SHORT PAPER

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Synthesis of 5-formyl-17-nitrocalix[4]arenes in the 1,3-alternate conformation†

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Three 1,3-alternate-5-formyl-17-nitrocalix[4]arenes (**4**, **5**, **7**) bearing two propoxyl groups at one side (at 25 and 27 positions) and two benzyloxyl or propoxyl groups at the other side were synthesized.

Calixarene and particularly calix[4]arene derivatives have been receiving increasing attention in the field of supramolecular chemistry.[1] As to the functional abilities of calix[4]arene, they can be strongly influenced (i) by changing the nature and the number of the binding sites introduced at both lower rim (phenolic OH) and upper rim (aromatic nuclei), (ii) by controlling the conformation of the calix:[2] cone, partial cone, 1,3-alternate, or 1,2-alternate. Among them, in particular, the structure of 1,3-alternate conformers has attracted interest[2,3] because of possessing two ionophoric cavities at the two sides of the ring, therefore it has found many applications[4] in the design of synthetic receptors and sophisticated molecular assemblies.

The selective introduction of formyl[5] and nitro group[6] into the para positions of calix[4]arenes, so at the upper rim, has been focused in order to be modified into supramolecules. We are now devoting an effort to develop the selective functionalization of calix[4]arenes at the upper rim to discriminate between two diametrically located para positions out of four.

In this paper, we describe the synthesis of 5-formyl-17-nitrocalix[4]arene derivatives fixed in the 1,3-alternate conformation for the first time.

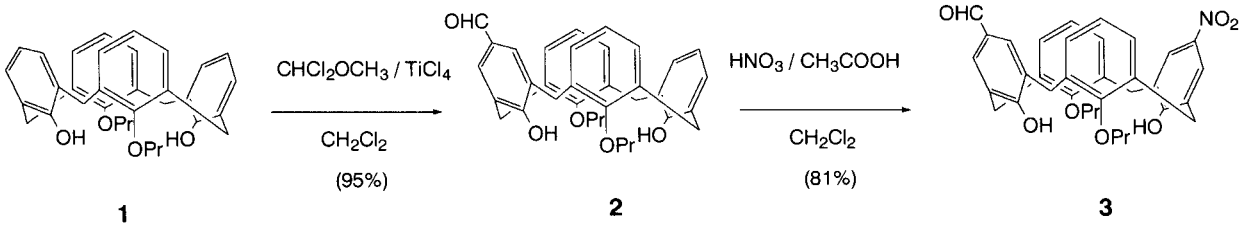
Results and Discussion

The starting material, cone-25,27-dipropoxy-26,28-dihydroxycalix[4]arene **1** was synthesized according to the literature.[7] Calix[4]arene **1** was formylated using dichloromethyl methyl ether in CH_2Cl_2 to give a 95% yield of the monoformyl derivative **2**. **2** was nitrated using HNO_3 in acetic acid/CH_2Cl_2 to give cone-5-formyl-17-nitro-25,27-dipropoxy-26,28-dihydroxycalix[4]arene **3** in a 81% yield. Benzylation of **3** with benzyl bromide and Cs_2CO_3 in DMF proceeded smoothly to give 1,3-alternate-5-formyl-17-nitro-25,27-dipropoxy-26,28-bis(benzyloxy)calix[4]arene **4** as the sole product in a 65% yield. No other isomers were isolated. However, treatment of **3** with 3,5-di-tert-butylbenzyl bromide afforded 1,3-alternate **5** and partial cone **6** in the isolated yields of 74% and 16%, respectively. The conformation of **6** was established as a partial cone on the basis of four doublets at δ 3.10, 3.59, 3.78, and 4.05 for the $ArCH_2Ar$ methylene protons in the ^1H NMR spectrum. The reaction of **3** with propyl tosylate in the presence of Cs_2CO_3 in DMF at room temperature did not proceed for 24h. When the reaction temperature was raised to 80°C, 1,3-alternate **7** and partial cone **8** was obtained in 11% and 43% yields, respectively. The present work shows that benzylation and propylation of the cone-5-formyl-17-nitro-25,27-dipropoxy-26,28-dihydoroxycalix[4]arene **3** yield the corresponding1,3-alternate calix[4]arenes.

