HETEROCYCLES, Vol. 80, No. 1, 2010, pp. 623 - 629. © The Japan Institute of Heterocyclic Chemistry
Received, 3rd June, 2009, Accepted, 6th July, 2009, Published online, 6th July, 2009
DOI: 10.3987/COM-09-S(S)31

A SYNTHETIC STUDY ON BAUHINOXEPIN J: CONSTRUCTION OF A DIBENZO[*b,f*]OXEPIN RING SYSTEM BY A DDQ-PROMOTED OXIDATIVE DEAROMATIZATION–CYCLIZATION APPROACH‡

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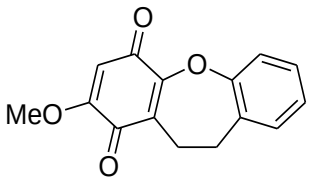
Abstract – Efforts to construct a dibenzo[*b,f*]oxepin ring system for a synthesis of bauhinoxepin J are described. A DDQ-promoted oxidative dearomatization–cyclization of the 2-phenoxyethyl-substituted tetramethoxybenzene was used to construct a tricyclic quinone monoacetal.

Bauhinoxepin J (**1**), a secondary metabolite isolated from the root extracts of *Bauhinia purpurea* (Figure 1),[1] is reported to exhibit antimycobacterial and antimalarial activities.[1] The dibenzo[*b,f*]oxepin structure containing a seven-membered cyclic ether with a functionalized quinone moiety consequently has attracted considerable synthetic interest. Herein, we describe a synthetic study on bauhinoxepin J (**1**), in which the dibenzo[*b,f*]oxepin ring system was constructed using a DDQ-promoted oxidative dearomatization–cyclization of the 2-hydroxyphenethyl-substituted tetramethoxybenzene.



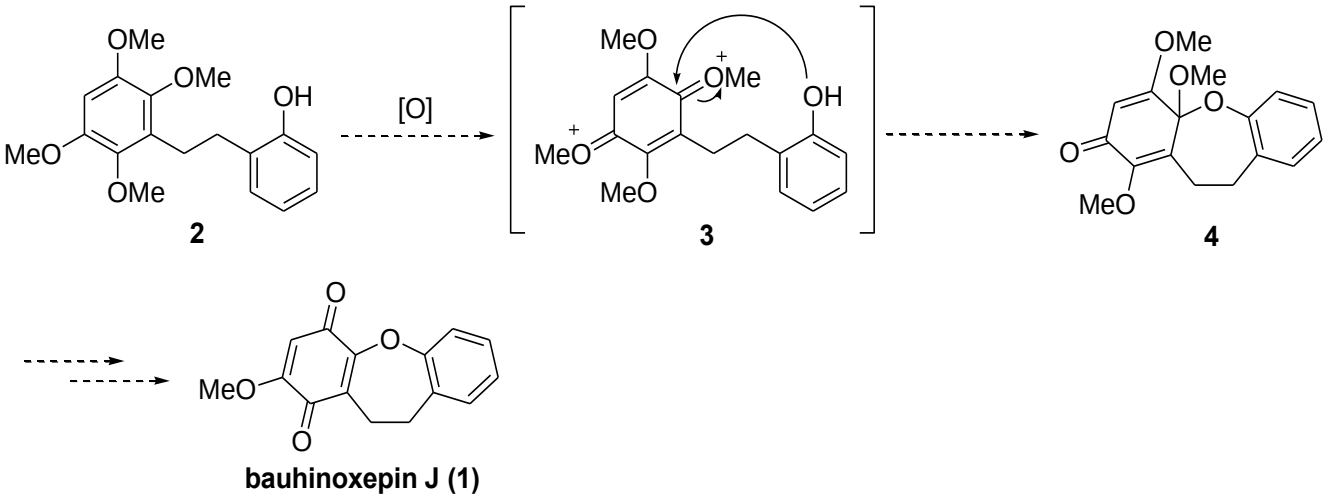
bauhinoxepin J (1)

Figure 1. Structure of bauhinoxepin J (**1**)

