Synthesis of Semi-Calix[4]indoles Containing Combinations of Direct Links and Methylene Linkages

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Abstract: Macrocyclic compounds containing four 3-substituted-4,6-dimethoxyindole units joined through the C2 and C7 positions, by a combination of direct links or methylene bridges, can be prepared by acid-catalyzed reactions of indole methanols and 2,7′-biindolyldimethanols with indoles and 2,7′-biindolyls.

Key words: indoles, 2,7′-biindolyls, diindolylmethanes, macrocyclic compounds, acid-catalyzed reaction, *ipso*-substitution reaction, formaldehyde extrusion

We have previously reported the syntheses of calix[3]-indoles and calix[4]indoles using one-pot and stepwise methods via acid-catalyzed addition reactions.[1–4] Furthermore, in a more recent paper,[5] the synthesis of a second type of calix[4]indole is described. In the calixindoles, indole units are joined by methylene groups, but related structures incorporating direct links are also synthetically feasible using different methodologies. Oxidative reactions of suitably activated indoles can give 2,7′-biindolyls **1**–**3**, and macrocyclic tetraindolyls (including indorphyrins), arising from head-to-head and head-to-tail coupling and containing combinations of direct 2,2-, 2,7- and 7,7-links.[6] We now describe our results on the further functionalization of biindolyls to afford biindolyl dimethanols which can be subsequently converted to tetraindole containing macrocycles with combinations of methylene and direct links. These new compounds can loosely be termed ‘semi-calix[4]indoles’.

Both C2 and C7′ sites on 2,7′-biindolyls **1**–**3** are active towards electrophilic substitution. Under Vilsmeier–Haack formylation conditions,[7] 2,7′-diformylbiindolyls **4**–**6** can be obtained in good yields from biindolyls **1**–**3**, respectively (Scheme 1). The X-ray crystal structure of 2,7′-biindolyldialdehyde **6**[8] was shown to have formyl groups at both the C2 and C7′ positions (Figure 1).

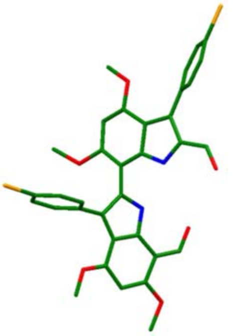
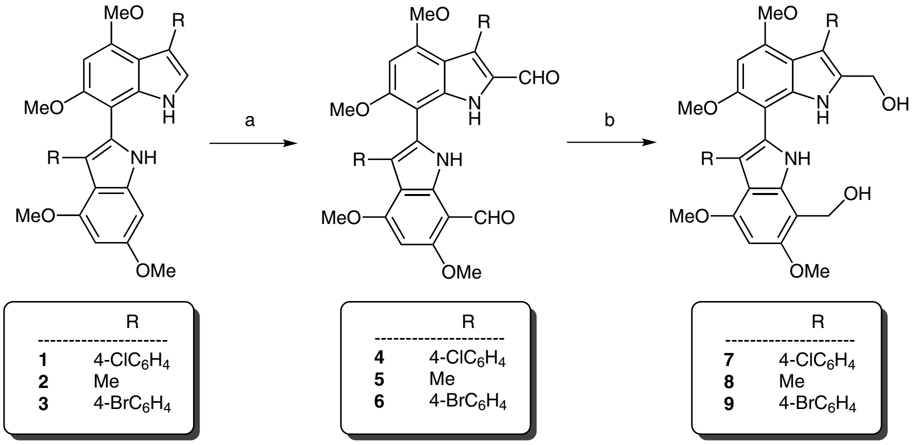


Figure 1 ORTEP diagram of 2,7′-diformyl biindolyl **6**

The 2,7′-diformyl biindolyls **4**–**6** could also undergo further reduction with sodium borohydride in a mixture of tetrahydrofuran and ethanol (1:1) to afford biindolyl dimethanols **7**–**9**, respectively as the precursors for the semi-calix[4]indoles (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) $POCl_3$, DMF, r.t., 8 h (75–81%); (b) $NaBH_4$, THF, EtOH, r.t., 8 h (90–99%).

