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Synthesis and Characterization of Optically Active, Homochiral Dendrimers

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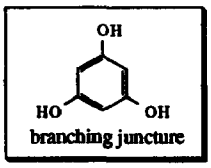
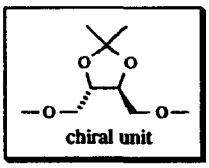
Abstract: The first synthesis and optical activity measurement of homochiral, monodisperse dendrimers is reported. Optically active (2*R*, 3*R*)-tartaric acid is used to construct the zero and first-generation optically active, homochiral dendrimers **1** and **2** in good yields. The relationship between the optical rotation of all these molecules and the number of chiral tartaric acid units resided in them is explored.

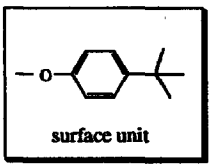
Dendrimer macromolecules are highly branched polymers with a dendritic, treelike structure and defined three-dimensional morphology[1]. This type of polymer has found potential applications as novel materials for engineering plastics[2], molecular devices[3], and biological mimics[1a, 4]. Since the publication of the review article by Tomalia[1a], new types of dendrimers with different branching skeletons, connectivity units and novel topological structures have been reported[5]. Apart from several reports[6] describing the use of biomolecules such as nucleotides or amino acids as building blocks for the construction chiral nucleic acid or peptide dendrimers, no other optically active, homochiral dendrimer has ever been disclosed. However, these papers put most emphasis on the automated synthesis and the biological roles of these biopolymers rather than on their chirality nature. In fact, no optical activity and spectroscopic data was reported for any of these compounds in these papers. We are interested in the optical activity relationship and the use of chiral dendrimers in chiral resolution and recognition applications. In this paper, we report the successful synthesis and characterization of some optically active, homochiral, monodisperse dendrimers, in which the chiral unit is derived from optically active tartaric acid, which is relatively inexpensive and is available both in (+) and (-) forms.



branching juncture

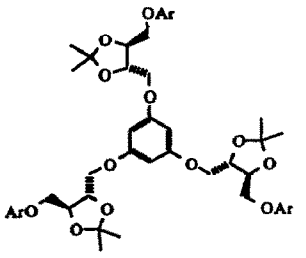


chiral unit



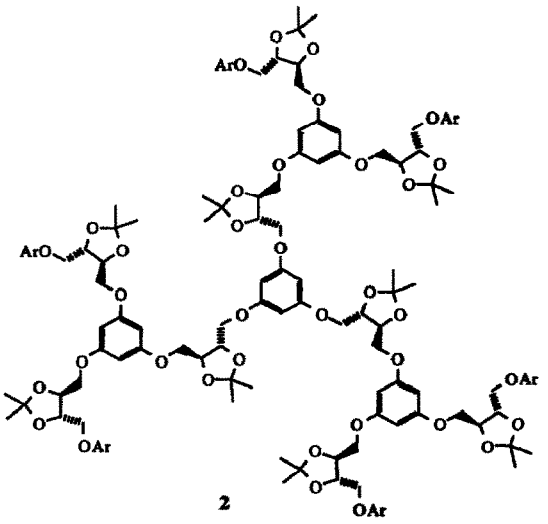
surface unit

Our chiral dendrimer utilizes phloroglucinol skeletons as the branching junctures, (2*R*, 3*R*)-tartaric acid derivatives as the chiral connectivity units and 4-*tert*-butylphenoxy moieties as the end groups. The convergent approach pioneered by Fréchet[7] was employed for the synthesis of chiral dendrimers of generation zero **1** and generation one **2**. Treatment of (2*S*, 3*S*)-(-)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol[8] **3** with 0.5 equivalent of 4-*tert*-butylphenol in the presence of potassium carbonate in DMF gave the mono-*O*-arylation product **4** (m.p. 65 - 67°C) in 74% yield together with a small amount (9%) of the bis-*O*-arylation compound. Bis-*O*-alkylation of 5-benzyloxy-resorcinol **5**[9] with 2.1 equivalent of **4** under similar condition (K_2CO_3 in DMF, 100°C) afforded the C_2 symmetric product **6** in 65% yield. Hydrogenolysis of **6** in the presence of 10% palladium on



