H-5α), 2.94 (1 H, dd, J = 10.5, 2.2 Hz, H-7α), 3.00 (1 H, dd, J = 10.5, 2.4 Hz, H-7β), 3.07 (1 H, dd, J = 15.9, 2.2 Hz, H-14α), 3.14 (1 H, dddd, J = 7.8, 2.4, 2.2, 0.5 Hz, H-6), 3.21 (1 H, ddd, J = 13.2, 3.7, 2.7 Hz, CHNH), 3.43 (1 H, ddd, J = 13.2, 7.8, 2.9 Hz, CHNH), 3.54 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 3.84 (1 H, dd, J = 2.9, 2.9 Hz, H-9), 3.88, 3.88, 3.89 (each 3 H, s, OCH_3), 4.08 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 6.67 (1 H, dd, J = 7.8, 3.7 Hz, NH); MS, m/z (relative intensity) 625 (M^+, 0.2), 525 (100), 276 (12), 234 (10).

Methylation of 41. Etheral diazomethane solution (0.5 mL) was added dropwise to a cooled (0 °C) solution of **41** (5.9 mg, 0.016 mmol) in dry ether (0.5 mL), and the reaction mixture was kept at the same temperature for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with water, dried, and concentrated in vacuo to obtain **40** (4.9 mg, 81.3%) as pale yellow needles, mp 203–205 °C dec, which were identical in all respects with **40** prepared as above.

Acknowledgment. We are grateful to Professor Tadashi Arai of Chiba University for his encouragement and for a sample of natural saframycin B. We are also indebted to Professor Shin-ichiro Sakai and Dr. K. Ogata of Chiba University for X-ray crystallographic determination of compounds **26** and **32**.

Supplementary Material Available: Tables of X-ray structural data of **26** and **32** (46 pages). Ordering information is given on any current masthead page.

Naphtho[2,1-*b*]thiophene-Linked 1,2-Dithia-5,8-diazacyclodecanes and Imidazolidino[1,2-*d*]dithiazepines: Synthesis, Structure Proof by X-ray Diffraction Analysis, and DNA Binding Properties

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Coupling of the metal-sequestering ligand 3,3,10,10-tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane with naphtho[2,1-*b*]thiophene-3-carboxylic acid in the presence of carbonyldiimidazole affords the ester and the 5,6-cyclic carbamate. The structure of the latter was secured and the conformation deduced from single-crystal X-ray diffraction. Similar reaction of 1,1,4,4-tetramethyl-8-(hydroxymethyl)imidazolidino[1,2-*d*]dithiazepine with the intercalative chromophore naphtho[2,1-*b*]thiophene affords the desired ester in addition to the 8,9-cyclic carbamate of the bicyclic disulfide compound. Both 7- and 8-substituted imidazolidino[1,2-*d*]dithiazepines react with tetrahydrofuran in the presence of the ether peroxide to afford the 9-(2-tetrahydrofuranyl) derivatives in a reaction that is analogous to recent anodic oxidation studies of amidyl anions in THF. The structure of a THF adduct was confirmed by X-ray diffraction analysis. The prototype sulfur ligand structures linked to the naphtho[2,1-*b*]thiophene chromophore **2** and **5** bind to double-helical DNA with binding constants of 4.3×10^6 and 3.6×10^6 M^{-1}, respectively.

The glycopeptide antitumor antibiotic bleomycin appears to act by a unique mechanism involving the site-selective binding to double-stranded DNA and oxygen-mediated scission of the strands catalyzed by the hexacoordinated iron binding domain thus brought into proximity with sensitive sites.[1,2,4-6]

Functional bleomycin models, in which the operational properties of the natural product are retained, were designed, synthesized, and tested.[7-10] Prototype structures, i.e., hemin–spermine–chromophores, reproduce many of the essential features of the natural glycopeptide in producing oxygen-mediated DNA scission in the presence of a thiol reducing agent, e.g., dithiothreitol or 2-mercaptoethanol, and at concentrations comparable with those employed with bleomycin itself.[7,8,10] The intercalative chromophores employed in the prototype structures (acridine, acodazole, naphtho[1,2-*b*]thiophene, and stilbene) resulted, as expected, in smooth and base-neutral cleavage at every base pair of test DNA sequences such as a 139 base pair HindIII/NciI fragment of pBR322.[10]

We are now exploring alternative metal-sequestering groups in addition to the porphyrins. Accordingly, we report the synthesis of structures in which both 1,2-dithia-5,8-diazacyclodecanes[11-14] and related imidazolidino-[1,2-*d*]dithiazepines[15] are linked to DNA intercalative naphtho[2,1-*b*]thiophene chromophores and initial exploration of their properties, including facile reversible aminol formation in the presence of tetrahydropyranyl hydroperoxide. We also describe the structural verification of key derivatives by X-ray diffraction and DNA binding studies of the final agents.

