$C_{30}H_{31}Cl_2FeNO$: C, 65.71; H, 5.70; N, 2.55. Found: C, 65.72; H, 5.57; N, 2.45.

3: from (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane and 4,4′-dimethoxybenzophenone, purified by TLC on silica gel (ether–CH_2Cl_2 = 1:1, R_f = 0.3); 47% yield; mp 84–90 °C; $[\alpha]^{22}_D$ +214.5° (*c* 0.667, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.20–1.44 (m, 6 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 2.25 (t, *J* = 4.5 Hz, 4 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 6 H), 4.02–4.17 (m, 1 H), 4.17–4.28 (m, 1 H), 4.38 (q, *J* = 6.9 Hz, 1 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 8.57 (s, 1 H); IR (KBr) 3450, 3100, 2948, 2840, 1605, 1580, 1508, 1378, 1360, 1250, 1170, 1107, 1035, 1000, 820 cm^{-1}. Anal. Calcd for $C_{32}H_{37}FeNO_3$: C, 71.24; H, 6.91; N, 2.60. Found: C, 70.98; H, 7.11; N, 2.73.

General Procedure for the Enantioselective Addition of Dialkylzinc Reagents to *o*-Phthalaldehyde in the Presence of Chiral 1,2-Disubstituted Ferrocenyl Amino Alcohols. To a mixture of chiral 1,2-disubstituted ferrocenyl amino alcohol (**1–4**) (0.048 mmol) and *o*-phthalaldehyde (129 mg, 0.962 mmol) in hexane (3 mL) was added dialkylzinc (1.2 mmol, about 1 M hexane solution) at rt. The whole was stirred at rt for 1–3 h. Aqueous HCl (1 N) was added under cooling with ice–water. The resulting mixture was extracted with ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by TLC on silica gel (CH_2Cl_2–ether, 5–6:1). The product was characterized by the ^{1}H NMR and IR spectra. The chiral 1,2-disubstituted ferrocenyl amino alcohol was recovered in over 90% yield from the aqueous acid solution by making it alkaline with concd aqueous NaOH followed by extraction with ether.

3-Ethyl-2-oxaindan-1-ol (6a): mp 62–66 °C in 98% ee; $[\alpha]^{22}_D$ +49.2° (*c* 1.03, C_6H_6) in 98% ee [lit.[3a] $[\alpha]_D$ −42.6° (*c* 5.35, C_6H_6) for the enantiomer in 88% ee]; R_f = 0.50 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 1.5 H), 1.00 (t, *J* = 7.1 Hz, 1.5 H), 1.46–2.25 (m, 2 H), 3.36 (br d, *J* = 7.5 Hz, 0.5 OH), 3.47 (br d, *J* = 7.5 Hz, 0.5 OH), 5.12 (t, *J* = 5.0 Hz, 0.5 H), 5.25–5.52 (m, 0.5 H), 6.28–6.60 (m, 1 H), 7.02–7.60 (m, 4 H); IR (KBr) 3370, 3040, 2960, 2940, 2880, 1610, 1460, 1360, 990, 910, 755 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.43; H, 7.38.

(3*R*)-3-*n*-Butyl-2-oxaindan-1-ol (6b): oil; $[\alpha]^{22}_D$ +42.7° (*c* 1.43, C_6H_6) in 94% ee [lit.[3a] $[\alpha]_D$ −36.9° (*c* 3.47, C_6H_6) for 3*S* isomer in 87% ee]; R_f = 0.60 (CH_2Cl_2–ether, 6:1); ^{1}H NMR (CCl_4)[10] δ 0.91 (br s, 3 H), 1.08–2.00 (m, 6 H), 3.70 (br s, OH), 5.02 (t, *J* = 4.5 Hz, 0.5 H), 5.10–5.40 (m, 0.5 H), 6.12–6.43 (m, 1 H), 6.90–7.48 (m, 4 H); IR (neat) 3370, 3030, 2930, 2860, 1600, 1460, 1350, 1180, 1110, 990, 750 cm^{-1}.