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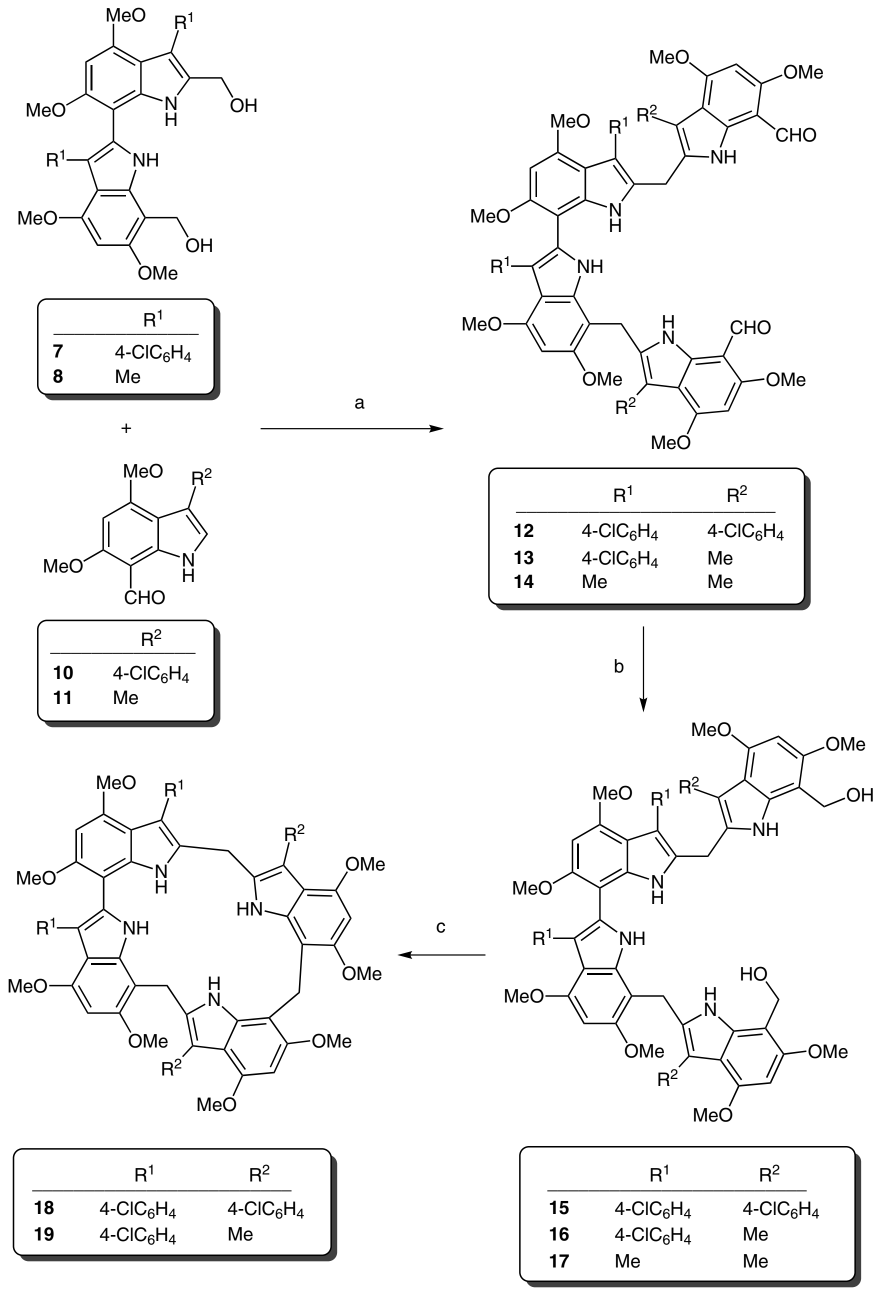
It has been reported previously that hydroxymethyl indoles can undergo acid-catalyzed addition reactions to couple with active sites of indoles.[1–5] In a similar manner, semi-calix[4]indoles can be obtained via stepwise synthesis. Diformyl tetraindolyls **12**–**14** were obtained in 40–63% yields from the acid-catalyzed addition of two equivalents of indole-7-carbaldehydes **10** and **11** to one equivalent of dihydroxymethyl biindolyls **7** and **8**. The diformyl tetraindolyls **12**–**14** were reduced by reacting with sodium borohydride to give the corresponding dihydroxymethyl tetraindolyls **15**–**17**, respectively. However, the 3-methyl-substituted compound **17** was not stable and decomposed quickly after formation. Thus the 3-aryl-substituted compounds **15** and **16** were treated with trifluoroacetic acid in dimethyl sulfoxide to afford semi-calix[4]indoles **18** and **19**, respectively in 24–40% yield (Scheme 2). These compounds represent a new class of indole-containing macrocycles. The acid-catalyzed ring closure is yet another example of an *ipso*-substitution resulting in loss of formaldehyde in the re-aromatization step.[5,9]