* Author to whom inquiries should be addressed.

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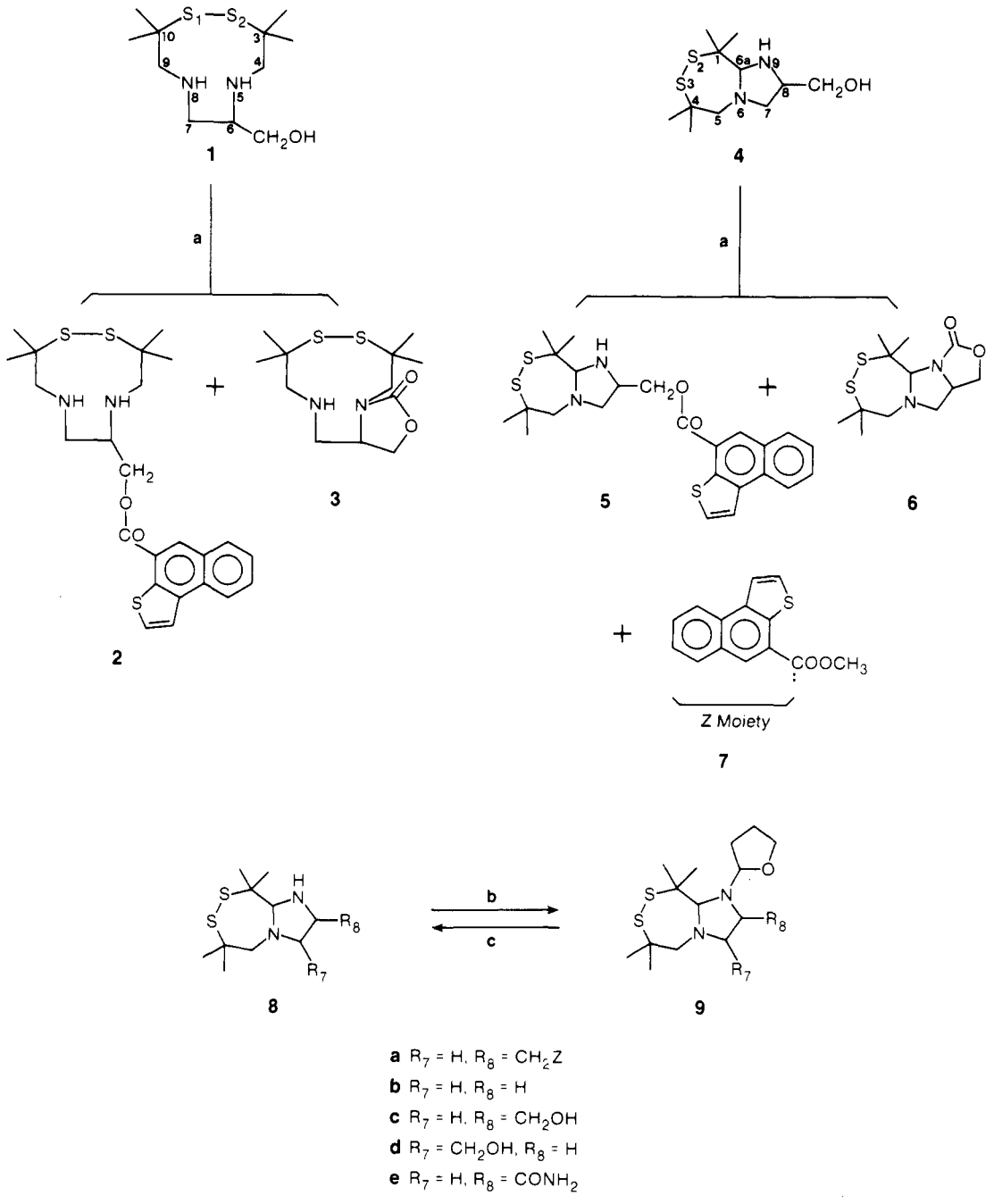
0022-3263/88/1953-4310$01.50/0

Scheme I[a]



[a] Reaction conditions: (a) naphtho[1,2-*b*]thiophene-4-carboxylic acid, carbonyldiimidazole, DMF, MeOH, at room temperature, 6 h; (b) undistilled THF, reflux, 6 h; (c) silica gel column chromatography.

Synthesis and Chemical Reactivity

Reaction of 3,3,10,10-tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane (**1**)[15] with naphtho[2,1-*b*]thiophene-3-carboxylic acid[16] in the presence of 1 equiv of carbonyldiimidazole in DMF affords the linked structure **2** in 57% yield (Scheme I). If greater than 1 equiv of the condensing agent is used, the cyclic carbamate **3** is also isolated in addition to **2**. The structure of **3** was confirmed by X-ray diffraction (vide infra).

Similarly, reaction of 1,1,4,4-tetramethyl-8-(hydroxymethyl)imidazolidino[1,2-*d*]dithiazepine[15] with naphtho-[2,1-*b*]thiophene-3-carboxylic acid in the presence of carbonyldiimidazole affords the linked structure **5** in 47% yield. Again when an excess of the condensing agent carbonyldiimidazole is used, the cyclic carbamate **6**[15] is isolated in addition to the desired linked structure **5**, and when methanol is present, some ester **7** is also obtained.

The relationship between the 1,2-dithia-5,8-diazacyclodecane **1** and the imidazolidino[1,2-*d*]dithiazepine **4** is that we have recently shown that both products result from the sodium borohydride reduction of 1,2-dithia-5,8-diazacyclodeca-4,8-dienes.[15]

The imidazolidino[1,2-*d*]dithiazepine structures display an unusual and facile reversible coupling with ethers under certain conditions. Treatment of structures **8** containing the imidazolidino[1,2-*d*]dithiazepine moiety with tetra-

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hydrofuran resulted in the incorporation of 1 equiv of THF to afford compounds **9**. The compositions of the latter were established by spectroscopic evidence, and, in one case, the structure was secured by X-ray diffraction (vide infra). This latter evidence confirms that the THF moiety is linked via carbon-2 to the N-9 position in an aminol link. The reaction appears to be general in that both 7- and 8-substituted imidazolidino[1,2-*d*]dithiazepines (**8d** and **8a,c**) react with THF containing its peroxide to afford structures **9d**, **9a**, and **9c**, respectively. The exception is the 8-amide derivative **8e**, which, like structure **1**, fails to react under these conditions.

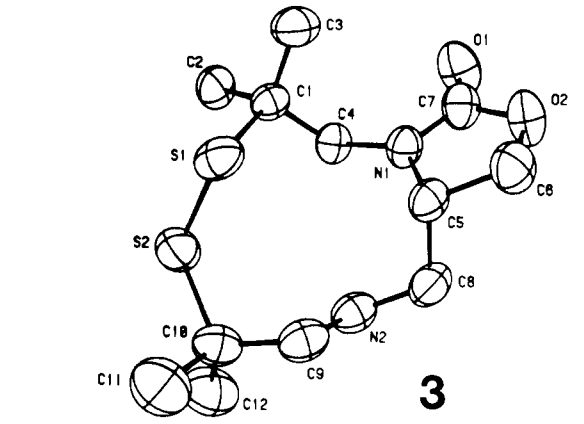
The formation of the THF adducts was studied by using **8b** as a reference compound. The disappearance of **8b** and conversion to **9b** were monitored by TLC on silica plates, employing 10:1 $CHCl_3$:MeOH as eluent. THF containing the hydroperoxide readily converts **8b** to **9b** either under nitrogen or when exposed to air. In contrast, no reaction of **8b** was observed with purified THF (i.e., distilled over sodium metal in the presence of benzophenone under an atmosphere of argon or from lithium aluminum hydride) either under nitrogen or under aerobic conditions. No reaction with purified THF was observed even after refluxing and allowing the solution to be exposed to air for 12 h. The addition of the metal ion sequestering agent diethylenetriaminepentaacetic acid has no effect on the course of the reactions; i.e., it does not prevent formation of **9b** by reaction with THF hydroperoxide nor alter the course of the reaction with purified THF.

The results suggest conversion of compounds **8** to **9** involves THF hydroperoxide, and there is no evident involvement of either atmospheric oxygen nor influence of chelated metal ions in the conversion of **8** to **9**. This reaction may be of significance in the application of cyclic disulfide agents in tumor imaging (SPECT) since it appears that several of the agents formerly assigned the 1,2-dithia-5,8-diazacyclodecane structures[12-14] are, in fact, imidazolidino[1,2-*d*]dithiazepines.[15] The facile coupling of THF hydroperoxide to position N-9 in **8** is analogous to the recent report of anodic oxidative amination of tetrahydrofuran which affords 2-aminotetrahydrofurans.[17]