Dimer 9: R_f = 0.90 (CH_2Cl_2–ether, 6:1, silica gel); ^{1}H NMR ($CDCl_3$)[10] δ 0.94 (br s, 6 H), 1.10–2.25 (m, 12 H), 5.15 (t, *J* = 6.0 Hz, 0.6 H), 5.29–5.58 (m, 1.4 H), 6.37–6.76 (m, 2 H), 6.97–7.70 (m, 8 H).

Determination of the Optical Purity of 3-Alkyl-2-oxaindan-1-ols (6). 3-Alkyl-2-oxaindan-1-ol (**6**) (20–30 mg) was reduced with $NaBH_4$ (3 equiv) in ethanol (1 mL) at 0 °C for 10 min. Water was added, and the resulting mixture was extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by TLC on silica gel gave 1-[2-(hydroxymethyl)phenyl]alkanol (**8**) in over 90% yield.

1-[2-(Hydroxymethyl)phenyl]propanol (8a): mp 53–56 °C in 98% ee; $[\alpha]^{22}_D$ +18.4° (*c* 0.870, $CHCl_3$) in 98% ee, which was determined by HPLC analysis: chiral column, Chiralcel OB, 4.6 × 250 mm; detection, 254-nm light; eluent, 6% 2-propanol in hexane; flow rate, 0.20 mL/min; t_R (min), 33.0 and 40.9; R_f = 0.30 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3 H), 1.58–2.05 (m, 2 H), 3.24 (br s, 2 H), 4.63 (d, *J* = 2.0 Hz, 2 H), 4.76 (t, *J* = 7.0 Hz, 1 H), 7.07–7.55 (m, 4 H).

(*R*)-1-[2-(Hydroxymethyl)phenyl]pentanol (8b): mp 72–73 °C in 94% ee; $[\alpha]^{22}_D$ +21.5° (*c* 0.805, $CHCl_3$) [lit.[2a] mp 73–74 °C; $[\alpha]_D$ −27° (*c* 1.07, $CHCl_3$), recrystallized from CH_2Cl_2 and petroleum ether] in 94% ee, which was determined by HPLC analysis: conditions of HPLC analysis were the same as mentioned as above except for using 4% 2-propanol in hexane as eluent; t_R (min), 46.8 and 56.0; R_f = 0.40 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.4 Hz, 3 H), 1.03–2.08 (m, 6 H), 3.09 (br s, 2 H), 4.65 (d, *J* = 2 Hz, 2 H), 4.85 (t, *J* = 6.8 Hz, 1 H), 7.10–7.65 (m, 4 H).

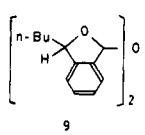
Optically Active 3-Ethyl- and 3-*n*-Butylphthalides (7a and 7b) were obtained by oxidation of the corresponding lactols **6a** and **6b** with silver oxide according to the reported procedure.[8] The compounds were purified by Kugelrohr distillation at 150–170 °C (1 mmHg) for **7a** and at 160–190 °C (1 mmHg) for **7b**.

3-Ethylphthalide (7a): yield, 58 mg (81%); $[\alpha]^{22}_D$ +76.9° (*c* 1.47, $CHCl_3$) in 98% ee; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3 H), 1.55–2.40 (m, 2 H), 5.45 (dd, *J* = 4.4 Hz, 7.5 Hz, 1 H), 7.32–8.03 (m, 4 H); IR (neat) 3050, 2970, 1758, 1610, 1595, 1460, 1280, 1060, 960 cm^{-1}.

(*R*)-3-*n*-Butylphthalide (7b): yield, 71 mg (80%); $[\alpha]^{22}_D$ +62.7° (*c* 1.20, $CHCl_3$) in 94% ee [lit.[2a] $[\alpha]_D$ −57° (*c* 1.96, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.10–2.30 (m, 6 H), 5.48 (dd, *J* = 4.2 Hz, 6.9 Hz, 1 H), 7.30–8.10 (m, 4 H); IR (neat) 3080, 2960, 1760, 1610, 1595, 1463, 1282, 1208, 1060, 720, 695 cm^{-1}.