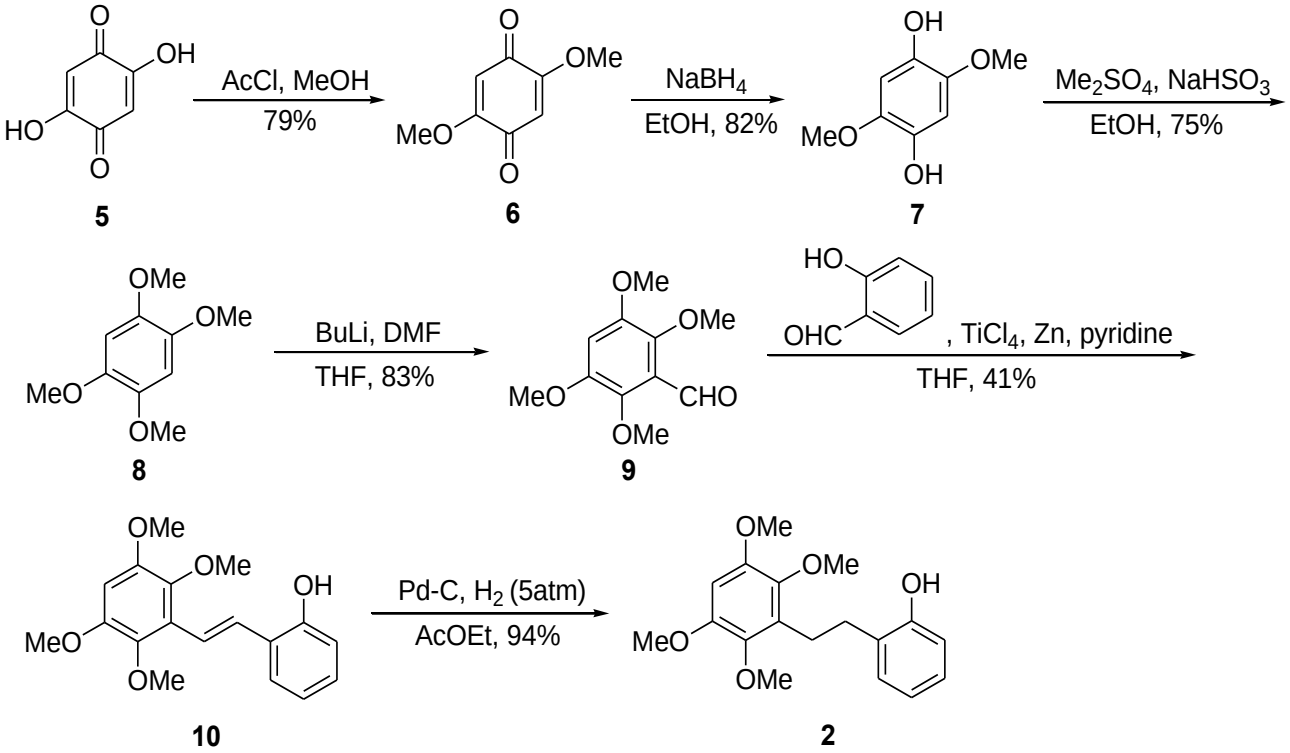
Our synthetic approach for bauhinoxepin J (**1**) is shown in Scheme 1. We anticipated that the electrophilic intermediate **3** would be generated when 2-hydroxyphenethyl-substituted tetramethoxybenzene **2** was

‡ This paper is dedicated to Dr. Akira Suzuki on the occasion of his 80th birthday.

treated with a suitable oxidant.[2] Subsequent intramolecular interception of **3** would yield the tricyclic quinone monoacetal **4**, which would be a promising precursor for **1**.



Scheme 1. Approach to bauhinoxepin J (**1**)



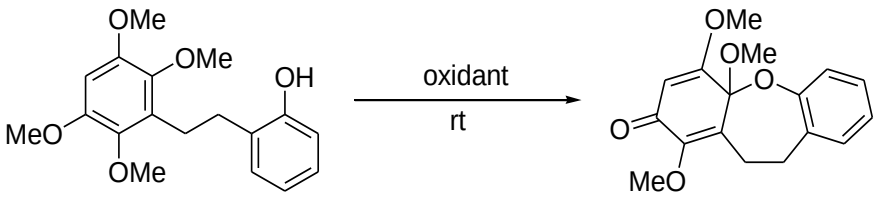
Scheme 2. Synthesis of 2-hydroxyphenethyl-substituted tetramethoxybenzene **2**

The synthesis of the 2-hydroxyphenethyl-substituted tetramethoxybenzene **2** was conducted as shown in Scheme 2. Treatment of 2,5-dihydroxy-*p*-benzoquinone (**5**) with AcCl in MeOH afforded the dimethoxyquinone **6** (79% yield), which was reduced with $NaBH_4$ to give the hydroquinone **7** (82% yield). After methylation with dimethyl sulfate (75% yield), formylation of the resulting

tetramethoxybenzene **8** with DMF in the presence of *n*-BuLi gave tetramethoxybenzaldehyde **9**[3] in 83% yield. McMurry coupling[4] of **9** with salicylaldehyde (41% yield) followed by hydrogenation of the resulting *trans*-stilbene **10** led to **2** in 94% yield.

