,2,3-trisubstituted benzenes<sup>8–11</sup> and 1,8-disubstituted naphthalenes<sup>12–15</sup> have been shown to adopt non-planar arrangements by X-ray, NMR and chemical reactivity analysis. As one example, the dendroid motif  $2^+$  may be synthesised from 1,2,3-trihydroxybenzene (Scheme 1). This type of molecule is able to achieve a non-planar structure by virtue of the electronic repulsion between the crowded 1,2,3-aryl ether oxygen atoms, so that the central 2-aryl ether oxygen substituent is forced out of plane with respect to the benzene ring.<sup>8,9</sup>

The 1,8-disubstituted naphthalene dendroids 3a-g are prepared from 8-hydroxy-*N*,*N*-dimethylnaphthalenecarboxamide<sup>12</sup> (Scheme 2). Such 1,8-naphthalenes have been shown by X-ray analysis to exhibit a non-planar preference *via* a truly remarkable stereoelectronic attraction between the 8-naphthalene oxygen substituent atom and the 1-substituted carbonyl group of the amide moiety,<sup>12</sup> allowing the attached groups R<sup>1</sup>–R<sup>5</sup> in **3** to be splayed into a polymodal surface. Examples of where this dendroid motif has been derivatised to give amino acid sidechains include the mimetics of phenylalanine **3b**,  $\beta$ -methyltryptophan **3c**, tyrosine (as its *O*-methyl ether) **3d** and tryptophan **3e**. The examples **3f** and **3g**† also mimic tryptophan and tyrosine side-chains bearing differing methylene spacer groups.

In these cases, the synthetic schemes allow *separate* functionalisation of the dendroid motif, which can be converted by further synthesis into separate amino acid side-chains. Hence

the polymodality of part protein structures can be mimicked by use of the dendroid motif. The elaboration of the dendroid motif to give protein mimetics of the 'hot spots' of key amino acids in interleukin-Ira,<sup>16</sup> interleukin-8<sup>17</sup> and the conotoxin derivative SNX-III<sup>18</sup> is under investigation in our laboratory.

## **Footnotes and References**

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† Selected data for **2**:  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 3.69 (s, 3 H, OCH<sub>3</sub>), 3.75 (s, 6 H, 2 × OCH<sub>3</sub>), 3.80 (s, 6 H, 2 × OCH<sub>3</sub>), 3.85 (s, 3 H, OCH<sub>3</sub>), 3.86 (s, 3 H, OCH<sub>3</sub>), 5.02 (s, 2 H, CH<sub>2</sub>), 5.04 (s, 2 H, CH<sub>2</sub>), 5.06 (s, 2 H, CH<sub>2</sub>), 6.40 (t, *J* 2.0, 1 H, ArH), 6.61 (d, *J* 2.0, 2 H, ArH), 6.65–6.68 (m, 4 H, ArH), 6.75 (d, *J* 8.4, 1 H, ArH), 6.92–6.97 (m, 2 H, ArH), 7.03 (d, *J* 1.6, 1 H, ArH). For **3g**:  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 2.45–2.50 (m, 1 H, CHH), 2.79–2.84 (m, 1 H, CHH), 3.00–3.18 (m, 1 H, CHH), 3.60 and 3.69 (2 × s, 3 H, OMe), 3.58–3.75 (m, 1 H, CHH), 4.40 (AB q, 1 H, CHH), 4.90 (AB qt, 1 H, CHH), 4.94–4.96 (m, 2 H), 5.01–5.02 (m, 1 H, ArH), 6.51–6.52 (m, 1 H, ArH), 6.67–6.68 (m, 1 H, ArH), 7.23–7.37 (m, 7 H, ArH), 7.68–7.78 (m, 2 H, ArH), 8.88 (br s, 1 H, NH).

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