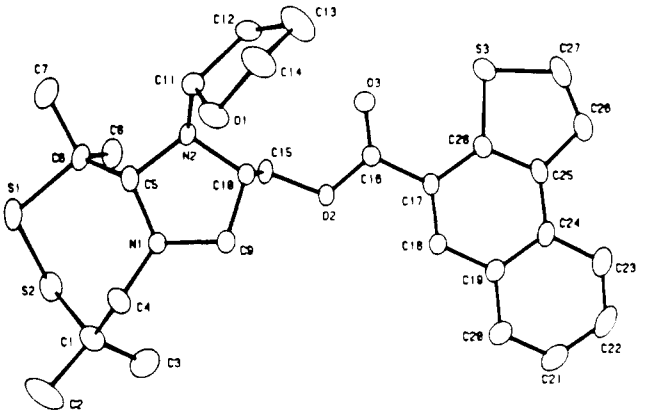
Single-Crystal X-ray Determination of Structure for the 5,6-Cyclic Carbamate of 3,3,10,10-Tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane (3) and [9-(2-Tetrahydrofuranyl)-1,1,4,4-tetramethylimidazolidino[1,2-*d*]dithiazepin-8-yl]methyl Naphtho[1,2-*b*]thiophenecarboxylate (9a)[18]

Drawings of the two structures are shown in Figure 1. The structural results on **3** clearly show the bicyclic nature of the carbamate derivative. Similarly, the X-ray diffraction results on structure **9a** clearly show the incorporation of the 2-tetrahydrofuranyl moiety at N-9 of the imidazolidino[1,2-*d*]dithiazepine.

Structure **9a** possesses a trans ring junction, as expected from the anti transannular addition to the imine bond in the 1,2-dithia-5,8-diazacyclodeca-4,8-diene from which it



3



9a

Figure 1. Perspective drawings of (a) **3** and (b) **9a** determined by crystallographic analysis, showing the atomic numbering scheme used. The atoms are represented by ellipsoids[21] at the 50% level in (a) and 20% in (b). In both drawings the hydrogen atoms have been omitted for clarity.

is formed.[15] The ester function bearing the naphtho[2,1-*b*]thiophene moiety is oriented trans to the bridgehead hydrogen at **6a** and is aligned pseudoequatorially. As a consequence the moiety at N-9 adopts a conformation trans to the ester function, although, as noted in the Experimental Section, the ^1H NMR spectra of **8** and **9** obtained preparatively indicated ca. 50:50 mixtures of cis and trans stereoisomers in each case.

Interaction of 2 and 5 with DNA

Compounds **2** and **5** bind to double-helical calf thymus DNA with approximate binding constants of 4.3×10^6 and 3.6×10^6 M^{-1}, respectively. These values are comparable with that of naphtho[2,1-*b*]thiophene-3-carboxylic acid (3.2×10^6 M^{-1}), and since neither **1** nor **4** binds to DNA, these data suggest intercalative binding of **2** and **5** via the naphtho[2,1-*b*]thiophene chromophore. The values of the binding constants are comparable with those found for the prototype functional bleomycin models, which are porphyrin–spermine agents bearing intercalative chromophores of 2-methoxy-7-chloro-9-aminoacridine, 7-methyl-9-aminoimidazole[4,5-*f*]quinoline, aminostilbene, and naphtho[2,1-*b*]thiophene-3-carboxyl, respectively.[7-9]

Biological evaluation of these compounds and their metal ion chelates will be reported elsewhere.

Experimental Section

Diethylenetriaminepentaacetic acid (97%) was from Aldrich Chemical Co., Milwaukee, WI. THF was HPLC grade (without inhibitor) from Caledon Laboratories Ltd., Georgetown, Ontario, and was purified, when necessary, by decomposition of peroxides

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(18) The X-ray crystallographic studies were carried out by Dr. R. G. Ball at the Structure Determination Laboratory, Department of Chemistry. Enquiries regarding the crystallographic results should be directed to the above address, quoting report numbers SR 121523-01-86 and 121523-05-86. (a) The diffractometer programs are those supplied by Enraf-Nonius for operating the CAD4F diffractometer with some local modifications and additions. (b) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. MULTAN 11/82. Other programs used during structure refinement and analysis are part of the Enraf-Nonius Structure Determination Package by: Frenz, B. A. *Computing in Crystallography*; Delft University Press: Delft, Holland, 1978; pp 4–71.

by lithium aluminum hydride and subsequent distillation from LAH.

Melting points are uncorrected. The ^1H NMR spectra were recorded on approximately 5–15% (w/v) solutions, in appropriate deuteriated solvents. Double-focusing high-resolution mass measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kieselgel 60 DC-Alufolien F_{254} (Merck, West Germany) and Eastman Kodak precoated sheets were used for thin-layer chromatography. In the workup procedures reported, solvents were removed with a rotary evaporator under reduced pressure without heating. Kieselgel (Fluka, Switzerland) was used for column chromatography.