Experimental

^1H and ^{13}C NMR spectra were measured on a Varian XL-300 spectrometer, and the chemical shifts are reported as δ values in ppm. FAB mass spectra were recorded on JEOL-DX303. All reactions were carried out in a nitrogen atmosphere.

5-Formyl-25,27-dipropoxy-26,28-dihydroxycalix[4]arene **(2)** *(Cone Conformer):* To a stirred solution of 9.2 g (18.0 mmol) of **1** in 400 ml of dry CH_2Cl_2 was added 2.26 g (19.8 mmol) of dichloromethyl methyl ether, with ice cooling, and the solution was stirred for 10 min. Then, 7.8 ml of titanium tetrachloride was added, the mixture was stirred for 1h. The reaction mixture was worked up by addition of H_2O and CH_2Cl_2. The dichloromethane extract was washed with water, dried over sodium sulfate, and concentrated. The purification by silica gel eluting with chloroform-MeOH gave 9.2 g (95%) of **2**: a colourless powder; mp 286–288°C; IR(KBr) υ 3279(OH), 2959, 2926, 2878, 1684(C=O), 1597, 1460, 1313, 1269, 1195, 1159, 1134, 1084, 1070, 962, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (6H, t, *J*=7.7 Hz, $OCH_2CH_2CH_3$), 2.04–2.11 (4H, m, $OCH_2CH_2CH_3$), 3.43 (4H, d, *J*=13.2 Hz, $ArCH_2Ar$), 4.01 (4H, t, *J*=6.3 Hz, $OCH_2CH_2CH_3$), 4.31 (4H, d, *J*=12.9 Hz, $ArCH_2Ar$), 6.65–6.67 (1H, m, Ar*H*), 6.74–6.79 (2H, m, Ar*H*), 6.92–6.96 (4H, m, Ar*H*), 7.06 (2H, d, *J*=7.4 Hz, Ar*H*), 7.63 (2H, s, Ar*H*), 8.28, 9.32 (each 1H, s, O*H*), 9.79 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 191.74, 160.56, 153.99, 152.48, 134.26, 132.95, 131.58, 130.09, 129.56, 129.48, 129.40, 129.14, 128.53, 126.14, 119.70, 79.02, 31.88, 31.82, 23.96, 11.38; FAB/MS *m/z* 536(M^+); HRMS *m/z* [M^+] calcd for $C_{35}H_{36}O_5$ 536.2563, found 536.2595. (Found:C, 77.74; H, 6.72. $C_{35}H_{36}O_5.0.24H_2O$ requires C, 77.71; H, 6.79%).



1 **2** **3**

Scheme 1

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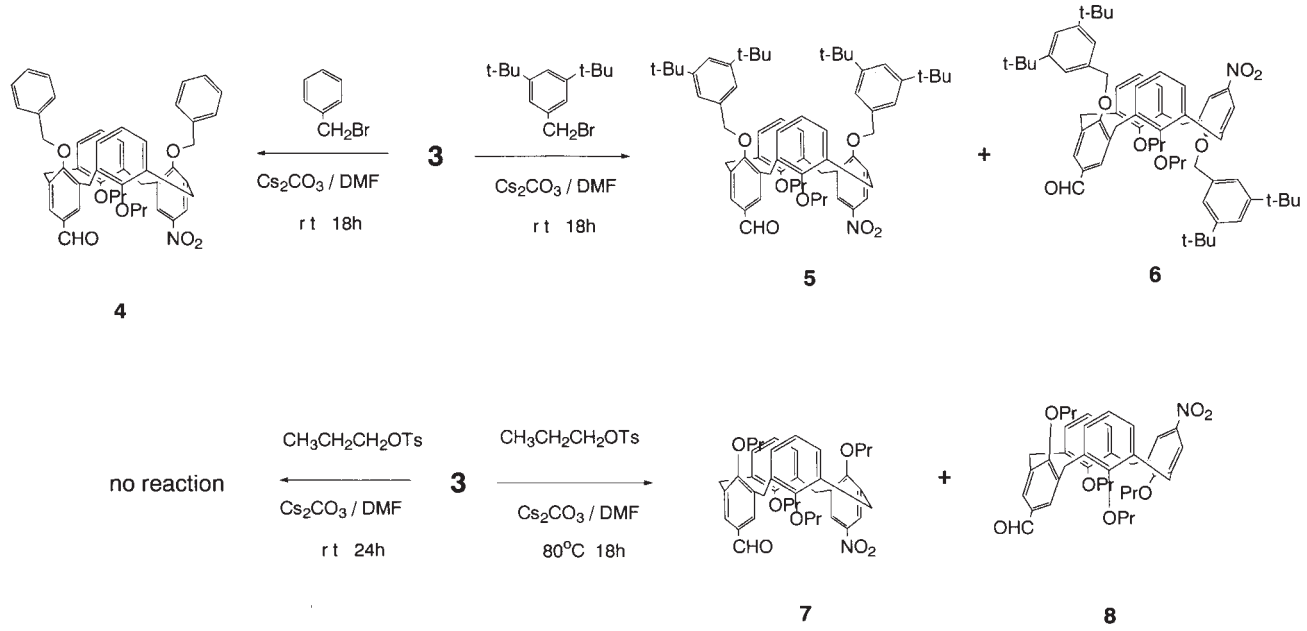
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