With the 2-hydroxyphenethyl-substituted tetramethoxybenzene **2** in hand, we next examined the key oxidative dearomatization–cyclization (Table 1). When compound **2** was treated with 2 equiv of CAN in aqueous MeCN, a complex mixture was obtained (entry 1). The reaction with diacetoxyiodobenzene in aqueous MeOH likewise resulted in the formation of a complex mixture (entry 2). Nevertheless, after several attempts,[5] we were pleased to find that the desired reaction successfully proceeded when carried out with 5 equiv of DDQ in dioxane to produce the tricyclic quinone monoacetal **4** in 81% yield (entry 3). The structure of **4** was unambiguously confirmed by an X-ray crystallographic analysis (Figure 2).

Table 1. Oxidative dearomatization cyclizations of **2** with oxidants.



2 **4**

Entry	Oxidant	Solvent	Yield (%)
1	CAN (2 equiv)	$MeCN/H_2O$ (4/1)	complex mixture
2	$PhI(OAc)_2$ (2 equiv)	$MeOH/H_2O$ (40/1)	complex mixture
3	DDQ (5 equiv)	dioxane	81

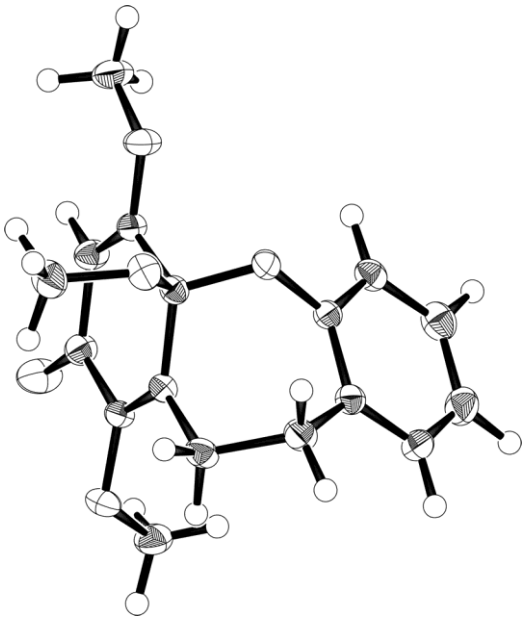


Figure 2. X-Ray Structure of tricyclic quinone monoacetal **4**

In conclusion, We have succeeded in constructing a dibenzo[*b,f*]oxepin ring system by a DDQ-promoted oxidative dearomatization–cyclization of the 2-hydroxyphenethyl-substituted tetramethoxybenzene. Further studies on the synthesis of bauhinoxepin J are currently underway.

EXPERIMENTAL

Solvents were dried and distilled according to standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure.

2,5-Dimethoxycyclohexa-2,5-diene-1,4-dione (6)

To a stirred suspension of 2,5-dihydroxy-*p*-benzoquinone (**5**) (20.0 g, 143 mmol) in MeOH (714 mL) was added AcCl (3.50 mL, 48.6 mmol) at rt, and the reaction mixture was stirred for 25 h at 80 ºC. The precipitate was filtered and washed with cold MeOH. The resulting solid was dried in vacuo to give dimethoxyquinone **6** (18.9 g, 79%) as a yellow solid; mp 202.3–205.7 ºC (AcOEt/hexane); IR (KBr): 1662, 1599, 1205 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 5.87 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.6 (CH_3), 105.5 (CH), 159.6 (Cq), 181.6 (Cq); HRMS (ESI) *m/z* calcd for $C_8H_8O_4Na$ [M^++Na^+] 191.0320, found 191.0323.