Condensation of 3,3,10,10-Tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane with Naphtho[2,1-*b*]thiophene-3-carboxylic Acid. Naphtho[2,1-*b*]thiophene-4-carboxylic acid[16] (228 mg, 1 mmol) and carbonyldiimidazole (227 mg, 1.4 mmol) were dissolved in dry DMF (10 mL), and the solution was stirred for 6 h at room temperature. 3,3,10,10-Tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane (**1**)[15] (268 mg, 1 mmol) was added, and the mixture was stirred at room temperature for 20 h. Methanol (5 mL) was then added and the solvents were removed in vacuo at 80 °C. The residue was subjected to chromatography over silica gel, and elution with $CHCl_3$ afforded naphtho[2,1-*b*]thiophene-3-carboxylic acid methyl ester (**7**)[16] (10% yield). Further elution with $CHCl_3$ gave the bicyclic carbamate **3**, which was recrystallized from $CHCl_3$/hexane: 28 mg (yield 10%); mp 128 °C; ^1H NMR ($CDCl_3$) δ 1.30 (d, 12 H, 4 × CH_3), 1.55 (s, 1 H, exch, NH), 2.55 (d, 1 H), 2.80 (dd, 1 H), 3.10 (m, 2 H), 3.45 (d, 1 H), 3.75 (q, 1 H), 4.35 (t, 1 H), 4.80 (m, 1 H), 4.95 (d, 1 H); IR ($CHCl_3$) ν_{max} 3330 (NH), 1742 cm^{-1} (NCOO); MS *m/z* (relative intensity) 292.1099 (10.39, M^+ + 2), 291.1159 (16.27, M^+ + 1), 290.1126 (100.0, M^+) (calcd for $C_{12}H_{22}N_2S_2O_2$, 290.1130), 226.1668 (8.61, $M^+ - S_2$), 225.1606 (20.01, *m/z* 226,1668 – H), 183.1135 (27.26, *m/z* 225.1606 – C_3H_8), 99.0320 (2.85, $C_4H_5NO_2$).

Further elution with 80:20 $CHCl_3$:MeOH gave **2** as a white solid, which was recrystallized from $CHCl_3$/hexane: 270 mg (yield 57%); mp 133 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, 6 H, 2 × CH_3), 1.35 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.25 (bs, 2 H, NH exch), 2.45, 2.72 (d, 1 H), 2.76–2.95 (m, 3 H), 3.08 (m, 1 H), 3.30 (m, 2 H), 4.45 (q, 2 H), 7.62 (t, 1 H, Ar), 7.80 (m, 2 H, Ar), 8.05 (m, 2 H, Ar), 8.40 (d, 1 H, Ar), 8.65 (d, 1 H, Ar); IR ($CHCl_3$) ν_{max} 1705 cm^{-1} (OCO); MS *m/z* (relative intensity) 476.1459 (6.0, M^+ + 2), 475.1502 (8.52, M^+ + 1), 474.1475 (29.19, M^+) (calcd for $C_{24}H_{30}N_2S_3O_2$, 474.1469), 246.1224 (8.71, $M^+ - C_{13}H_8O_2S$), 228.0243 (100.0, $C_{13}H_{18}SO_2$), 211.0219 (*m/z* 228.0243 – OH), 183.0262 (51.85, $C_{12}H_7S$), 74.0183 (2.35, C_3H_6S).

Condensation of 1,1,4,4-Tetramethyl-8-(hydroxymethyl)-imidazolidino[1,2-*d*]dithiazepine with Naphtho[2,1-*b*]-thiophene-3-carboxylic Acid. Naphtho[2,1-*b*]thiophene-3-carboxylic acid[16] (228 mg, 1 mmol) and carbonyldiimidazole (227 mg, 1.4 mmol) were dissolved in dry DMF (15 mL), and the solution was stirred for 6 h at room temperature. The imidazolidino[1,2-*d*]dithiazepine **4**[15] (261 mg, 1 mmol) was added, and the solution was stirred at ambient temperature for 40 h. Methanol (5 mL) was added to the reaction mixture, and the solvents were removed in vacuo at 80 °C. The residue was subjected to chromatography over silica gel. Elution with 50:50 $CHCl_3$:hexane gave methyl naphtho[2,1-*b*]thiophene-3-carboxylate 7:121 mg (50% yield); mp 156 °C; ^1H NMR ($CDCl_3$) δ 4.12 (s, 3 H, CO_2CH_3), 7.60 (q, 1 H, Ar), 7.75 (m, 2 H, Ar), 8.05 (m, 2 H, Ar), 8.40 (d, 1 H, Ar), 8.64 (s, 1 H, Ar); IR ($CHCl_3$) ν_{max} 1710 cm^{-1} (ester); MS *m/z* (relative intensity) 243.0431 (16.19, M^+ + 1), 242.0399 (100.0, M^+) (calcd for $C_{14}H_{10}SO_2$, 242.0401), 211.0215 (47.42, $M^+ - OCH_3$), 183.0260 (41.53, $M^+ - CO_2CH_3$).

Further elution with 50:50 $CHCl_3$:hexane afforded a thick syrup that upon trituration with ether gave a white crystalline solid, which was collected and washed with ether to give **6**.[15] This product was purified by recrystallization from $CHCl_3$/ether: 29 mg (10% yield); mp 170 °C; ^1H NMR ($CDCl_3$) δ 1.2–1.64 (m, 12 H, 4 × CH_3), 2.6 (d, 1 H), 2.75 (q, 1 H), 3.35 (m, 2 H), 4.05 (m, 1 H), 4.15 (s, 1 H), 4.25 (q, 1 H), 4.5 (q, 1 H); IR ($CHCl_3$) ν_{max} 1751 cm^{-1} (NCOO); MS *m/z* (relative intensity) 290.0937 (1.38 M^+ + 2), 289.0998 (2.66, M^+ + 1), 288.0967 (10.41, M^+) (calcd for $C_{12}H_{20}N_2S_2O_2$, 288.0966), 214.0772 (100, $M^+ - C_3H_6S$), 140.0589 (60.07, $C_6H_8N_2O_2$).

After removal of the solvent from the filtrate, the residual thick syrup was dissolved in a minimum of ether, diluted with petroleum ether, and chilled. A white solid separated, which was recrystallized from ether/hexane to give compound **5**: 120 mg (yield 25%); mp 115 °C; ^1H NMR ($CDCl_3$) δ 1.18–1.50 (m, 12 H, 4 × CH_3), 2.25 (bs, 1 H, NH, exch), 2.60 (dd, 1 H), 2.85, 3.06 (dt, 1 H), 3.32 (t, 1 H), 3.45 (q, 1 H), 3.75 (d, m, 2 H), 4.50 (m, 2 H), 7.60 (m, 1 H, Ar), 7.76 (m, 2 H, Ar), 8.10 (m, 2 H, Ar), 8.40 (d, 1 H, Ar), 8.64 (s, 1 H, Ar); IR ($CHCl_3$) ν_{max} 1707 cm^{-1} (CH_2OCO); CIMS *m/z* (relative intensity) 475 (3.6, M^+ + 3), 474 (4.8, M^+ + 2), 473 (15.6, M^+ + 1), 472 (8.1, M^+). Anal. Calcd for $C_{24}H_{28}N_2S_3O_2$: C, 61.2; H, 5.9; N, 5.9; S, 20.3; O, 6.78. Found: C, 60.7; H, 6.0; N, 5.8; S, 20.5; O, 7.1.

When the condensation was conducted with 1.10 molar equiv of carbonyldiimidazole, **5** was obtained in 47% yield.

[9-(2-Tetrahydrofuranyl)-1,1,4,4-tetramethylimidazolidino[1,2-*d*]dithiazepin-8-yl]methyl Naphtho[2,1-*b*]thiophene-3-carboxylate (9a). A solution of **8a** (50 mg) in 50 mL of THF was heated under reflux for 2 h. The solvent was removed in vacuo and the residue treated with ether (5 mL). A white solid (**9a**) separated, which was collected and recrystallized from $CHCl_3$/ether: ~40 mg (yield 70%); mp 170 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, 6 H, 2 × CH_3), 1.34 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.88 (m, 2 H), 2.02 (m, 2 H), 2.56 (d, 1 H), 3.15 (t, 1 H), 3.24 (d, 1 H), 3.44 (d, 1 H), 3.70 (m, 1 H), 3.80 (q, s, 2 H), 3.96 (q, 1 H), 4.50 (m, 2 H), 4.86 (t, 1 H), 7.60 (t, 1 H, Ar), 7.86 (m, 2 H, Ar), 8.08 (ddd, 2 H, Ar), 8.40 (d, 1 H, Ar), 8.62 (s, 1 H, Ar); IR ($CHCl_3$) ν_{max} 1707 cm^{-1} (OCO); CIMS *m/z* (relative intensity) 545 (2.0, M^+ + 3), 544 (4.7, M^+ + 2), 543 (12.8, M^+ + 1), 471 (38.8, $M^+ - C_4H_7O$). Anal. Calcd for $C_{28}H_{34}N_2S_3O_3$: C, 61.9; H, 6.3; N, 5.2; S, 17.7; O, 8.9. Found: C, 61.5; H, 6.4; N, 5.1; S, 18.1.