Registry No. **3**, 137333-73-4; **4**, 137333-74-5; **5**, 643-79-8; **6a**, 75141-86-5; **6b**, 75141-85-4; (*R*)-**7a**, 137333-66-5; (*S*)-**7a**, 137333-67-6; (*R*)-**7b**, 125412-70-6; (*S*)-**7b**, 3413-15-8; (*R*)-**8a**, 137333-68-7; (*S*)-**8**, 137333-69-8; (*R*)-**8b**, 137333-70-1; (*S*)-**8b**, 137333-71-2; **9**, 137333-72-3; (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane, 132644-66-7; 4,4′-dichlorobenzophenone, 90-98-2; 4,4′-dimethoxybenzophenone, 90-96-0.

(10) When the lactol **6b** was dissolved in $CDCl_3$, the solution soon became turbid and the hydroxy peak in the ^{1}H NMR spectrum gradually disappeared, probably owing to the presence of a trace of acid, to form the dimer **9**.



9

Quinolone Antibacterials: A Hydroxymethylation–Intramolecular Cyclization Route to Pyrido[3,2,1-*ij*]-1,3,4-benzoxadiazines

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Of the many structural variations of quinolone antibacterials examined to date, the incorporation of the N-1-α carbon atom into a ring joined at position 8 continues to show great promise. The prototype flumequine (FLU, Figure 1) contains an all carbocyclic bridge and was the first clinically useful quinolone possessing a 1,8-bridge. From this, a number of modifications of the 1,8-bridge ensued,[1] including replacement of carbon with heteroatoms,[2–4] variations of ring size[5] and substituents,[1] and stereocontrol of chiral centers within the bridge.[6–9]

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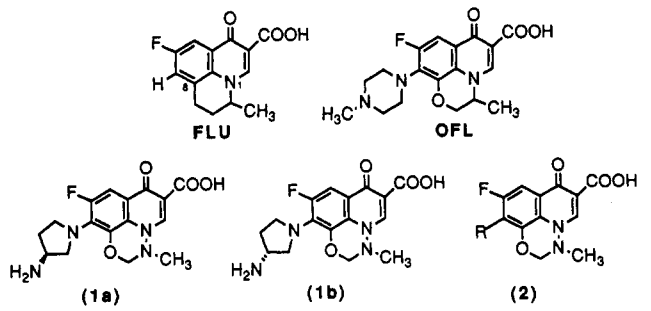


Figure 1.

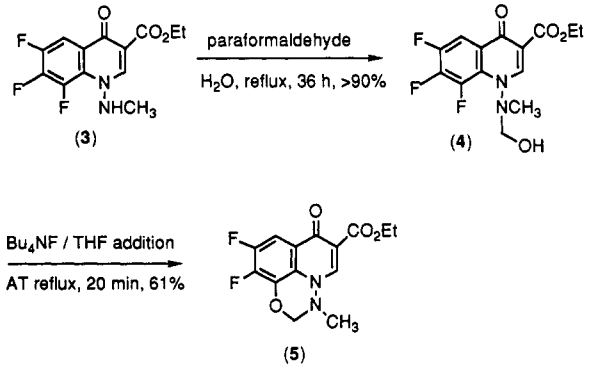
Ofloxacin (OFL, Figure 1), more specifically the (*S*)-(−) isomer DR-3355, is today's dominant 1,8-bridged quinolone owing to its excellent potency both in vitro and in vivo and good pharmacokinetic properties.[10,11]

Pyrido[3,2,1-*ij*]-1,3,4-benzoxadiazines **2** (Figure 1) are analogues in which the N-1-α carbon is replaced by a nitrogen atom and are among the most potent 1,8-bridged quinolones.[12] To date, two synthetic strategies have been used to construct the oxadiazine ring from a quinolone intermediate.[13-15] In one approach, a difluoroaminophenol was subjected to modified Gould–Jacobs cyclization[16] to afford an 8-hydroxyquinolone which was then aminated at N-1 and ultimately cyclized via the net addition of one carbon unit upon treatment with paraformaldehyde. An improved route entailed a cycloaracylation process[17] to afford a trifluoroquinolone upon which the C-7 amd C-8 substituents were sequentially added. While a piperazine or pyrrolidine commonly found in quinolone antibacterials readily displaced fluoride at C-7, benzyl alkoxide was needed to displace fluoride and to serve as a latent hydroxyl group at C-8.[18] In both of these strategies, the presence or introduction of the 8-oxa substituent demands additional manipulations which complicate these syntheses.