5-Formyl-17-nitro-25,27-dipropoxy-26,28-dihydroxycalix[4]arene **(3)** *(cone conformer)*: To the solution of 6.0 g (11.1 mmol) of **2**, 540 ml of dry CH_2Cl_2, and 5.6 ml of acetic acid was added 930 μL of 61% nitric acid. After the solution was stirred for 2.5 h at room temperature, it was poured into a large amount of water. The organic layer was washed with water, dried over sodium sulfate, and evaporated under vacuum, and 5.3 g (81%) of **3** was obtained as yellow prisms: mp>300°C; IR(KBr) υ 3155(OH), 2962, 2932, 2878, 1680(C=O), 1595, 1512, 1458, 1334, 1277, 1197, 1159, 1132, 993, 952, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (6H, t, *J*=7.4 Hz, $OCH_2CH_2CH_3$), 2.03–2.14 (4H, m, $OCH_2CH_2CH_3$), 3.51 (4H, d, *J*=13.1 Hz, $ArCH_2Ar$), 4.02 (4H, t, *J*=6.3 Hz, $OCH_2CH_2CH_3$), 4.30 (4H, d, *J*=13.1 Hz, $ArCH_2Ar$), 6.80–6.88 (2H, m, Ar*H*), 6.97-7.01 (4H, m, Ar*H*), 7.64 (2H, s, Ar*H*), 8.04 (2H, s, Ar*H*), 9.23, 9.50 (each 1H, s, O*H*), 9.79 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 191.63, 160.49, 160.29, 152.39, 140.50, 142.30, 133.18, 132.46, 131.61, 130.37, 130.05, 129.17, 129.09, 126.46, 126.21, 79.26, 31.76, 31.42, 23.94, 11.35; FAB/MS *m/z* 581(M^+); HRMS *m/z* [M^+] calcd for $C_{35}H_{35}NO_7$ 581.2414, found 581.2440. (Found: C, 71.39; H, 5.97; N, 2.03. $C_{35}H_{35}NO_7.0.5H_2O$ requires C, 71.17; H, 6.14; N, 2.37%).

General procedure for the benzylation and the propylation of **(3)**. *Formation of* **(4)** *(1,3-alternate),* **(5)** *(1,3-alternate),* **(6)** *(partial cone),* **(7)** *(1,3-Alternate), and* **(8)** *(partial cone):* To a solution of 2.51 g (4.31 mmol) of **3**, 43.1 g (130 mmol) of Cs_2CO_3, and 380 ml of DMF was added 9.76 g (34.5 mmol) of 3,5-di-tert-butylbenzyl bromide. After the solution was stirred at room temperature for 18 h, it was poured into water and neutralized with HCl solution to give white semisolid which was extracted into CH_2Cl_2. The organic layer was removed, concentrated to give the residue. It was purified by silica gel column chromatography to afford 3.14 g (74%) of 1,3-alternate **5** ($CHCl_3$ eluent) and 0.67 g (16%) of partial cone **6** (benzene eluent).

5-Formyl-17-nitro-25,27-dipropoxy-26,28-bis(3,5-di-tert-butylbenzyloxy)calix[4]arene **(5)**. **5** (1,3-alternate) a pale yellow powder: mp 86–88°C; IR(KBr) υ 2962, 2870, 1695(C=O), 1601, 1521, 1456, 1342, 1277, 1199, 1124, 1005, 962, 895, 875, 760, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (6H, t, *J*=7.3 Hz, $OCH_2CH_2CH_3$), 1.28, 1.31, 1.33, 1.40 (each 9H, s, t-*Bu*), 1.97-2.04 (4H, m, $OCH_2CH_2CH_3$), 3.36, 3.40, 3.52, 3.57 (each 2H, d, *J*=5.8 Hz, $ArCH_2Ar$), 3.71–3.74 (4H, m, $OCH_2CH_2CH_3$), 4.87, 4.88 (each 2H, s, OCH_2Ar), 6.60 (2H, t, *J*=7.5 Hz, ArH), 6.86-6.92 (4H, m, Ar*H*), 7.26, 7.36 (each 1H, s, Ar*H*), 7.44–7.48 (2H, m, Ar*H*), 7.57, 7.95, 8.01 (each 2H, s, Ar*H*), 9.76 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 191.76, 161.77, 156.79, 151.82, 151.70, 142.45, 137.22, 136.88, 135.46, 135.12, 133.57, 132.82, 132.58, 131.27, 131.18, 130.71, 126.01, 122.39, 122.23, 122.17, 122.09, 122.03, 121.98, 76.43, 76.11, 75.51, 53.38, 35.44, 32.05, 31.90, 24.47, 11.15; FAB/MS *m/z* 985(M^+); HRMS *m/z* [M^+] calcd for $C_{65}H_{79}NO_7$ 985.5857, found 985.5854. (Found: C, 78.75; H, 8.09; N, 1.43. $C_{65}H_{79}NO_7 \cdot 0.5CH_3OH$ requires C, 78.49; H, 8.14; N, 1.39%).

5-Formyl-17-nitro-25,27-dipropoxy-26,28-bis(3,5-di-tert-butylbenzyloxy)calix[4]arene **(6)**. **6** (Partial cone) a pale yellow powder mp 227–230°C; IR(KBr) υ 2962, 2870, 1689(C=O), 1599, 1518, 1458, 1340, 1249, 1199, 1124, 1008, 964, 877, 758, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (6H, t, *J*=7.3 Hz, $OCH_2CH_2CH_3$), 1.19, 1.38 (each 18H, s, t-*Bu*), 1.88–1.95 (4H, m, $OCH_2CH_2CH_3$), 3.10 (2H, d, *J*=13.8 Hz, $ArCH_2Ar$), 3.57–3.80 (4H, m, $OCH_2CH_2CH_3$), 3.59, 3.78 (each 2H, d, *J*=12.9 Hz, $ArCH_2Ar$), 4.05 (2H, d, *J*=13.8 Hz, $ArCH_2Ar$), 4.59, 4.99 (each 2H, s, OCH_2Ar), 6.22 (2H, d, *J*=7.5 Hz, Ar*H*), 6.47 (2H, t, *J*=7.5 Hz, Ar*H*), 6.76 (2H, s, Ar*H*), 6.92 (2H, d, *J*=7.5 Hz, ArH), 7.19, 7.45 (each 1H, s, Ar*H*), 7.31 (2H, s, Ar*H*), 7.86, 7.96 (each 2H, s, Ar*H*), 10.05 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 192.55, 163.18, 161.62, 156.66, 151.85, 150.83, 142.54, 139.08, 137.11, 135.98, 135.75, 133.07, 132.50, 132.38, 131.59, 130.19, 129.30, 124.61, 124.34, 122.75, 122.65, 122.29, 122.19, 76.56, 74.59, 77.06, 35.86, 35.76, 35.46, 35.07, 32.02, 31.72, 24.28, 11.06; FAB/MS *m/z* 985(M^+); HRMS *m/z* [M^+] calcd for $C_{65}H_{79}NO_7$ 985.5857, found 985.5850. (Found: C, 78.39; H, 8.15; N, 1.49. $C_{65}H_{79}NO_7.0.5CH_3OH$ requires C, 78.49; H, 8.14; N, 1.39%).

5-Formyl-17-nitro-25,27-dipropoxy-26,28-bis(benzyloxy)calix[4]arene **(4)** *(1,3-alternate conformer)*: **4** (1,3-alternate conformer) was obtained from **3** with benzyl bromide as a pale yellow powder (65%): mp 68–70°C; IR(KBr) υ 2962, 2935, 2874, 1691(C=O), 1585, 1518, 1454, 1336, 1278, 1205, 1159, 1134, 1006, 962, 761, 734 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 0.97 (6H, t, *J*=7.4 Hz, $OCH_2CH_2CH_3$), 1.73–1.80 (4H, m, $OCH_2CH_2CH_3$), 3.48, 3.53 (each 2H, d, *J*=7.5 Hz, $ArCH_2Ar$), 3.64–3.71 (8H, m, $OCH_2CH_2CH_3$ and $ArCH_2Ar$), 4.87 (4H, s, OCH_2Ar), 6.48 (2H, d, *J*=7.8 Hz, Ar*H*), 6.70-6.73 (4H, m, Ar*H*), 7.18–7.25 (4H, m, Ar*H*), 7.35–7.43 (6H, m, Ar*H*), 7.59 (2H, s, Ar*H*), 7.97 (2H, s, Ar*H*), 9.80 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 192.01, 162.03, 156.93, 142.67, 137.46, 135.84, 135.47, 133.59, 133.49, 132.83, 131.76, 131.37, 131.27, 129.05, 128.95, 128.83, 128.58, 128.34, 128.13, 127.98, 126.32, 126.22, 122.65, 77.80, 74.32, 74.00, 36.83, 31.43, 24.06, 10.80; FAB/MS *m/z* 761(M^+); HRMS *m/z* [M^+] calcd for $C_{49}H_{47}NO_7$ 761.3352, found 761.3353. (Found: C, 76.11; H, 6.11; N, 1.66. $C_{49}H_{47}NO_7 \cdot 0.5CH_3OH$ requires C, 76.42; H, 6.34; N, 1.79%).

5-Formyl-17-nitro-25,26,27,28-tetrapropoxycalix[4]arene **(7)** *(1,3-alternate conformer)*: **7** (1,3-alternate conformer) was obtained from **3** as a pale yellow powder (11%): mp 200–203ºC; IR(KBr) υ 2961, 2935, 2876, 1695(C=O), 1587, 1520, 1450, 1340, 1215, 1194, 1122, 1089, 1066, 960, 908, 895, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96–1.06 (12H, m, $OCH_2CH_2CH_3$), 1.77–1.83 (8H, m, $OCH_2CH_2CH_3$), 3.60–3.70 (16H, m, $OCH_2CH_2CH_3$ and $ArCH_2Ar$), 6.69 (2H, t, *J*=7.5 Hz, Ar*H*), 6.97–7.02 (4H, m, Ar*H*), 7.54 (2H, s, Ar*H*), 7.93 (2H, s, Ar*H*), 9.74 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 191.82, 163.50, 156.88, 151.54, 143.61, 142.32, 135.26, 134.96, 132.41, 130.91, 130.71, 129.27, 125.87, 122.70, 119.99, 76.36, 76.06, 74.93, 36.10, 31.42, 24.94, 24.14, 22.78, 12.90, 12.14, 10.97; FAB/MS *m/z* 665(M^+); HRMS *m/z* [M^+] calcd for $C_{41}H_{47}NO_7$ 665.3353, found 665.3351. (Found: C, 72.59; H, 6.92; N, 2.10. $C_{41}H_{47}NO_7 \cdot 0.7CH_3OH$ requires C, 72.77; H, 7.29; N, 2.03%).