The following tetrahydrofuranyl derivatives were similarly prepared by refluxing compounds in THF for 4 h, setting aside the solutions at room temperature for 12 h, and purifying by column chromatography over alumina using chloroform as eluent.

9b: 125 mg (yield 40%), oil; ^1H NMR ($CDCl_3$) δ 1.3 (m, 12 H, 4 × CH_3), 1.90 (m, 4 H), 2.6–4.05 (m, 9 H), 4.80 (t, 1 H); IR ($CHCl_3$) ν_{max} 1708 cm^{-1} (OCO); CIMS *m/z* (relative intensity) 305 (10.7, M^+ + 3), 304 (19.2, M^+ + 2), 303 (100.0, M^+ + 1).

9c: 152 mg (yield 25%), oil; ^1H NMR ($CDCl_3$) δ 1.10–2.0 (m, 16 H), 2.1–2.4 (b, 1 H, exch), 2.5 (dt, 0.5 H), 2.65 (d, 0.5 H), 2.78 (s, 1 H), 3.3–3.55 (m, 2 H), 3.70 (m, 3 H), 3.90 (t, 1 H), 4.06 (m, 1 H); IR ($CHCl_3$) ν_{max} 3440 cm^{-1} (OH); CIMS *m/z* (relative intensity) 335, (12.3, M^+ + 3), 334 (20.5, M^+ + 2), 333 (100.00, M^+ + 1), 71 (27.3, C_4H_7O).

9d: 95 mg (yield 25%), oil; ^1H NMR ($CDCl_3$) δ 1.1–1.52 (m, 12 H, 4 × CH_3), 1.6–2.10 (m, 4 H), 2.6–3.3 (m, 6 H), 3.4–4.10 (m, 5 H), 4.75 (m, 1 H); IR ($CHCl_3$) ν_{max} 3420 cm^{-1} (OH); CIMS *m/z* (relative intensity) 335 (13.5, M^+ + 3), 334 (19.3, M^+ + 2), 333 (100.0, M^+ + 1).

Investigation of the Conversion of Imidazolidino[1,2-*d*]-dithiazepine 8b to the Tetrahydrofuranyl Aminol 9b. A stock solution of compound **8b** (10 mM) in freshly purified and distilled THF was used. Aliquots (0.5 mL) of the stock solution were added to 1.5 mL of purified or unpurified THF, as required, yielding a final concentration of 2.5 mM. The consumption of **8b** was monitored by TLC (Kieselgel 60 F_{254}, Merck, Darmstadt, with 10:1 chloroform:methanol as eluent): **8b**, R_f 0.45; **9b**, origin, R_f 0; visualization UV at λ_{254} nm and ninhydrin reagent. The reaction mixtures were refluxed under nitrogen or in air for 2 h. Samples containing purified THF only were additionally maintained for 12 h at ambient temperature and then refluxed for 2 h. In certain experiments 2 mg of the metal ion chelating agent diethylenetriaminepentaacetic acid (DETAPAC) was added. The following experiments were performed:

(i) Stock solution (0.5 mL) and purified THF (1.5 mL) were refluxed 2 h under nitrogen. No reaction of **8b** was observed.

(ii) Stock solution (0.5 mL) and purified THF (1.5 mL) were refluxed for 2 h in air. No reaction of **8b** was observed.

(iii) Stock solution (0.5 mL) and unpurified THF (1.5 mL) were refluxed for 2 h under nitrogen. A quantitative conversion of **8b** to **9b** resulted.

(iv) Stock solution (0.5 mL) and unpurified THF (1.5 mL) were refluxed for 2 h in air. A quantitative conversion of **8b** to **9b** resulted.

(v) Stock solution (0.5 mL) and purified THF (1.5 mL) were refluxed for 2 h, maintained at ambient temperature for 12 h, and then refluxed for 2 h, all either under nitrogen or in air. Compound **8b** was unchanged.

(vi) Conditions were as for ii but 2 mg of DETAPAC was added prior to reflux. Compound **8b** was unchanged.

(vii) Conditions were as for iv but with the addition of 2 mg of DETAPAC. Quantitative conversion of **8b** to **9b** resulted.

X-ray Crystallography.[18] Single crystals of **3** and **9a** were prepared by the slow diffusion of hexane vapor into $CHCl_3$ solutions.