1,4-Dihydroxy-2,5-dimethoxybenzene (7)

To a stirred suspension of dimethoxyquinone **6** (7.70 g, 45.9 mmol) in EtOH (60 mL) was added $NaBH_4$ (4.50 g, 119 mmol) in portions at 0 ºC, and stirring was continued for 3 h at the same temperature. The reaction mixture was quenched with 1 M HCl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup gave hydroquinone **7** (6.40 g, 82%) as a yellow solid; mp 181.8–188 ˚C (AcOEt/hexane). IR (KBr): 3406, 1520, 1450, 1240, 1192 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 6H), 5.23 (s, 2H), 6.58 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.6 (CH_3), 99.8 (CH), 138.6 (Cq), 140.3 (Cq); HRMS (ESI) *m/z* calcd for $C_8H_{10}O_4Na$ [M^++Na^+] 193.0477, found 193.0477.

1,2,4,5-Tetramethoxybenzene (8)

To a stirred suspension of hydroquinone **7** (14.0 g, 82.3 mmol), Me_2SO_4 (55.0 mL, 370 mmol) and $NaHSO_3$ (1.37 g, 13.2 mmol) in EtOH (90 mL) was added dropwise 10 N NaOH (47 mL) at 0 ºC. After stirring for 5.5 h at 80 ºC, the resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup gave tetramethoxybenzene **8** (12.3 g, 75%) as colorless needles; mp 99.7–101.8 ˚C (AcOEt/hexane); IR (KBr): 2945, 1525, 1471, 1203 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 12H), 6.61 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 57.0

(CH_3), 100.7 (CH), 143.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{10}H_{15}O_4$ [M^++H^+] 199.0970, found 199.0968.

2,3,5,6-Tetramethoxybenzaldehyde (9)[3]

To a stirred solution of tetramethoxybenzene **8** (12.3 g, 62.1 mmol) in dry THF (310 mL) was added dropwise *n*-BuLi (1.57 M, 47.4 mL, 74.5 mmol) at –78 ºC. The reaction mixture was warmed to –10 ºC over 1 h and stirred at the same temperature for an additional 1 h. The mixture was then cooled to –78 ºC, and DMF (24.0 mL, 310 mmol) was added in one portion. The reaction was allowed to warm to 0 ºC over 1 h. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (85:15, v/v) as eluent to give tetramethoxybenzaldehyde **9** (11.7 g, 83%) as colorless needles; mp 79.5–81.4 ˚C (AcOEt/hexane); IR (KBr): 2995, 1697 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 6H), 3.89 (s, 6H), 6.79 (s, 1H), 10.41 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.8 (CH_3), 62.1 (CH_3), 105.1 (CH), 124.3 (Cq), 143.9 (Cq), 149.2 (Cq), 189.9 (CH); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_5Na$ [M^++Na^+] 249.0739, found 249.0739.

(*E*)-2-(2,3,5,6-Tetramethoxystyryl)phenol (10)

To a stirred solution of activated zinc powder (9.50 g, 146 mmol) and pyridine (11.8 mL, 146 mmol) in dry THF (180 mL) was added dropwise $TiCl_4$ (8.0 mL, 72.9 mmol) at 0 ºC. The reaction was warmed to room temperature and stirred for 0.5 h, then heated at reflux for 2.5 h. After cooling to 0 ºC, a solution of tetramethoxybenzaldehyde **9** (3.00 g, 13.4 mmol) and salicylaldehyde (2.8 mL, 26.5 mmol) in dry THF (100 mL) was slowly added to the mixture. After refluxing for 17 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was filtered through Celite, and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (85:15, v/v) as eluent to give the *trans*-stilbene **10** (1.70 g, 41%) as colorless prisms; mp 145.6–147.2 ˚C (AcOEt/hexane); IR (KBr): 3319, 1587, 1219 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 3.88 (s, 6H), 5.19 (s, 1H), 6.51 (s, 1H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.96 (t, 1H, *J* = 8.0 Hz), 7.15 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 16.8 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 16.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.5 (CH_3), 60.5 (CH_3), 98.5 (CH), 116.0 (CH), 120.8 (CH), 121.3 (CH), 125.5 (Cq), 125.8 (Cq), 127.0 (CH), 128.4 (CH), 128.7 (CH), 141.3 (Cq), 149.2 (Cq), 153.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_5Na$ [M^++Na^+] 339.1208, found 339.1199.