5-Formyl-17-nitro-25,26,27,28-tetrapropoxycalix[4]arene **(8)** *(partial cone conformer):* **8** (Partial cone conformer) was obtained from **3** as a pale yellow powder (43%): mp 195–198ºC; IR(KBr) υ 2962, 2934, 2874,1693(C=O), 1585, 1516, 1456, 1433, 1385, 1338, 1197, 1126, 1091, 1001, 962, 889, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (3H, t, *J*=7.4 Hz, $OCH_2CH_2CH_3$), 1.06–1.14 (9H, m, $OCH_2CH_2CH_3$), 1.25–1.34 (2H, m, $OCH_2CH_2CH_3$), 1.85–1.99 (6H, m, $OCH_2CH_2CH_3$), 3.18, 4.09 (each 2H, d, *J*=13.4 Hz, $ArCH_2Ar$), 3.32–3.88 (8H, m, $OCH_2CH_2CH_3$), 3.69, 3.78 (each 2H, d, *J*=13.2 Hz, $ArCH_2Ar$), 6.26 (2H, d, *J*=7.7 Hz, Ar*H*), 6.48 (2H, t, *J*=7.7 Hz, Ar*H*), 6.96 (2H, d, *J*=7.7 Hz, Ar*H*), 7.81 (2H, s, Ar*H*), 8.03 (2H, s, Ar*H*), 9.98 (1H, s, C*H*O); ^{13}C NMR(300 MHz, $CDCl_3$) δ 192.60, 163.99, 163.79, 156.17, 143.08, 138.65, 135.57, 133.11, 132.57, 132.16, 131.46, 130.46, 129.24, 124.97, 122.65, 76.98, 76.63, 75.74, 36.10, 30.92, 24.62, 24.25, 22.79, 11.29, 11.02, 9.67; FAB/MS *m/z* 665(M^+); HRMS *m/z* [M^+] calcd for $C_{41}H_{47}NO_7$ 665.3353, found 665.3355. (Found: C, 73.06; H, 7.01; N, 2.09. $C_{41}H_{47}NO_7.0.7CH_3OH$ requires C, 72.77; H, 7.29; N, 2.03%).

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References

1 J. Vicens; V. Böhmer, eds. *Calixarenes, a versatile class of macrocyclic compounds*, Kluwer; Dordrecht, 1991.
2 E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A.A. El-Fadl and D.N. Reinhoudt, *J. Am. Chem. Soc.*, 1990, **112**, 6979.
3 (a) M. Pitarch, V. Mckee, M. Nieuwenhuyzen and M. A. McKervey, *J. Org. Chem.*, 1998, **63**, 946. (b) W. Verboom, S. Datta, Z. Asfari, S. Harkema and D.N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 5394. (c) M. Pitarch, J.K. Browne and M.A. McKervey, *Tetrahedron*, 1997, **53**, 10503.
4 (a) R. Ungaro, A. Casnati, F. Ugozzoli, A. Pochini, J.–F. Dozol, C. Hill and H. Rouquette, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1506. (b) R.J.W. Lutenberg, R.J.M. Egberink, J.F.J. Engbersen and D.N. Reinhoudt, *J. Chem. Soc., Perkin Trans.* 1997, **2**, 1353. (C) V. Lamare, J.–F. Dozol, S. Fuangswasdi, F. Arnaud-Neu, P. Thnéry, M. Nierlich, Z. Asfari and J. Vicens, *J. Chem. Soc., Perkin Trans.* 1999, **2**, 271. (d) A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.–J. Schwing, R. J. M. Egberink, F. Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1995, **117**, 2767.
5 (a) A. Arduini, G. Manfredi, A. Pochini, A.R. Sicuri and R. Ungaro, *J. Chem. Soc., Chem. Commum.*, 1991, 936. (b) O. Struck, W. Verboom, W.J.J. Smeets, A.L. Spek and D.N. Reinhoudt, *J. Chem. Soc., Perkin Trans.* 1997, **2**, 223.
6 (a) S. Shinkai, K. Araki, T. Tsubaki, T. Arimura and O. Manabe, *J. Chem. Soc., Perkin Trans.* 1987, **1**, 2297. (b) W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari and D. N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 1313. (c) A. Arduini, L. Mirone, D. Paganuzzi, A. Pinalli, A. Pochini, A. Secchi and R. Ungaro, *Tetrahedron*, 1996, **52**, 6011.
7 K. Iwamoto, K. Araki and S. Shinkai, *Tetrahedron*, 1991, **47**, 4325.