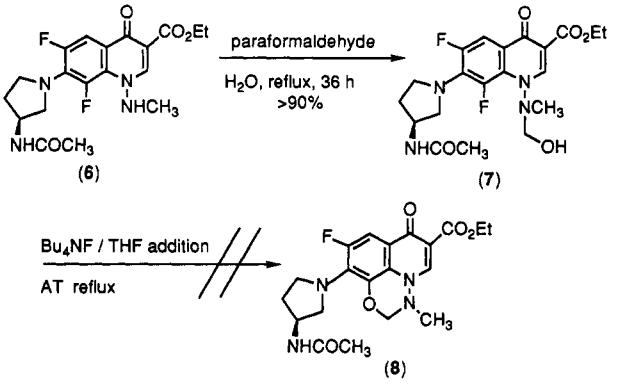
Results and Discussion

We wish to report a novel "hydroxymethylation–intramolecular cyclization" process which provides direct and facile oxadiazine ring formation en route to 8-oxa-1,8-bridged quinolones. The intermediate N-hydroxymethylated quinolones are a new class of compounds found to be isolable, stable to storage, and easy to handle. This is noteworthy since formaldehyde addition to amines often leads to other processes which preclude isolation of hydroxymethylamines (further addition of formaldehyde, polymerization, dehydration, loss of formaldehyde upon isolation, etc.). The weakly basic and poorly nucleophilic nature of the N-1-amino group[19,20] may be responsible for the ease of isolation of our intermediates. In our strategy, the need for amination, the need for hydroxyl-group equivalents, and the need for protecting group manipulations are eliminated. We have used this chemistry to construct quinolone antibacterials **1a** and **1b** containing optically active C-7 aminopyrrolidine substituents.

Scheme I



Scheme II



6,7,8-Trifluoro-1-(methylamino)quinolone[15] **3** (Scheme I) was suspended with excess paraformaldehyde in water. Upon heating, the mixture became homogeneous and the product (**4**) could be isolated in excellent yield. Nonaqueous conditions gave mixtures of starting material and product, which although separable, were considered unsatisfactory. Gaseous formaldehyde, produced from the thermolysis of paraformaldehyde, also gave hydroxymethylated product upon workup, but in low yields isolated from complex reaction mixtures.

With hydroxymethylated quinolone **4** in hand, ring closure was attempted using a variety of basic conditions (NaH/THF or dioxane, low temperature to reflux; BuLi/THF, low temperature to rt; KF/CH_3CN) but only deformylated product **3** and/or starting material along with a dark tarry residue were observed. Interestingly, basic conditions (NaH, dioxane) have been used to induce the analogous cyclization to an oxazine bridged ofloxacin precursor when treatment with fluoride (KF) was unsuccessful.[17] Previous work[21] suggested that tetrabutylammonium fluoride in THF may be effective in inducing cyclization of **4**. Accordingly, our early attempts consisted of a reflux period of hours and gave low yields of complex mixtures from which the desired product could be identified. Optimum conditions required *the addition of tetrabutylammonium fluoride to a THF solution of hy-*

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(18) In our hands, simple hydroxide introduction at C-8 of 6,7,8-trifluoro-1-(methylamino)quinolone was not possible as displacement of the C-7 fluoride occurred and/or ester cleavage to the C-3 carboxylate rendered the aromatic system inert to reaction at C-8.
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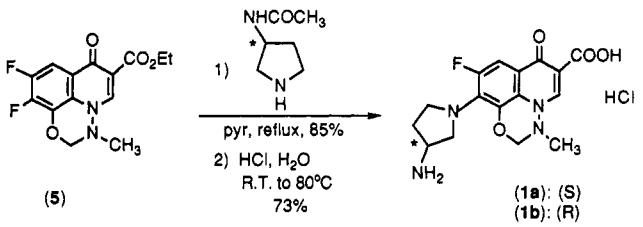
Scheme III



droxymethylated quinolone 4 at reflux under anhydrous conditions. In doing so, we were able to isolate the desired product **5** in good yield providing reaction times were kept short (Scheme I).

