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Novel synthesis of *o*-naphthothiophenequinone derivatives via regioselective Diels–Alder reaction

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Abstract—A novel procedure to construct *o*-naphthothiophenequinones has been achieved from readily available *o*-benzothiophenquinones and *N*-dienes via Diels–Alder reaction-aromatization sequence as key steps. The absolute regioselectivity was established via Diels–Alder reaction of *o*-benzothiophenquinones with rich electron *N*-dienes.

1. Introduction

The derivatives of synthetic and natural polycyclic quinoid structure are a large category of very significative compounds, which possess a broad spectrum of biological activities.[1–7] Among heterocyclic quinones with a variety of bioactivities, those containing a thiophene ring fused to a quinone system have received an increasing attention.[8]

As part of our ongoing research for hetero polycyclic *o*-quinones,[9] more structurally diversified *o*-quinoid derivatives were called for. In contrast to extensive study of oxoheterocyclic-fused *o*-quinones, that of thioheterocyclic-fused *o*-quinones was quite scarce.[8c,10] Therefore, synthesis of novel thiophen-fused *o*-quinones was proposed, these novel derivatives were characterized as 3-aryl and 6-acylamino substituted *o*-naphthothiophenquinones **I** (Fig. 1).

However, efficient methods for the synthesis of *o*-naphthothiophenequinones could be seldom found.[11] Furthermore, the reported synthetic procedure[11] was unapplicable for us to prepare the proposed derivatives **I** for unavailable starting materials.

In this paper, we described a novel and regiospecific procedure to synthesize the target substrates **I**. The retrosynthetic analysis (Scheme 1) showed that compounds **I** could be achieved facilely from inexpensive and easily available starting materials **II**, **III**, **VI**, **VII** via condensation, intramolecularly cyclization, deprotection, IBX

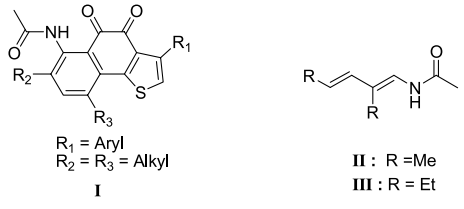
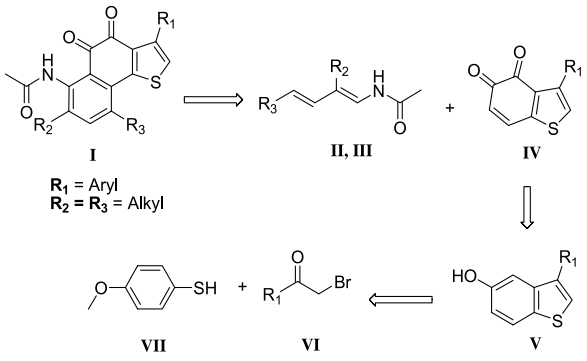


Figure 1.



Scheme 1. Retrosynthesis route of target compounds **I**.

Keywords: *o*-Naphthothiophenequinone; IBX; Diels–Alder; Regioselectivity.
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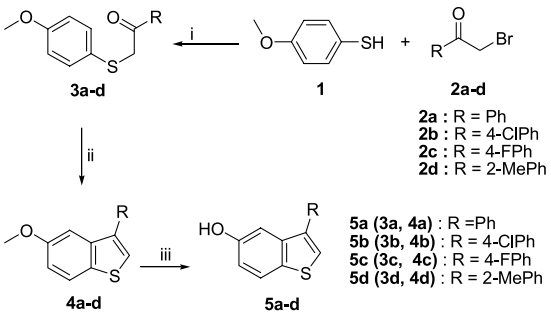
oxidation, and then Diels–Alder reaction-aromatization sequence.

2. Results and discussion

2.1. Synthesis of benzothiophen-5-ols (5a–d)

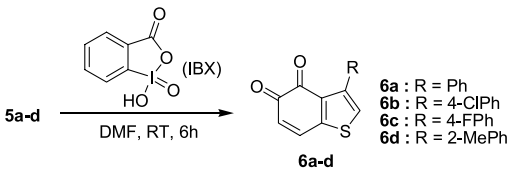
Our strategies were started from synthesis of benzothiophen-5-ol moieties detailed in Scheme 2. Compounds **3a–d** were prepared in MeOH/H_2O by condensing 4-methoxyphenylthiol **1** with an equiv of 2-bromo-1-arylyethanones **2a–d** at 5–10 °C in the presence of an equiv of KOH.[12] Compounds **3a–d** were then cyclized into 3-aryl-5-methoxybenzothiophenes **4a–d** in refluxing toluene by using PPA.[13] Finally, benzothiophene-5-ols **5a–d** were achieved in moderate to good overall yield (see Section 4) after deprotection of **4a–d** by refluxing in a mixture of Ac_2O and 48% HBr (1:1 v/v).