The ^{1}H NMR spectrum (DMSO-d_6) of the semi-calix[4]indole **18** displayed six three-proton singlets and a six-proton singlet from δ = 3.34–3.90 ppm corresponding to eight methoxy groups. Two types of methylene groups can also be identified from the spectrum. Two broad singlets (each with two protons) appear at δ = 3.72 and 4.38 ppm; the remaining methylene group shows an AB pattern at δ = 4.10 and 4.30 ppm, and this phenomenon, which re-



	R1
7	4-ClC6H4
8	Me

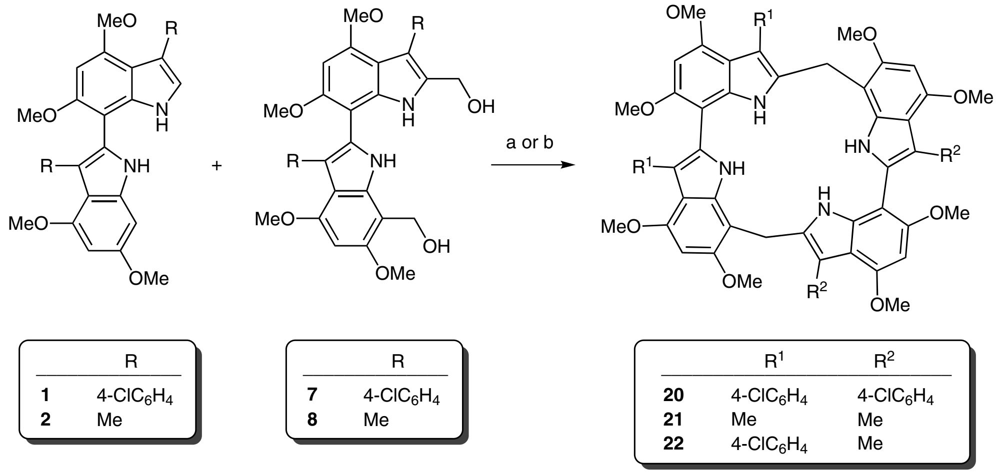
	R2
10	4-ClC6H4
11	Me

	R1	R2
12	4-ClC6H4	4-ClC6H4
13	4-ClC6H4	Me
14	Me	Me

	R1	R2
15	4-ClC6H4	4-ClC6H4
16	4-ClC6H4	Me
17	Me	Me

	R1	R2
18	4-ClC6H4	4-ClC6H4
19	4-ClC6H4	Me

Scheme 2 *Reagents and conditions*: (a) *para*-toluenesulfonic acid, isopropanol, 32 h (**12**, 63%; **13**, 56%; **14**, 40%); (b) NaBH$_4$, THF, EtOH, r.t, 8 h (**15**, 90%; **16**, 72%); (c) TFA, DMSO, r.t, 10 min (**18**, 24%; **19**, 40%).