We attempted cyclization on a substrate in which the C-7 pyrrolidine was introduced prior to our hydroxymethylation–cyclization sequence (Scheme II). Pyrrolidine displacement of fluoride at C-7 occurred smoothly as reported,[15] and reaction with paraformaldehyde as previously described afforded hydroxymethylated quinolone **7** in excellent yield. However, all attempts to induce cyclization under the conditions successful for the trifluoro analogue **4** led only to deformylation (**6**) and tar formation. Apparently, the presence of the amino substituent at C-7 renders the aromatic system inert to fluoride-induced cyclization (as well as C-8 displacements in general[17]) via its electron-donating properties and/or its steric bulk.

With cyclized product **5** in hand, we were able to introduce either (*S*)- or (*R*)-3-aminopyrrolidine at C-7 to afford quinolone antibacterials **1a** and **1b**. Both pyrrolidines were prepared according to literature methods[22,23] and readily displaced fluoride at C-7 upon heating in pyridine.[15] Treatment of the corresponding adducts with aqueous acid accomplished removal of the amino *t*-Boc protecting group as well as ester cleavage as reported,[13-15] giving the final products **1a** and **1b** (Scheme III).

Experimental Section

6,7,8-Trifluoro-1,4-dihydro-1-[(hydroxymethyl)methylamino]-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (4). Ethyl 1-(Methylamino)-4-oxo-6,7,8-trifluoro-1,4-dihydro-3-quinoline carboxylate (**3**) (4.5 g, 15.0 mmol) and paraformaldehyde (20 g) were added to water (750 mL). The resulting heterogeneous mixture was heated at reflux for approximately 36 h and then cooled. The product was extracted into chloroform (3×) and the combined organic extracts were washed with water (2×). The organic solution was dried over magnesium sulfate and the solvent removed via rotary evaporation. The off-white solid obtained was further dried by vacuum pump to afford pure hydroxymethylated quinolone **4** (4.5 g, 90%): mp 138–139 °C; NMR (ppm, $CDCl_3$) 8.89 (s, 1 H, vinylic), 7.43 (ddd, J = 2,7,10 Hz, 1 H, aromatic), 5.90 (app t, 1 H, OH), 5.24 (AB dd, 1 H, NCH_2O), 4.60 (AB dd, 1 H, NCH_2O), 4.00–4.25 (m, 2 H, ester CH_2), 3.16 (s, 3 H, NMe), 1.32 (t, 3 H, CH_3); IR (cm^{-1}, $CHCl_3$) 3400 (b, OH), 2800–3050 (CH alkyl and aryl), 1730 (C=O ester), 1620 (C=O ketone); MS 330 (M^+), 312 ($M^+ - H_2O$), 300 ($M^+ - CH_2OH$).

3,7-Dihydro-9,10-difluoro-3-methyl-7-oxo-2*H*-pyrido[3,2,1-*ij*][1,3,4]benzoxadiazine-6-carboxylic Acid Ethyl Ester (5). The hydroxymethylated quinolone **4** (0.9 g, 2.72 mmol) was dissolved in dry tetrahydrofuran (205 mL) and heated to reflux as quickly as possible (<5 min). Tetrabutylammonium fluoride (6.0 mL of 1.0 M solution in THF, 6.0 mmol) was added as quickly as possible via syringe, and the mixture was heated at reflux for 22 min. After this time, the reaction mixture was poured into saturated sodium bicarbonate solution and the product was extracted into ethyl acetate (3×). The combined organic extracts were washed with brine solution and dried over sodium sulfate and the solvents removed by rotary evaporation. The remaining orange-brown oil was subjected to a silica gel plug (ethyl acetate) to obtain pure product as an off-white solid (434 mg). The plug was then "washed" with an ethyl acetate/methanol (3:1) solution to afford a tan residue from which more product was obtained via trituration with ethyl ether (85 mg). The total amount of pure product **5** isolated was 0.52 g, which represents a 61% yield: mp 274 °C dec; NMR (ppm, $CDCl_3$) 8.46 (s, 1 H, vinylic), 7.84 (dd, J = 7, 10 Hz, 1 H, aromatic), 5.12 (bs, 2 H, methylene), 4.40 (q, 2 H, CH_2), 3.05 (s, 3 H, NMe), 1.41 (t, 3 H, CH_3); ^{19}F NMR (ppm, $CHCl_3$) 151.0, 135.8; IR (cm^{-1}, $CHCl_3$) 2800–3050 (CH alkyl and aryl), 1720 (C=O ester), 1620 (C=O ketone); MS 310 (M^+), 265 ($M^+ - OEt$), 238 ($M^+ - CO_2Et$).