1

Ar = 4-*tert*-butylphenyl



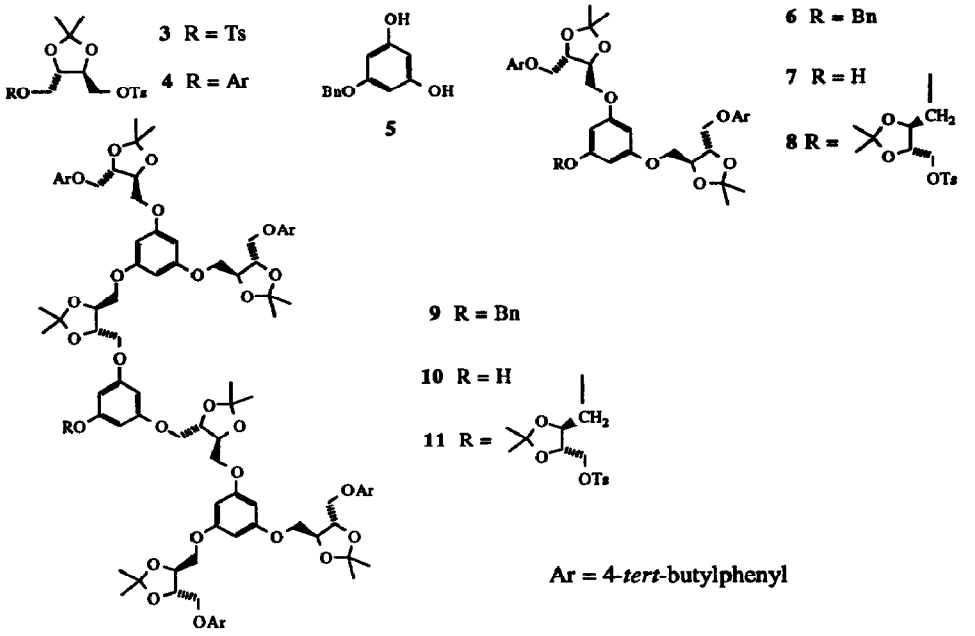
2

charcoal gave the phenol **7** in 94% yield. Coupling of **7** with 1 equivalent of **4** (K_2CO_3 in DMF, 120°C) gave the G0 dendrimer **1**[10] in 80% yield. On the other hand, direct tris-*O*-alkylation of phloroglucinol with an excess of **4** gave **1** in relatively poor yield (26%). This could be due to the poor solubility of the phloroglucinol anion in DMF.

The G0 dendrimer **1** contains three chiral tartarate units and has a C_3 symmetry. The high symmetry of this compound allowed its structural identification relative simple. There are five regions of interest in the ^{1}H-NMR spectrum[10]: (1) The aromatic protons of 4-*tert*-butylphenoxy moiety at δ 7.3 - 6.8, (2) the aromatic protons (δ 6.18) of phloroglucinol, (3) the aliphatic protons on the tartarate units (δ 4.4 - 4.0), (4) the isopropylidene groups (δ = 1.49) and (5) the *tert*-butyl groups (δ = 1.28). The relative integration of these five regions has a ratio of 12.0: 2.9: 18.2: 17.8: 27.2, which is very close to the calculated value of 12: 3: 18: 18: 27. In contrast to compounds **6** and **7**, where the aromatic protons of phloroglucinol are non-equivalent (1 doublet and 1 triplet with relative intensity of 2:1), the corresponding protons in G0 appear as a sharp singlet (δ = 6.18), thus confirming the presence of a C_3 rotational axis.

The synthesis of the first generation dendrimer **2** could be accomplished by using the reaction sequences described above. Thus, mono-*O*-alkylation of the phenol **7** with the di-*O*-tosylate **3** (3 eq., K_2CO_3, DMF) gave **8** in 82% yield. Treatment of **8** (2.1 eq.) with **5** gave the dendritic 'wedge' **9** in 70% yield. Subsequent debenzylation and *O*-alkylation with **8** afforded the G1 dendrimer **2**[10] as an oil in overall 50% yield. The relative integration of the above-mentioned protons is 24.0: 11.1: 52.9: 50.4: 54.4 (calculated: 24: 12: 54: 54: 54). The phloroglucinic protons appear as sharp singlets at slightly different places (δ = 6.15 and 6.16, rel. intensity = 1:3). These correspond to the protons on the central and peripheral phloroglucinol rings. The peripheral isopropylidene groups also appear at slightly different positions compared with the internal isopropylidene groups (δ at 1.48 and 1.47 respectively, rel. intensity ~ 2 : 1). Interestingly, the ^{13}C-NMR of G1 is almost identical to that of G0, except that the relative intensities of each peak is different. This suggested that the central phloroglucinol ring has nearly the same micro-environment as that of the peripheral phloroglucinol rings.

Reaction of **10** with 1 equivalent of **3** gave **11** in 71% yield. Unfortunately, compound **11** could not be



arylated with phenol **5** because of steric and solubility problems.

Preliminary investigation of the optical rotation of these compounds reveals that the molar rotation is proportional to the number of tartarate units (Table 1). In conclusion, we have synthesized and studied the optical activity of a series of homochiral, monodisperse dendrimer. We are continuing to modify this synthetic strategy in order to synthesize higher generation dendrimers and layer-block dendrimers[11] with alternating D- and L-tartarate units. The relationship between the optical rotation and the number and absolute configuration of the tartarate unit will be disclosed in due course.

Table 1. Optical activity of selected compounds (20°C in $CHCl_3$)

Compound	Specific rotation $[\alpha]_D$	Molar rotation	Molar rotation per tartarate unit
1	-59.6° (*c* = 2.60)	-569°	-190°
2	-69.7° (*c* = 0.37)	-1769°	-197°
6	-55.3° (*c* = 0.38)	-425°	-212°
7	-52.4° (*c* = 0.53)	-355°	-178°
8	-56.0° (*c* = 0.41)	-547°	-182°
9	-60.1° (*c* = 0.38)	-1096°	-183°
10	-57.3° (*c* = 0.47)	-994°	-166°

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10. Selected NMR data (δ, 250 MHz for ^{1}H-NMR and 62.5 MHz for ^{13}C-NMR in $CDCl_3$): **1**: ^{1}H-NMR: 7.29 (d, J = 8.9 Hz, 6 H; ArH), 6.86 (d, J = 8.8 Hz, 6 H; ArH), 6.18 (s, 3 H, ArH), 4.39 - 4.24 (m, 6 H; CH-O), 4.22 - 4.07 (m, 12 H; CH_2O), 1.49 (s, 18 H; 6 Me), 1.29 (s, 27 H; 3 *t*-Bu). ^{13}C-NMR: 160.6, 156.4, 144.1, 126.3, 114.3, 110.4, 95.1, 77.2, 76.9, 69.0, 68.9, 34.1, 31.5, 27.1. **2**: ^{1}H-NMR: 7.28 (d, J = 8.9 Hz, 12 H; ArH), 6.85 (d, J = 8.9 Hz, 12 H; ArH), 6.16 (s, 9 H; ArH), 6.15 (s, 3 H; ArH), 4.37 - 4.25 (m, 18 H; CH-O), 4.22 - 4.04 (m, 36 H; CH_2O), 1.48 (s, 36 H; 12 Me), 1.47 (s, 18 H; 6 Me), 1.28 (s, 54 H; 6 *t*-Bu). ^{13}C-NMR: 160.6, 156.4, 144.2, 126.3, 114.3, 110.4, 95.2, 77.2, 76.9, 69.0, 68.9, 34.1, 31.6, 27.2.
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