Scheme 2. Conditions: (i) MeOH, equiv KOH, 5–10 °C; (ii) PPA, toluene, RF, 6 h; (iii) AC_2O–HBr (48%) (1:1, v/v), 140 °C, 4 h.

2.2. Synthesis of benzothiophen-4, 5-diones (6a–d)

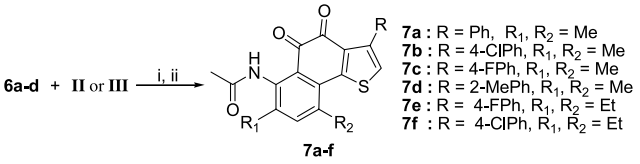
The next step was to convert benzothiophen-5-ols **5a–d** into benzothiophen-4,5-diones **6a–d**. Fremy's salt is well known for its application in transforming single phenolic hydroxyl group into *o*-quinone group.[14] Our first attempt was focused on the oxidation of benzothiophen-5-ols **5a–d** to produce *o*-quinones **6a–d**. However, most of the reaction failed to give the desired products in satisfactory yield. After an in-depth screening of mild oxidants, we found that *o*-iodoxybenzoic acid (IBX) could be a good choice in these reactions, as it was reported that IBX was a good oxidant for transforming phenols to *o*-quinones.[15] However, few reports on transformation of hetero biscyclic phenolic hydroxyl group into *o*-quinone by IBX could be found. Our results indicated that IBX worked very well in our system, the desired product benzothiophen-4,5-diones **6a–d** were obtained regioselectively (Scheme 3) in almost quantitative yields. The isolation of the diquinone intermediates was not pursued as most of these *o*-quinone compounds were volatile and highly reactive.



Scheme 3.

2.3. Synthesis of target *o*-quinones (7a–f)

After the completion of IBX oxidation, the reaction mixture was first diluted with water, and then extracted with benzene. The extraction containing benzothiophen-4,5-diones was dried with anhydrous sodium sulfate and *N*-diene **II** or **III**[16] was added for cycloaddition. The reaction was carried out at 45 °C and monitored by TLC (noticeably, only one new fluorescent substance was found, which indicated that the single regiomer was produced). About 16 h later, the reaction mixtures were subsequently aromatized into the final products by refluxing with DDQ. After purification by chromatography on silica gel ($CHCl_3$/MeOH), regiospecific compounds **7a–f** were obtained in 78–86% yields (Scheme 4).



Scheme 4. Conditions: (i) benzene, 45 °C, 16 h; (ii) DDQ, benzene, RF, 10 h.

Structures of all final products were assigned according to ^1H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, ESI-MS and element analysis data. The structure of **7a** was also proved unanimously by X-ray crystal structure analysis[17] (Fig. 2).

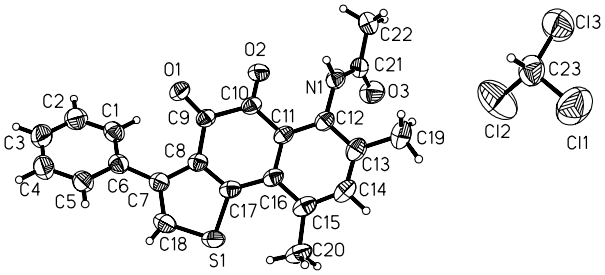


Figure 2. X-ray crystal structure for **7a** (CCDC no. 267293).

It is interesting that the cycloaddition reactions of our procedure were essentially regiospecific and high reactive, which was reasoned that an intermolecular hydrogen bond (HB) would form between the amide group (NH) of the *N*-dienes and the oxygen atom of carbonyl groups in *o*-quinones. The role of intermolecular hydrogen bonding in the regio and stereo-chemical outcome of Diels–Alder reactions has been well recognized.[18]

3. Conclusions

In summary, we developed a novel route to prepare thiophen-fused *o*-naphthoquinone derivatives via the key IBX oxidation–cycloaddition–aromatization sequence. Noticeably, the cycloaddition was regiospecific and highly efficient. To the best of our knowledge, none relative reports have surfaced. Furthermore, this work produced a series of novel thiophene fused *o*-quinoid derivatives. Studies on the bioactivities and further synthesis of these compounds are well under way.

4. Experimental

4.1. General

All reagents were available commercially. Solvents were purified using standard techniques. Reactions were monitored by TLC. Separation by vacuum chromatographic column were performed on Silica gel H. ^{1}H NMR, ^{13}C NMR, DEPT, HMQC and HMBC spectra were measured on a Varian UNITY INOVA 500 or 300 MHz spectrometer using TMS as an internal standard. For the electrospray (ESI) MS analysis, a Finnigan LCQ Deca XP ion trap mass spectrometer was equipped with a Microsoft Windows NT data system and an ESI interface was used. Elementary analysis was recorded on an Elementar Vario EL elementary analysis device. *N*-Dienes **II**, **III** are prepared by using the reported method.[16]

4.2. General procedure for 3-arylbenzothiophen-5-ols (5a–d)

To a freshly prepared solution of 70 mL of MeOH, 30 mL of water, and 3.3 g of KOH (85% purity; 0.05 mol) at room temperature was added 4-methoxybenzenethiol **1** (7.0 g, 0.05 mol) in one portion, and the solution was cooled to between 5 and 10 °C. A saturated solution of 2-bromo-1-arylyethanones (**2a–d**) (0.05 mol) in MeOH was added at a rate that the temperature did not exceed 15 °C. The reaction was continued for further 1 h at 15 °C, and then was allowed to stir overnight at room temperature. The reaction was diluted with water and extracted with ether. The organic layers were washed with 1 M HC1 solution, water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organics were dried over anhydrous Na_2SO_4, filtered, and evaporated to give crude products (**3a–d**) as yellow oils.

A mixture of 2-(4-methoxyphenylthio)-1-arylethanones (**3a–d**), polyphosphoric acid (40 g), and toluene (100 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, poured into water, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation gave crude compounds (**4a–d**), which were used directly for the next reaction without further purification.

Unpurified 3-aryl-5-methoxybenzo[*b*]thiophenes (**4a–d**) were added to mixed solution (40 mL) of 48% HBr and acetic anhydride (1:1, v/v). The mixture was refluxed at 140 °C for 4 h. The reaction mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate solution and extracted with ether. The organic extracts were washed with saturated aqueous sodium chloride and dried over anhydrous Na_2SO_4. Evaporation and purification by chromatography on silica gel (eluent: EtOAc/Petroleum-II 1:8) gave 3-arylbenzo[*b*]thiophene-5-ols (**5a–d**) in moderate to good overall yields.

4.2.1. 3-Phenylbenzo[*b*]thiophene-5-ol (5a). This compound was obtained as a yellow oil in 53% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_{10}OS$: C, 74.31; H, 4.45; S, 14.17; Found: C, 74.27; H, 4.48; S, 14.14; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 1H, J=8.7 Hz), 7.55–7.58 (m, 2H), 7.41–7.48 (m, 5H), 7.05 (dd, 1H, J=2.4, 8.6 Hz), 6.46 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.0, 114.3, 123.6, 124.8, 127.2, 128.2, 128.4, 133.0, 135.6, 137.1, 138.8, 152.7.

4.2.2. 3-(4-Chlorophenyl)benzo[*b*]thiophene-5-ol (5b). This compound was obtained as a yellow oil in 58% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_9ClOS$: C, 64.49; H, 3.48; S, 12.30; Found: C, 64.47; H, 3.52; S, 12.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, J=8.6 Hz), 7.31–7.41 (m, 6H), 7.00 (dd, 1H, J=2.0, 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.7, 114.6, 123.6, 125.1, 128.6, 129.5, 132.7, 133.1, 134.1, 135.9, 138.6, 153.4.

4.2.3. 3-(4-Fluorophenyl)benzo[*b*]thiophene-5-ol (5c). This compound was obtained as a yellow oil in 60% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_9FOS$: C, 68.84; H, 3.71; S, 13.12; Found: C, 68.79; H, 3.74; S, 13.09; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, J=8.6 Hz), 7.49 (dd, 1H, J=5.5, 8.5 Hz), 7.37 (s, 1H), 7.29 (d, 1H, J=2.3 Hz), 7.14 (t, 2H, J=8.6 Hz), 6.99 (dd, 1H, J=2.3, 8.6 Hz), 5.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.7, 114.5, 115.6 (d, J=21.0 Hz), 123.7, 124.9, 130.0 (d, J=7.3 Hz), 131.8, 132.8, 136.2, 139.0, 153.3, 162.1 (d, J=245.6 Hz).

4.2.4. 3-(2-Methylphenyl)benzo[*b*]thiophene-5-ol (5d). This compound was obtained as a yellow oil in 62% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03; S, 13.34; Found: C, 74.94; H, 5.28; S, 13.29; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 1H, J=8.6 Hz), 7.28–7.33 (m, 5H), 6.95 (dd, 1H, J=2.4, 8.6 Hz), 6.84 (d, 1H, J=2.4 Hz), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 108.0, 114.3, 123.4, 125.0, 125.6, 127.8, 130.1, 130.3, 132.1, 135.2, 136.7, 136.9, 140.2, 153.2.

4.3. General procedure for substituted naphtho [1,2-*b*] thiophene-4,5-diones (7a–f)

Compound **5a–d** (1 mmol) and IBX (1.2 mmol) were added to dry DMF (5 mL) and then stirred at the room temperature for 6 h. The reaction mixture was diluted with water (120 mL), extracted with benzene, washed with saturated aqueous sodium chloride, dried over Na_2SO_4, and concentrated to 50 mL, *N*-dienes **II** or **III** (1 mmol) was added and then the mixture was stirred at 45 °C for 16 h. The solution containing cycloaddition products was added DDQ (0.75 mmol) and refluxed for further 16 h. Evaporation and purification by chromatography on silica gel ($CHCl_3$/MeOH) gave **7a–f** in good yields.

4.3.1. 7,9-Dimethyl-3-phenyl-6-acetamidonaphtho[1,2-*b*] thiophene-4,5-dione (7a). This compound was obtained as a red solid in 86% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73; S, 8.54; Found: C, 70.35; H, 4.61; N, 3.70; S, 8.49; MS (ESI) *m/z*: 374 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.0 (br s, 1H), 7.35–7.43 (m, 6H), 7.18 (s, 1H), 2.65 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 24.2, 24.33, 122.0, 125.0, 127.8, 128.1, 128.7, 129.9, 131.6, 132.9, 134.4, 136.8, 139.6, 142.4, 144.4, 151.5, 168.8, 174.9, 185.4.

4.3.2. 7,9-Dimethyl-3-(4-chlorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7b). This compound was obtained as a red solid in 83% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{16}ClNO_3S$: C, 64.47; H, 3.93; N, 3.42; S, 7.82; Found: C, 64.44; H, 3.96; N, 3.39; S, 7.78; MS (ESI) *m/z*: 408 $(M-H)^-$; ^1H NMR (500 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.26 (s, 3H), 2.68 (s, 3H), 7.20 (s, 1H), 7.36 (s, 4H), 7.40 (s, 1H), 10.03 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 24.1, 24.3, 122.2, 125.2, 127.9, 128.2, 129.9, 130.3, 130.6, 131.7, 133.0, 133.1, 134.3, 137.2, 140.0, 142.7, 143.3, 152.0, 169.0, 175.1, 185.5.

4.3.3. 7,9-Dimethyl-3-(4-fluorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7c). This compound was obtained as a red solid in 85% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{16}FNO_3S$: C, 67.16; H, 4.10; N, 3.56; S, 8.15; Found: C, 67.13; H, 4.14; N, 3.54; S, 8.11; MS (ESI) *m/z*: 392 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.25 (s, 3H), 2.67 (s, 3H), 7.06 (t, 2H, $J=8.6$ Hz), 7.17 (s, 1H), 7.36–7.41 (m, 3H), 10.01 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 24.3, 24.4, 114.9 (d, $J=21.6$ Hz), 122.0, 125.0, 129.8, 130.4, 130.6 (d, $J=7.9$ Hz), 131.5, 133.0, 137.0, 139.7, 142.5, 143.3, 151.8, 162.5 (d, $J=247.4$ Hz), 168.9, 174.9, 185.4.

4.3.4. 7,9-Dimethyl-3-(2-methylphenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7d). This compound was obtained as red solid in 80% yield (eluent: MeOH/$CHCl_3$ 1:20). Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60; S, 8.23; Found: C, 70.89; H, 4.95; N, 3.57; S, 8.25; MS (ESI) *m/z*: 388 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 7.10 (s, 1H), 7.13–7.31 (m, 4H), 7.37 (s, 1H), 9.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 20.3, 24.5, 24.6, 122.7, 125.2, 125.6, 128.4, 129.3, 129.9, 130.3, 133.2, 133.3, 135.1, 136.9, 137.2, 140.1, 142.7, 143.7, 151.1, 169.3, 174.5, 185.2.

4.3.5. 7,9-Diethyl-3-(4-fluorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7e). This compound was obtained as a red solid in 78% yield (eluent: MeOH/$CHCl_3$ 1:200). Anal. Calcd for $C_{24}H_{20}FNO_3S$: C, 68.39; H, 4.78; N, 3.32; S, 7.61; Found: C, 68.36; H, 4.82; N, 3.30; S, 7.58; MS (ESI) *m/z*: 420 $(M-H)^-$; ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J=7.5$ Hz), 1.42 (t, 3H, $J=7.4$ Hz), 2.24 (s, 3H), 2.66 (q, 2H, $J=7.5$ Hz), 3.11 (q, 2H, $J=7.4$ Hz), 7.07 (t, 2H, $J=8.7$ Hz), 7.16 (s, 1H), 7.40 (dd, 2H, $J=5.3$, 8.7 Hz), 7.48 (s, 1H), 9.81 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 14.3, 24.2, 24.7, 28.8, 114.9 (d, $J=21.7$ Hz), 122.9, 124.8, 129.3, 130.6, 130.7 (d, $J=8.3$ Hz), 131.9, 138.4, 138.8, 139.4, 143.0, 143.2, 150.9, 162.7 (d, $J=247.5$ Hz), 169.5, 175.7, 186.2.

4.3.6. 7,9-Diethyl-3-(4-chlorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7f). This compound was obtained as red solid in 80% yield (eluent: MeOH/$CHCl_3$ 1:200). Anal. Calcd for $C_{24}H_{20}ClNO_3S$: C, 65.82; H, 4.60; N, 3.20; S, 7.32; Found: C, 65.78; H, 4.65; N, 3.21; S, 7.34; MS (ESI) *m/z*: 436 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J=7.5$ Hz), 1.40 (t, 3H, $J=7.4$ Hz), 2.23 (s, 3H), 2.64 (q, 2H, $J=7.5$ Hz), 3.08 (q, 2H, $J=7.4$ Hz), 7.15 (s, 1H), 7.32 (s, 4H), 7.45 (s, 1H), 9.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 14.3, 24.3, 24.7, 28.8, 122.8, 125.0, 128.0, 129.1, 130.1, 131.6, 132.8, 134.0, 138.2, 138.6, 139.3, 142.7, 142.9, 150.9, 169.4, 175.4, 185.8.

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17. Crystal data for **7a**: $C_{22}H_{17}NO_3S\cdot CHCl_3$, $M=494.79$, monoclinic, space group $P2(1)/c$, $a=17.413(6)$ Å, $b=16.235(5)$ Å, $c=8.054(3)$ Å, $\alpha=90.00°$, $\beta=95.706(6)°$, $\gamma=90.00°$, $V=2265.8(13)$ Å^3, $Z=4$, $D_c=1.451$ g/m^3, $F(000)=1016$, $1.18°<\theta<27.13°$, $-22\le h\le 22$, $-20\le k\le 14$, $-10\le l\le 10$, $T=293$ K, colorless red, $0.54\times0.42\times0.21$. $R_1=0.0595$ ($[I>2\sigma(I)]$), 0.1040 (all data), $\omega R_2=0.1817$ ($[I>2\sigma(I)]$), 0.2224 (all data). Crystallographic data for the structures in this paper have been deposited with the Cambridge crystallographic data centre as supplementary publication numbers CCDC 267293. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: eposit@ccdc.cam.ac.uk].
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