	R
1	4-ClC$_6$H$_4$
2	Me

	R
7	4-ClC$_6$H$_4$
8	Me

	R^1	R^2
20	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$
21	Me	Me
22	4-ClC$_6$H$_4$	Me

Scheme 3 *Reagents and conditions*: (a) concd HCl (one drop), isopropanol (**20**, 30%); (b) TFA, MeCN (**21**, 43%; **22**, 6%).

lates to the rigidity of the linkage, is consistent with observations in the case of calix[4]indoles.[2,5] Furthermore, four separate resonances for indole H5 protons were found at δ = 6.35, 6.44, 6.45 and 6.51 ppm. The structure of the semi-calix[4]indole **18**[10] (containing one direct link and three methylene links) was further confirmed by the high resolution mass spectrum which displayed the expected peak at *m/z* = 1184.2689 [M$^+$].

Additionally, semi-calix[4]indoles containing two direct links and two methylene links can be formed using this strategy. When biindolyl dimethanol **7** was reacted with biindolyl **1** in the presence of hydrochloric acid, the resulting semi-calix[4]indole **20**[11] was afforded in 30% yield (Scheme 3). Similarly, with modified conditions, the semi-calix[4]indole **21** was obtained from compounds **8** and **2** in 43% yield. A hybrid system **22** was also generated from biindolyl dimethanol **8** and biindolyl **1** under the same conditions but the yield was only 6%, as there were many other compounds generated (Scheme 3).

The ^{1}H NMR spectrum (acetone-d_6) of compound **20** showed eight singlets from δ = 3.71–3.94 ppm representing the eight methoxy groups. Two methylene groups were represented by the singlet of four protons at δ = 4.36 ppm which indicated that the two methylene linkages were in the same environment, and this further proved the structure to have a head-to-tail configuration. Four H5 proton resonances appeared from δ = 6.49–6.57 ppm. Three singlets at δ = 9.63 (1 H), 9.81 (1 H) and 10.05 (2 H) represented four indole NH protons. High resolution mass spectrometry displayed the expected peak at *m/z* = 1169.2538 [M$^+$]. Furthermore the head-to-tail configuration was confirmed by an X-ray crystal structure (Figure 2).

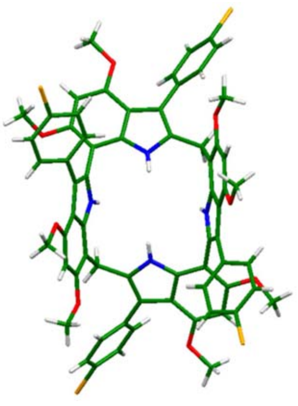


Figure 2 ORTEP diagram of semi-calix[4]indole **20**

In summary, systems of cyclized indole macrocycles with different linkages can be synthesized. In these systems, four indole units can be linked with four methylene groups, three methylene groups and one direct link, two methylene groups and two direct links, and four direct links. The structural differences and capabilities of these tetraindoles as hosts in supramolecular chemistry will be studied and the results subsequently reported.