2-(2,3,5,6-Tetramethoxyphenethyl)phenol (2)

To a stirred suspension of Pd-C (197 mg, 20 wt%) in AcOEt (11 mL) was added the *trans*-stilbene **10** (987 mg, 3.10 mmol) at rt, and stirring was continued for 4.5 h at the same temperature under 5 atm of

hydrogen gas. The resulting solution was filtered through Celite, and the residue upon evaporation of the solvent was chromatographed with hexane-AcOEt (85:15, v/v) as eluent to give the 2-hydroxyphenethyl-substituted tetramethoxybenzene **2** (924.7 mg, 94%) as colorless prisms; mp 104.9–107.2 ˚C (AcOEt/hexane); IR (KBr): 3357, 1592, 1460, 1226 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.70–2.74 (m, 2H), 2.82–2.86 (m, 2H), 3.86 (s, 6H), 3.88 (s, 6H), 6.47 (s, 1H), 6.58 (s, 1H), 6.85 (dt, *J* = 1.2, 7.2 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 7.13-7.17 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.4 (CH_2), 32.3 (CH_2), 56.3 (CH_3), 61.3 (CH_3), 97.2 (CH), 115.8 (CH), 120.1 (CH), 127.1 (Cq), 127.9 (CH), 129.4 (Cq), 129.8 (CH), 140.5 (Cq), 149.0 (Cq), 154.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}O_5Na$ [M^++Na^+] 341.1365, found 341.1356.

1,4,4a-Trimethoxy-10,11-dihydrodibenzo[*b,f*]oxepin-2(4*aH*)-one (4)

To a stirred solution of the 2-hydroxyphenethyl-substituted tetramethoxybenzene **2** (50 mg, 0.16 mmol) in dioxane (4 mL) was added DDQ (178 mg, 0.79 mmol) in portions at rt. After the reaction mixture was stirred at the same temperature for 10 h, the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (70:30 v/v) as eluent to give tricyclic quinone monoacetal **4** (38.5 mg, 81%) as colorless prisms; mp 137.6–138.5 ˚C (AcOEt/hexane); IR (KBr): 3442, 2937, 1637, 1458, 1232 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34–2.42 (m, 1H), 2.73–2.81 (m, 1H), 3.11–3.24 (m, 5H), 3.59 (s, 3H), 3.91 (s, 3H), 5.61 (s, 1H), 6.95–7.15 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.2 (CH_2), 29.8 (CH_2), 51.9 (CH_3), 56.4 (CH_3), 60.8 (CH_3), 98.7 (Cq), 103.1 (CH), 122.7 (CH), 125.1 (CH), 127.5 (CH), 129.0 (CH), 134.4 (Cq), 136.4 (Cq), 150.6 (Cq), 151.9 (Cq), 169.1 (Cq), 182.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_5$ [M^++H^+] 303.1232, found 303.1231.

X-Ray crystallographic analysis of compound 4.[6] A colorless block crystal having approximate dimensions of 0.60 x 0.60 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 13,033 observed reflections ($I > 0.00\sigma(I)$) and 218 variable parameters, and converged (largest parameter shift was 0.54 times its esd) with unweighted and weighted agreement factors of $R = 0.043$ and $R_W = 0.110$. Crystal data for **4**: $C_{17}H_{18}O_5$, M = 302.33, monoclinic, space group $P2_1/n$, a = 13.6538(8) Å, b = 8.4884(4) Å, c = 13.9424(9) Å, β = 113.237(2)°, V = 1484.8(1) $Å^3$, Z = 4, D_c = 1.352 g/cm^3, F(000) = 640, μ(MoKα) = 0.99 cm^{-3}.

ACKNOWLEDGEMENT

This study was supported in part by a Grant-in-Aid for the Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) and the Program for the Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

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2. For representative examples of the oxidative formation of quinone monoacetals, see: (a) K. Miyashita, T. Sakai, and T. Imanishi, *Org. Lett.*, 2003, **5**, 2683; (b) S. Bäsler, A. Brunck, R. Jautelat, and E. Winterfeldt, *Helv. Chim. Acta*, 2000, **83**, 1854; (c) S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, *J. Am. Chem. Soc.*, 1985, **107**, 3891.
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5. When the DDQ-promoted reaction was carried out under aqueous conditions, the corresponding 2-hydroxyphenethyl-substituted *p*-quinone was obtained in 31% yield. More than 50% of the starting material was recovered when 2equiv of DDQ was subjected to the reaction.
6. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733689. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].