(*S*)-7-[3-(Acetylamino)-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-1-[(hydroxymethyl)methylamino]-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (7). (*S*)-7-[3-(Acetylamino)-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-1-(methylamino)-4-oxo-3-quinolinecarboxylic acid ethyl ester (**6**) (0.70 g, 1.71 mmol) and paraformaldehyde (2.3 g) were added to water (80 mL). The resulting heterogeneous mixture was heated at reflux for approximately 30 h and then cooled. The product was extracted into chloroform (3×), and the combined organic extracts were washed with water (2×). The organic solution was dried over magnesium sulfate and the solvent removed via rotary evaporation. The yellow solid obtained was further dried by vacuum pump to afford hydroxymethylated quinolone **7** (0.68 g, 90%): mp >150 °C dec; NMR (ppm, $CDCl_3$) 8.76 (s, 1 H, vinylic), 7.49 (d, 1 H, aromatic), 7.05 (d, 1 H, NH), 6.12 (bs, 1 H, OH), 5.20 (bs, 1 H, NCH_2O), 4.55 (bm, 2 H, NCH_2O and CHNHAc), 4.20–4.40 (m, 2 H, ester CH_2), 3.50–4.00 (4 H, pyrrolidinyl CH_2s), 3.10 (s, 3 H, NMe), 1.90–2.30 (m, 2 H, pyrrolidinyl CH_2), 2.07 (s, 3 H, CH_3), 1.38 (t, 3 H, CH_3); IR (cm^{-1}, $CHCl_3$) 3440 (NH), 3330 (b, OH), 2800–3050 (CH alkyl and aryl), 1720 (C=O ester), 1670 (C=O amide), 1610 (C=O ketone); MS 408 ($M^+ - CH_2O$), 379 ($M^+ - MeC(O)NH_2$), 320 ($M^+ - MeNCH_2OH$).

Acknowledgment. We wish to thank Dr. I. Kompis and his colleagues at Roche Basle along with Dr. D. D. Keith and Dr. M. Weigele at Roche Nutley for their help during the course of these studies. We are also thankful to Ms. BettyAnn Hedemus for the preparation of this manuscript.

Registry No. **1a**, 137435-04-2; **1a** free base, 137435-05-3; **1b**, 137435-06-4; **1b** free base, 137435-07-5; **3**, 100276-66-2; **4**, 137435-08-6; **5**, 137435-09-7; **6**, 137435-10-0; **7**, 137435-11-1; (*S*)-3-(acetylamino)pyrrolidine, 114636-31-6; (*R*)-3-(acetylamino)pyrrolidine, 131900-62-4.

Supplementary Material Available: NMR spectra of **3**, **4**, and **5** (5 pages). Ordering information is given on any current masthead page.

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Synthesis of Hydrophenaleno[1,9-*bc*]thiophenes and [2]Metacyclo[2](2,4)thiophenophane

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We have recently reported that metacyclo[2](2,3)-, -(2,4)-, -(2,5)-, and -(3,4)thiophenophane derivatives were prepared from the corresponding dithia[3]metacyclo[3]thiophenophanes.[1] However, except for the (2,5)phane system, unsubstituted parent compounds could not be obtained by this method. This result prompted us to try

(1) Takeshita, M.; Tashiro, M. *J. Org. Chem.* **1991**, *56*, 2837.

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