Acknowledgment

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(8) To an ice cold solution of phosphoryl chloride (0.37 mL, 4.00 mmol) in anhyd *N*,*N*-dimethylformamide (5 mL) was added a cold solution of biindolyl **3** (1.0 g, 1.5 mmol) in anhyd *N*,*N*-dimethylformamide (1 mL). The mixture was stirred at r.t. for 30 min, and then at 50–60 °C for an additional 8 h. After cooling to r.t., the mixture was diluted with ice-water, basified with 20% aq NaOH and stirred for 1 h. The crude solid was filtered, washed with H_2O, dried and purified by flash chromatography (CH_2Cl_2–*n*-hexane, 9:1) to yield compound **6** (0.86 g, 80%) as a yellow solid; mp 175 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 6.18 (s, 1 H, H5), 6.27 (s, 1 H, H5), 7.25 (d, *J* = 9.5 Hz, 2 H, ArH), 7.30 (d, *J* = 9.5 Hz, 4 H, ArH), 7.49 (d, *J* = 8.5 Hz, 2 H, ArH), 8.75 (s, 1 H, NH), 9.26 (s, 1 H, CHO), 10.24 (s, 1 H, CHO), 10.74 (s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.1, 55.3, 56.2, 56.3 (OMe), 86.6, 89.0 (C5), 96.3 (C7), 104.2, 111.2, 111.6, 115.1, 119.9, 121.8, 126.7, 128.2 (ArC), 130.3, 130.5(ArCH), 131.0, 131.1 (ArC), 131.6, 132.7 (ArCH), 134.3, 137.0, 137.9, 157.4, 158.7, 161.0, 162.8 (ArC), 180.4, 187.9 (CH=O). IR (KBr): 3418, 2936, 2842, 1639, 1583, 1342, 1214, 1136, 1120, 987, 784, 714 cm^{-1}. UV/Vis (THF): λ_{max} = 226 nm (ε 49,300 $cm^{-1}M^{-1}$), 267 (43,800), 328 (26,700). HRMS (+ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{27}Br_2N_2O_6$: 717.0230; found: 717.0233. Single crystals were obtained from $CDCl_3$. Crystal data for compound **6**: $2(C_{34}H_{26}Br_2N_2O_6)/5(CDCl_3)$, M = 1906.73, triclinic, a = 14.7856(11) Å, b = 16.0855(12) Å, c = 19.0647(14) Å, α = 76.490(4)°, β = 78.004(3)°, γ = 68.849(3)°, V = 4073.4(5) $Å^3$, T = 150(2) K, space group P–1, Z = 2, $\mu(MoK_\alpha)$ = 2.428 mm^{-1}, 42158 reflections measured, 11460 independent reflections (R_{int} = 0.1944). The final $R1$ values were 0.1769 $[I > 2\sigma(I)]$. The final $wR(F^2)$ values were 0.4235 $[I > 2\sigma(I)]$. The final $R1$ values were 0.3679 (all data). The final $wR(F^2)$ values were 0.5123 (all data). The goodness of fit on F^2 was 1.362 (all data). Crystallographic data for compound **6** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 895310. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk].

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(10) To a solution of tetraindolyl dimethanol **15** (1.00 g, 0.80 mmol) in anhyd dimethyl sulfoxide (100 mL), trifluoroacetic acid (3 drops) was added. The mixture was allowed to stir at r.t. for 10 min before the addition of H_2O (100 mL). The mixture was then extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2–*n*-hexane, 1:1) to yield **18** (0.23 g, 24%) as a white solid; mp 243 °C. ^1H NMR (300 MHz, acetone-d_6): δ = 3.34 (s, 3 H, OMe), 3.72 (s, 6 H, OMe), 3.72 (s, 2 H, CH_2), 3.73 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 4.10 (d, *J* = 16.8 Hz, 1 H, CH_2), 4.30 (d, *J* = 16.8 Hz, 1 H, CH_2), 4.38 (br s, 2 H, CH_2), 6.35 (s, 1 H, H5), 6.44 (s, 1 H, H5), 6.45 (s, 1 H, H5), 6.51 (s, 1 H, H5), 7.09–7.41 (m, 16 H, ArH), 8.31 (s, 1 H, NH), 8.92 (s, 1 H, NH), 9.08 (s, 1 H, NH), 9.18 (s, 1 H, NH). ^{13}C NMR (75 MHz, acetone-d_6): δ = 20.9, 21.7, 23.6 (CH_2), 132.8, 133.5, 134.5, 134.9, 135.2, 135.8, 136.6, 136.8, 137.1, 54.5, 54.6, 54.7, 55.4, 55.6, 56.3, 56.5, 56.7 (OMe), 88.9, 89.3, 89.8 (C5), 97.6, 100.1, 102.6, 103.5, 111.5, 111.9, 112.2, 112.2, 112.4, 112.5, 113.4, 114.7 (ArC), 126.5, 126.9, 127.0, 127.1 (ArCH), 127.3, 127.5, 129.6, 129.9, 130.0, 130.6, 130.7, 130.9, 131.0, 131.4 (ArC), 131.5, 131.9, 132.0, 132.4, 132.5 (ArCH), 137.5, 138.3, 152.4, 152.6, 153.3, 153.7, 153.9, 154.0, 154.1, 154.5 (ArC). IR: 3401, 3369, 3323, 2932, 2836, 1595, 1549, 1490, 1334, 1196, 1117, 1088, 997, 817, 788, 740 cm^{-1}. UV/Vis (THF): λ_{max} = 224 nm (ε 203400 $cm^{-1}M^{-1}$), 287 (77600). HRMS (+ESI): *m*/*z* $[M]^+$ calcd for $C_{67}H_{54}Cl_4N_4O_8$: 1184.2666; found: 1184.2689.