Crystal data for 9a: $C_{28}H_{34}N_2O_3S_3$; fw 542.79; triclinic, $P\bar{1}$, a = 10.456 (4) Å, b = 14.110 (2) Å, c = 10.404 (4) Å, α = 99.50 (2)°, β = 109.91 (3)°, γ = 99.11 (3)°, V = 1385 Å^3, Z = 2. Monochromatized Mo K_α radiation (λ = 0.71073 Å) was used. Data were collected for the index range $h,\pm k,\pm l$, on a CAD4F diffractometer[18a] using an ω-2θ scan to a 2θ limit of 50.00° at 23 °C. A total of 4735 unique data were collected, with 2666 observed with $I > 3\sigma(I)$. The structure was solved by direct methods.[18b] Final unweighted and weighted R values of 0.047 and 0.063, respectively, were obtained for 325 variables. The highest peak in the final difference Fourier was 0.37 (5) e Å^{-3} with no chemical significance.

Crystal data for 3: $C_{12}H_{22}N_2O_2S_2$; fws 290.45; monoclinic, $P2_1/c$, a = 9.163 (2) Å, b = 15.710 (6) Å, c = 10.635 (4) Å, β = 96.96 (2)°, V = 1520 Å^3, Z = 2. Monochromatized Mo K_α radiation (λ = 0.71073 Å) was used. Data were collected for the index range $h,k,\pm l$ on a CAD4F diffractometer[18a] using an ω-2θ scan to a 2θ limit of 54.00° at 23 °C. A total of 3442 unique data were collected, with 2435 observed at $I > 3\sigma(I)$. The structure was solved by direct methods.[18b] Final unweighted and weighted R values of 0.052 and 0.076, respectively, were obtained for 163 variables. The highest peak in the final difference Fourier was 0.42 (6) e Å^{-3} with no chemical significance.

Determination of Binding Constants to DNA. The relative binding constants of **2**, **5**, and naphtho[2,1-*b*]thiophene-3-carboxylic acid were estimated by displacement of intercalative binding of ethidium to calf thymus DNA and employing a value of $K_{assoc} = 1 \times 10^7$ M^{-1} at pH 7.0, 37 °C, and 40 mM NaCl for ethidium bound to calf thymus DNA.[19,20] It was determined that none of the compounds interferes with the fluorescence measurements, which were performed on a Turner 430 spectrofluorometer. The procedure, which involves following the displacement of the ethidium upon titrating in the drugs and determining the concentration of drug required to displace 50% of the ethidium, follows that of Morgan et al.[20] and gives relative rather than absolute values for binding constants. Higher concentrations of drugs displace all the ethidium from the DNA.

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Registry No. 1, 115509-23-4; **2**, 115420-69-4; **3**, 115420-70-7; **4**, 115420-71-8; **5**, 115420-72-9; **6**, 108168-20-3; **7**, 115420-73-0; **8b**, 115420-74-1; **8d**, 115461-83-1; **8e**, 108168-12-3; **9a**, 115420-75-2; **9b**, 115420-76-3; **9c**, 115420-77-4; **9d**, 115420-78-5; naphtho[2,1-*b*]thiophene-3-carboxylic acid, 37094-53-4.

Supplementary Material Available: Positional and thermal parameters, derived hydrogen atom parameters, anisotropic thermal parameters, root-mean-square amplitudes of vibration, bond distances and angles, and torsion angles for **3** and **9a** (16 pages). Ordering information is given on any current masthead page.

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Preparation, Reactivity, and Spectral Properties of 1,3-Dioxin Vinylogous Esters: Versatile β-Ketovinyl Cation Equivalents†

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A full account of the preparation, reactivity, and spectral properties of three 1,3-dioxin vinylogous esters (**4**–**6**) is presented. The synthetic approach to these versatile β-ketovinyl cation equivalents involves a BF_3·Et_2O-promoted Prins reaction between cyclic 1,3-diketones (i.e., 1,3-cyclopentanedione, 1,3-cyclohexanedione, and 1,3-cycloheptanedione) and either formaldehyde or trioxane. The reactions explored include reductive and alkylative 1,3-ketone transpositions, affording a variety of simple β-unsubstituted and β-substituted α-hydroxymethyl α,β-enones, alkylations with carbon electrophiles, and hydroxylations with oxygen electrophiles.

Introduction

In connection with our recent synthesis of (−)-bertyadionol (**1**),[2] we required a versatile β-ketovinyl cation equivalent for α-(hydroxymethyl)cyclopentenone synthon **3**. Ideal in this regard appeared to be vinylogous ester **4**, wherein nucleophilic addition of the dianion of **7** to the carbonyl group of **4**, followed by an acidic workup would lead to enone **2** with concomitant loss of formaldehyde.[3]

As recently communicated, this tactic proved quite successful in that it permitted rapid assembly of the carbon skeleton of bertyadionol.[2] Having demonstrated the utility

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