(11) To a solution of biindolyl **1** (0.9 g, 1.57 mmol) and dihydroxymethyl biindolyl **7** (1.00 g, 1.57 mmol) in a mixture of isopropanol (100 mL) and CH_2Cl_2 (100 mL), concentrated hydrochloric acid (3 drops) was added. The mixture was stirred at r.t. for 5 min before the addition of H_2O (200 mL). The mixture was then extracted with CH_2Cl_2 (3 × 100 mL) and the organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2–*n*-hexane, 1:1) to yield **20** (0.60 g, 30%) as a white solid; mp 262 ºC. ^1H NMR (300 MHz, acetone-d_6): δ = 3.71 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.36 (s, 4 H, CH_2), 6.49 (s, 2 H, H5), 6.54 (s, 1 H, H5), 6.57 (s, 1 H, H5), 7.09–7.63 (m, 16 H, ArH), 9.63 (s, 1 H, NH), 9.81 (s, 1 H, NH), 10.05 (s, 2 H, NH). ^{13}C NMR (75 MHz, acetone-d_6): δ = 18.1, 21.5 (CH_2), 54.5, 54.6, 54.7, 54.9, 56.0, 56.1, 56.8, 57.0 (OMe), 89.1, 89.2 (C5), 97.6, 98.1 (C7), 103.6, 103.7, 110.3, 111.2, 112.4, 114.4, 114.5, 114.7, 116.8, 122.2, 126.5 (ArC), 126.6, 126.8, 127.4, 128.9 (ArCH), 127.5, 127.6, 130.3, 130.5, 130.7 (ArC), 130.8 (ArCH), 130.9 (ArC), 131.9 (ArCH), 132.4, 134.5, 135.3, 135.8, 136.3, 137.5, 137.6, 137.9, 151.3, 151.4, 153.2, 153.3, 154.9, 155.0, 155.1 (ArC). IR: 3440, 3330, 2932, 2837, 1595, 1487, 1327, 1207, 1088, 995, 832, 792, 740 cm^{-1}. UV–vis (THF): λ_{max} = 240 nm (ε 113900 $cm^{-1}M^{-1}$), 291 (55200). HRMS (+ESI): *m*/*z* $[M + H]^+$ calcd for $C_{66}H_{52}Cl_4N_4O_8$: 1169.2539; found: 1169.2538. Single crystals were obtained from $(CD_3)_2CO$. Crystal data for compound **20**: $C_{40\cdot50}H_{41}Cl_2N_2O_{6\cdot50}$, M = 730.65, monoclinic, a = 21.490(4) Å, b = 10.494(2) Å, c = 33.299(7) Å, α = 90.00°, β = 95.71(3)°, γ = 90.00°, V = 7472(3) $Å^3$, T = 100(2) K, space group $C2/c$, Z = 8, μ(Synchrotron) = 0.225 mm^{-1}, 45914 reflections measured, 6568 independent reflections (R_{int} = 0.0377). The final $R1$ values were 0.0736 $[I > 2\sigma(I)]$. The final $wR(F^2)$ values were 0.1951 $[I > 2\sigma(I)]$. The final $R1$ values were 0.0809 (all data). The final $wR(F^2)$ values were 0.2015 (all data). The goodness of fit on F^2 was 1.037 (all data). Crystallographic data for compound **20** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 895299. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk].