ca. 20 mL of $CHCl_3$, adding 2-propanol dropwise (ca. 2–3 mL) until the solid dissolved, diluting, while still hot, with ca. 10 mL of petroleum ether, and slowly cooling to −20 °C to give 6.11 g (90%) of **4** as white crystals: mp 97–100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (9 H, s), 6.19 (1 H, br s), 7.33 (1 H, apparent dd, J = 7.5, 5.1 Hz), 8.03 (1 H, dd, J = 7.5, 1.8 Hz), 8.44 (1 H, dd, J = 5.1, 1.8 Hz). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 56.47; H, 6.12; N, 13.18. Found: C, 56.59; H, 5.83; N, 13.27.

***N*-*tert*-Butyl-2-methoxynicotinamide (5).** A solid mixture of anhydrous copper(II) acetate (80 mg) and *N*-*tert*-butyl-2-chloronicotinamide (**4**, 3.75 g, 17.6 mmol) was added portionwise at room temperature to a stirring methanolic sodium methoxide solution which was prepared from 25 mL of anhydrous methanol and 2.0 g (87 mmol) of sodium metal. The resultant, deep-blue mixture was stirred at reflux for 60 min and cooled to 0 °C. Approximately 5 mL of glacial acetic acid was added dropwise to the stirring mixture, which was then partitioned between $CHCl_3$ and water. The organic phase was removed, washed with water (2×), 1 N aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to yield a yellow oil. Flash chromatography[10] on a 2.5-cm × 23-cm silica gel column eluting with 15:85 ethyl acetate/petroleum ether afforded a clear oil that solidified to a white, waxy solid upon standing at 0 °C (2.71 g, 74%): mp 22–24 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9 H, s), 4.09 (3 H, s), 7.05 (1 H, apparent dd, J = 7.5, 5.1 Hz), 7.91 (1 H, br s), 8.24 (1 H, dd, J = 5.1, 1.8 Hz), 8.49 (1 H, dd, J = 7.5, 1.8 Hz). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.74; H, 7.71; N, 13.24.

1,1-Dimethyl-4-methoxyfuro[3,4-*c*]pyridin-3(1*H*)-one (9). To a stirred solution of *N*-*tert*-butyl-2-methoxynicotinamide (**5**, 219 mg, 1.05 mmol) in 3 mL of dry (from sodium benzophenone ketyl) diethyl ether at −78 °C under a nitrogen atmosphere was added 0.94 mL (2.2 mmol) of a 2.36 M solution of *n*-butyllithium in hexanes dropwise over a period of approximately 5 min to give a yellow suspension. The cooling bath was removed; the mixture gradually (ca. 30 min) warmed to ambient temperature and was stirred at that temperature an additional 45 min. The mixture was recooled to −78 °C, and dry, HPLC-grade acetone (0.085 mL, 1.2 mmol) was added in one portion. The cooling bath was removed, and the mixture was stirred an additional 2 h after it had reached room temperature. The reaction was quenched with water, and the resultant mixture was partitioned between ethyl acetate and water. The aqueous phase was separated and extracted with ethyl acetate (2×). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to yield an amber oil which was taken up in $CHCl_3$ (5 mL) and treated with *p*-toluenesulfonic acid (ca. 15 mg) at reflux for 2 h (to convert residual **8** to **9**). The solution was cooled back to room temperature, quenched with water, washed with 1 N aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to afford 248 mg of a pale-yellow oil whose ^1H NMR showed it to be principally a ~1:1 mixture of **5** and **9**. Flash chromatography on a 2-cm × 25-cm silica gel column eluting with 30:70 ethyl acetate/petroleum ether afforded 56 mg (26%) of recovered **5** and 70 mg (35%, 47% based on unrecovered **6**) of **9** as a white, crystalline solid: mp 111–113 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (6 H, s), 4.13 (3 H, s), 6.94 (1 H, d, J = 5.1 Hz), 8.39 (1 H, d, J = 5.1 Hz). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.18; H, 5.70; N, 7.25. Found: C, 62.32; H, 6.01; N, 7.41.

1,1,5-Trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (Cerpegin, 1). A portion of **9** (100 mg, 0.52 mmol) was dissolved in neat iodomethane (1 mL) and heated at 140 °C for 24 h in a sealed tube. The burgundy mixture that resulted was diluted with CH_2Cl_2, washed successively with 1 N aqueous HCl and brine, dried over $MgSO_4$, and concentrated to dryness to yield 90.3 mg (90%) of **1**: mp 268–271 °C (lit.[1a] mp 268–270 °C), which was pure as judged by ^1H NMR. The melting point of a mixture of synthetic and natural **1** is undepressed, the two are identical by TLC using cospotting and a variety of solvent systems, and the spectra of synthetic **1** are identical to those of natural **1**.[11]

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(11) Due to a faulty calibration, the ^1H NMR chemical shifts reported in ref 1a are incorrect. The correct ^1H NMR spectral data are as follows: (300 MHz, $CDCl_3$) δ 1.59 (6 H, s) 3.64 (3 H, s), 6.23 (1 H, d, J = 6.9 Hz), 7.68 (1 H, s, J = 6.9 Hz).

Acknowledgment. We thank Dr. P. Thirugnanasambantham[1a] for a sample of **1** and its spectra.

Registry No. **1**, 129748-28-3; **3**, 2942-59-8; **4**, 144084-34-4; **5**, 144084-35-5; **9**, 144084-36-6.

Ring Expansion of Halo Dithiolanes and Dithianes: A Facile Synthesis of Medium-Ring Dithiacycloalkenes

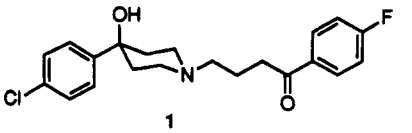
Zhihua Sui, Paul S. Furth, and James J. De Voss*

Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143-0446

Received June 23, 1992

Medium ring containing compounds have long attracted the attention of synthetic chemists as they are generally resistant to attempts to prepare them via standard cyclization methodologies.[1] This difficulty is thought to be essentially due to an enthalpic effect caused by the high intrinsic strain of medium-ring systems.[2] Fragmentation of a bicyclic system containing smaller, more easily synthesized rings is a well-recognized strategy for the construction of these systems.[3] We have developed such an approach in which the bicyclic intermediate, derived from the cyclization of a halo thioketal, is generated in situ and fragments to a 1,4- or 1,5-dithiacycloalkene.

While investigating the synthesis of a number of analogs of haloperidol (**1**),[4,5] a promising lead compound for the development of nonpeptidic HIV-1 protease inhibitors,[6] we attempted the alkylation of a piperidine moiety with the dithiolane-containing γ-halobutyrophenone **2a**.



1

Surprisingly, the desired product was not formed. Instead, we isolated a small amount of the 1,5-dithiacyclooctene **3a**, derived from ring expansion of the starting thioketal. We report here an optimized version of this reaction that provides a facile entry into medium ring 1,4- and 1,5-dithiacycloalkenes *for which no general synthesis is currently available* (see Table I). A brief survey of the literature reveals that while oxidative ring expansions of cyclic thioketals are relatively common,[7] few are driven by an alkylation reaction and most are limited to only one or two carbon ring enlargements.[8] There is only one report of a related reaction in which a thioketal sulfur interacts

(1) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.

(2) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131–9166.

(3) Fuhrhop, J.; Penzlin, G. *Organic Synthesis Concepts, Methods, Starting Materials*; Verlag Chemie: Weinheim, 1983; p 80–82.

(4) Sui, Z., De Voss; J. J.; Ortiz de Montellano, P. R. Unpublished.

(5) De Voss, J. J.; Sui, Z.; Ortiz de Montellano, P. R. Unpublished.

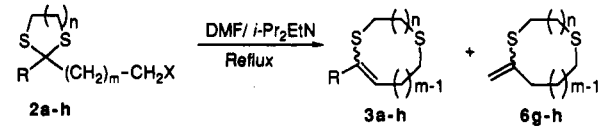
(6) DesJarlais, R. L.; Seibel, G. L.; Kuntz, I. D.; Furth, P. S.; Alvarez, J. C.; Ortiz de Montellano, P. R.; DeCamp, D. L.; Babé, L. M.; Craik, C. S. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6644–6648.

(7) See, for example: Tani, H.; Inamasu, T.; Tamura, R.; Suzuki, H. *Chem. Lett.* **1990**, 1323–1326. Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1621–1624. Hiroi, K.; Sato, S.; Matsuo, K. *Chem. Pharm. Bull.* **1980**, *28*, 558–566.

(8) Nikkon, A.; Rodriguez, A. D.; Shirhatti, V.; Ganguly, R. *J. Org. Chem.* **1985**, *50*, 4218–4226. Weintraub, P. M. *J. Heterocycl. Chem.* **1979**, *16*, 1081–1082.

0022-3263/92/1957-6658$03.00/0

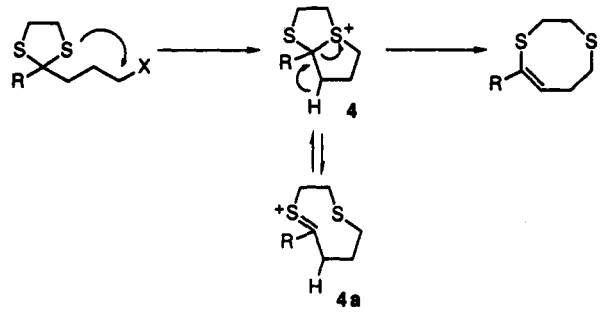
Table I. Ring Expansion of Various Halo Dithianes and Dithiolanes



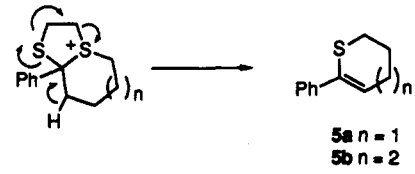
entry	compd	R	*n*	*m*	X	ring size	time (h)	product	yield[a] (%)
1	**2a**	Ph	1	2	Cl	8	0.5	*Z*-**3a**	71
2	**2b**	Ph	2	2	Cl	9	0.5	*Z*-**3b**	62
3	**2c**	Ph	1	3	Br	9	0.5	*Z*-**3c**	72
4	**2d**	Ph	2	3	Br	10	0.5	**3d** *E*:*Z* 6.7:1[b]	98
5	**2e**	Ph	1	4	Br	10	12	*Z*-**3e**	54
6	**2f**	Ph	2	4	Br	11	12	**3f** *E*:*Z* 2–4:1[b]	57
7	**2g**	Me	1	2	Cl	8	0.5	*Z*-**3g** **6g**	84 4
8	**2h**	Me	2	2	Cl	9	0.5	**3h, 6h** *E*:*Z*:exo[b] 1:3:6	80

[a] Isolated yield. [b] Ratios calculated from NMR integration.

Scheme I



Scheme II



with a γ-vinyl carbon under strongly acidic conditions.[9]

The ring expansion of **2** is readily carried out under relatively mild conditions: simply heating a DMF solution of the appropriate halo thioketal[10] at reflux in the presence of excess diisopropylethylamine produces the ring-expanded product in fair to excellent yield. Scheme I delineates the postulated mechanism for an illustrative dithiolane. Thus, the intermediate sulfonium salt **4** is produced by alkylation of one of the thioketal sulfur atoms by the primary alkyl halide. Intermediate **4** then decomposes via the loss of a proton to the dithiacycloalkene. Support for this mechanism can be garnered from three sources. First, the ring expansion is dramatically faster in DMF than in xylene: a reaction that is incomplete after 24 h at reflux in xylene is finished in less than 30 min in DMF. This solvent effect is consistent with the existence of the charged intermediate **4**, which would be stabilized by a polar aprotic solvent such as DMF. Second, in some reactions a minor side product (<3%) was isolated and identified as a thiacycloalkene (**5a**, entry 4; **5b**, entries 5 and 6). The presence of this compound is easily rationalized by an alternative fragmentation of the charged intermediate (Scheme II[11]). Finally, similar sulfonium salts have been isolated and shown to decompose in the presence of base to dithiacycloalkenes.[7]

The scope of the reaction, outlined in Table I, shows that γ-, δ-, and ε-halo dithiolanes and dithianes react to give the desired product. It is interesting to note that the ε-halo compounds (entries 5 and 6), for which the proposed mechanism requires the formation of a seven-membered ring in the transition state, need a much longer reaction time than those with a γ or δ substituent. A phenyl thioketal was chosen in most cases (entries 1–6) for convenience but is obviously not required, as is demonstrated in entries 7 and 8. In these cases, however, mixtures of the endo and exo double bond isomers were isolated (**3g**:**6g** 20:1, entry 7, and **3h**:**6h** 1:1, entry 8). These mixtures were poorly separated by flash column chromatography.

The stereochemistry of the double bond was assigned in all cases by NOE difference spectroscopy. For example, in the 10-membered ring *Z*-**3e**, a strong NOE was observed between the vinyl proton and the ortho hydrogens of the adjacent phenyl ring, clearly defining the cis relationship of these substituents. In contrast, the isomeric *E*-**3d** showed no enhancement of the aromatic hydrogens when the vinyl proton was irradiated. Instead the signal for the methylene attached to the vinylic sulfur intensified, consistent with an *E* geometry for the double bond.

In the eight-membered rings (**3a** and **3g**) and *Z* isomer was produced exclusively, as might be expected, while in the case of the 11-atom heterocycle **3f**, which is large enough to accommodate a trans double bond, the *E* isomer was the major product. For the dithiacyclononenes **3b,c,h** the *Z* isomer was once again formed either exclusively (entries 2 and 3) or predominantly (entry 8). Interestingly, in the 10-membered rings **3d,e** the *Z* isomer was either the sole product (entry 5) or the *E* isomer was by far the main form produced (entry 4).

The stereochemical outcome of these ring expansions can be rationalized by examining the transition state for the elimination reaction in the intermediate **4**.[12] If one

(9) Marchand, A. P.; Kaya, R.; Muchmore, S. W.; van der Helm, D. *J. Org. Chem.* **1986**, *51*, 825–829.

(10) The halothioketals **2a–h** were prepared by the boron trifluoride etherate catalyzed condensation of a dithiol with the appropriate halo ketone. See the Experimental Section for details.

(11) A number of different mechanisms can be envisaged that give rise to **5**: the one that is shown is attractive as the elimination generates an additional stable molecule and elemental sulfur.

assumes that the phenyl ring occupies the equatorial position of the thioketal ring, the alkyl halide chain, necessarily axial, will react to form a cis-fused bicyclic system. For the 5,5, 5,6, and 6,5 systems, elimination of the hydrogen antiperiplanar to the cleaved C–S bond leads to the observed *Z* isomer. In the 6,6 system, the same reaction leads to the observed *E* isomer. In the 5,7 and 6,7 frameworks, the more flexible seven-membered ring allows access to a greater number of possible conformations, making it difficult to rationalize the preference for one over another. However, from models one can readily see conformations that lead to the observed products. Finally, it is interesting to note that in the conformations leading to *Z* double bonds, the hydrogen of the methylene that usually becomes the vinylic proton is antiperiplanar to the other sulfur of the thioketal. It is thus possible to speculate that, as loss of this proton leads to the cyclic sulfides **5** observed as minor products, only conformations that would lead to a *Z* isomer produce these alternate fragmentations. For the methyl-substituted compounds (entries 7 and 8) the same conformational considerations apply. However, the methyl group is not as sterically demanding as a phenyl ring, making the starting material less conformationally constrained. This flexibility combined with the fact that the methyl may lose a proton to form an exocyclic isomer results in the observed mixture of products.

In summary, we have introduced a novel, high-yielding method for the synthesis of medium-ring dithiaheterocycles. Extension of this methodology to other heteroatoms and rings containing one heteroatom is currently being investigated.

Experimental Section

General. Melting points are uncorrected. Proton and carbon NMR spectra were obtained at 300 and 75 MHz, respectively. Elemental analyses were performed by the Microanalysis laboratory, University of California, Berkeley. DMF was dried over 4-Å molecular sieves and then distilled at reduced pressure and stored over 4-Å sieves under argon. Diisopropylethylamine was heated at reflux over calcium hydride and then distilled under argon and stored over 4-Å sieves under argon.

General Procedure for Preparation of Thioketals 2a–h. The ketone[13] (4 mmol) was dissolved in dry CH_2Cl_2 (15 mL), and the dithiol (6 mmol) and $BF_3{\cdot}OEt_2$ (8 mmol) were added. After being stirred at room temperature for 1 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and 5% NaOH solution (30 mL). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by flash column chromatography (silica gel, 1.2% ethyl acetate/hexane) to give the thioketals.

2-Phenyl-2-(3-chloropropyl)-1,3-dithiolane (2a): 60%; colorless oil; IR (NaCl) 3058 (w), 2959 (w), 1595 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71–1.80 (m, 2 H, CH_2CH_2Cl), 2.46 (t, 2 H, J = 7 Hz, $SCCH_2$), 3.19–3.38 (m, 4 H, SCH_2CH_2S), 3.43 (t, 2 H, J = 7 Hz, CH_2Cl), 7.20–7.31 (m, 3 H, meta and para H's of C_6H_5), 7.65 (d, 2 H, J = 7.5 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 32.5, 33.0, 39.1, 45.0, 73.7 (SCS), 126.8, 127.0, 127.8, 144.5; MS *m/z* (relative intensity) (CI) 259 (40), 241 (100), 181 (31), 163 (49), 147 (67); HRMS calcd for $C_{12}H_{15}ClS_2$ 258.0304, found 258.0308.

2-Phenyl-2-(3-chloropropyl)-1,3-dithiane (2b): 63%; colorless oil; IR (NaCl) 3044 (w), 2959 (w), 1595 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72–1.77 (m, 2 H, CH_2CH_2Cl), 1.89–1.95 (m, 2 H, SCH_2CH_2), 2.14–2.20 (m, 4 H, $SCCH_2$), 2.64–2.72 (m, 4 H, 2 SCH_2), 3.39 (t, 2 H, J = 7.4 Hz, CH_2Cl), 7.26–7.41 (m, 3 H, meta and para H's of C_6H_5), 7.90 (d, 2 H, J = 8.0 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.1, 27.4, 41.9, 44.6, 58.0, 126.9 and 128.3 (Ar CH's), 141.2 (Ar C); MS *m/z* (relative intensity) (EI) 272 (28), 236 (10), 195 (68), 162 (40), 136 (100); HRMS calcd for $C_{13}H_{17}ClS_2$ 272.0460, found 272.0459.

2-Phenyl-2-(4-bromobutyl)-1,3-dithiolane (2c): 63%; colorless oil; IR (NaCl) 3051 (w), 2931 (w), 1595 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.45 (m, 2 H, $CH_2CH_2CH_2Br$), 1.79 (m, 2 H, $CH_2CH_2CH_2Br$), 2.31–2.37 (m, 2 H, $SCCH_2$), 3.18–3.37 (m, 6 H, SCH_2CH_2 and CH_2Br), 7.20–7.31 (m, 3 H, meta and para H's of C_6H_5), 7.67 (d, 2 H, J = 7.7 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.5, 39.2, 43.2, 44.6, 73.2, 126.8, 127.0, 127.9, 144.3; MS *m/z* (relative intensity) 318 (M + 2, 29), 316 (M, 32), 287 (60), 236 (71), 208 (54), 181 (100); HRMS calcd for $C_{13}H_{17}BrS_2$ 315.9955, found 315.9936.

2-Phenyl-2-(4-bromobutyl)-1,3-dithiane (2d): 64%; white crystals; mp 64–65 °C IR (NaCl) 3051 (w), 2945 (w), 1595 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.45 (m, 2 H, $CH_2CH_2CH_2Br$), 1.74 (m, 2 H, $CH_2CH_2CH_2Br$), 1.89–2.03 (m, 4 H, SCH_2CH_2 and $SCCH_2$), 2.64–2.70 (m, 4 H, 2 SCH_2), 3.26 (t, 2 H, J = 7 Hz, CH_2Br), 7.25 (t, 1 H, J = 7.2 Hz, para H of C_6H_5), 7.37 (t, 2 H, J = 7.2 Hz, meta H's of C_6H_5), 7.90 (d, 2 H, J = 7.2 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 25.0, 27.4, 32.5, 32.9, 44.0, 58.6, 126.8, 128.3, 128.5, 141.4; MS *m/z* (relative intensity) 332 (M + 2, 12), 330 (M, 10), 250 (10), 195 (74), 177 (100); HRMS calcd for $C_{14}H_{19}BrS_2$ 330.0112, found 330.0092. Anal. Calcd for $C_{14}H_{19}BrS_2$: C, 50.75; H, 5.77. Found: C, 50.93; H, 5.88.

2-Phenyl-2-(5′-bromopentyl)-1,3-dithiolane (2e): 83%; colorless oil; IR ($CHCl_3$) 3058, 2938, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.40 (m, 4 H, $CH_2CH_2CH_2Br$), 1.73–1.81 (m, 2 H, CH_2CH_2Br), 2.32–2.37 (m, 2 H, $SCCH_2$), 3.19–3.44 (m, 6 H, SCH_2CH_2S and CH_2Br), 7.19–7.32 (m, 3 H, meta and para H's of C_6H_5), 7.67 (d, 2 H, J = 7.6 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 28.0, 32.4, 33.6, 39.1, 45.7, 74.0, 126.9, 127.0, 127.9, 144.8; MS *m/z* (relative intensity) 330 ($M^{\cdot+}$, 1.4), 181 ($C_6H_5C_3H_4S_2$, 100), 121 (21); HRMS calcd for $C_{14}H_{19}S_2Br$ 330.0112, found 330.0120.

2-Phenyl-2-(5′-bromopentyl)-1,3-dithiane (2f): 78%; colorless oil; IR ($CHCl_3$) 3058, 2954, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.33 (m, 4 H, $CH_2CH_2CH_2Br$), 1.73–1.78 (m, 2 H, CH_2CH_2Br), 1.90–2.04 (m, 4 H, $SCCH_2$ and SCH_2CH_2), 2.64–2.70 (m, 4 H, 2 SCH_2), 3.30 (t, 2 H, J = 6.8 Hz, CH_2Br), 7.25–7.40 (m, 3 H, meta and para H's of C_6H_5), 7.90 (d, 2 H, J = 7.7 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 25.2, 27.5, 28.0, 32.3, 33.5, 44.9, 58.9, 126.8, 128.4, 128.6, 141.7; MS *m/z* (relative intensity) 344 ($MH^{\cdot+}$, 12), 195 ($C_6H_5C_4H_6S_2$, 100), 157 (19), 136 (78), 121 (30), 91 (19); HRMS calcd for $C_{15}H_{21}S_2Br$ 344.0268, found 344.0254.

2-Methyl-2-(3′-chloropropyl)-1,3-dithiolane (2g): 40%; colorless oil; IR ($CHCl_3$) 2988, 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 3 H, CH_3), 2.01–2.06 (m, 4 H, $CH_2CH_2CH_2Cl$), 3.31–3.37 (m, 4 H, SCH_2CH_2), 3.57 (m, 2 H, CH_2Cl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 32.5, 40.0, 42.8, 44.9, 66.0; MS *m/z* (relative intensity) 196 ($M^{\cdot+}$, 9), 161 ($M^{\cdot+}$ – Cl, 17), 144 (60), 132 (19), 120 (35), 101 (100), 85 (67); HRMS calcd for $C_7H_{13}S_2Cl$ 196.0147, found 196.0142.

2-Methyl-2-(3′-chloropropyl)-1,3-dithiane (2h): 63%; colorless oil; IR ($CHCl_3$) 2981, 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3 H, CH_3), 1.92–2.12 (m, 6 H, $CH_2CH_2CH_2Cl$ and SCH_2CH_2), 2.81, 2.88 (AB of ABXY, 4 H, J_{AB} = 14.4 Hz J_{AX} = 4 Hz, J_{AY} 6.6 Hz, J_{BX} = 3.6 Hz, J_{BY} = 8.3 Hz, 2 SCH_2), 3.60 (t, 2 H, J = 6 Hz, CH_2Br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 26.3, 27.7, 27.8, 38.4, 45.0, 48.3; MS *m/z* (relative intensity) 210 ($M^{\cdot+}$,

(12) It may also be possible to rationalize the stereochemistry of the double bond in the product by consideration of the conformations available to an intermediate such as **4a**. Conformations that lead to the *E* geometry of the double bond would be more accessible as the size of the ring in **4a** increases. This appears to be a less likely explanation for several reasons. First, an X-ray crystal structure of a compound like **4** exists and shows that the stable form is indeed the bicyclic form **4** and not the macrocyclic **4a**. Secondly, the presence of the side products **5** show that **4** is a reactive intermediate, whereas the formation of **5** from **4a** is difficult to rationalize (cf. Scheme II). Finally, if **4a** is the reactive intermediate and its ring size determines which conformations are available for elimination, it is difficult to explain the differences seen among the larger rings (entries 4–6).

(13) The ketones employed for the preparation of **2a,b** and **2g,h** were commercially available while those used for the synthesis of **2c,d**[14] and **2e,f**[15] have previously been described in the literature.

(14) Wagner, P. J.; Lindstrom, M. J.; Sedon, J. H.; Ward, D. R. *J. Am. Chem. Soc.* **1981**, *103*, 3842–3849.

(15) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642. Bird, R.; Griffiths, G.; Griffiths, G. F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 579–584.

39), 133 ($CH_3C_4H_6S_2$, 70), 101 (16), 74 (100), 59 (30); HRMS calcd for $C_8H_{15}S_2Cl$ 210.0304, found 210.0305.

General Procedure for Ring Expansion. The thioketal (0.5 mmol) and diisopropylethylamine (2 equiv) were dissolved in dry DMF (4 mL) under argon, and the solution was heated at reflux for the length of time specified in Table I. After cooling to room temperature, the reaction mixture was diluted with ether (30 mL), washed with saturated brine (3 × 20 mL), dried over magnesium sulfate, and evaporated. The residue was purified by flash column chromatography (silica gel, 10% CH_2Cl_2/hexane) to yield the dithiacycloalkenes **3a–h** and **6g,h**.

(*Z*)-8-Phenyl-1,4-dithiacyclooct-7-ene (3a). Ring expansion of **2a** by the general procedure gave **3a** as a colorless oil (71%): IR (NaCl) 3051 (w), 2910 (w), 1588 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75–2.79 (m, 2 H, $=CCH_2CH_2$), 2.88 (s, 4 H, SCH_2CH_2), 3.05–3.11 (m, 2 H, $=CCH_2CH_2$), 6.70 (t, 1 H, J = 8 Hz, CH=C), 7.26–7.36 (m, 3 H, meta and para H's of C_6H_5), 7.65 (dd, 2 H, J = 9, 2 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 32.8, 33.5, 38.1, 126.6, 127.6, 128.2, 134.5, 139.8, 140.7; MS m/z (relative intensity) 222 (7), 194 (43), 161 (100), 147 (13), 115 (43); HRMS calcd for $C_{12}H_{14}S_2$ 222.0537, found 222.0530.

(*Z*)-9-Phenyl-1,5-dithiacyclonon-8-ene (3b). Ring expansion of **2b** by the general procedure gave **3b** as a colorless oil (65%): colorless oil; IR (NaCl) 3051 (w), 2917 (w), 1673 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (q, 2 H, $SCH_2CH_2CH_2S$), 2.75 (m, 2 H, $=CCH_2CH_2$), 2.82–2.95 (m, 4 H, 2 SCH_2), 3.05–3.11 (m, 2 H, $=CCH_2CH_2$), 6.25 (t, 1 H, J = 8 Hz, CH=C), 7.24–7.34 (m, 3 H, meta and para H's of C_6H_5), 7.65 (dd, 2 H, J = 9, 2 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 27.9, 28.1, 30.5, 33.1, 127.3 and 128.0 (Ar CH's), 135.9, 139.0, 141.6; MS m/z (relative intensity) 236 (M, 33), 162 (100), 129 (18), 115 (26); HRMS calcd for $C_{13}H_{16}S_2$ 236.0693, found 236.0691.

(*Z*)-9-Phenyl-1,4-dithiacyclonon-8-ene (3c). Ring expansion of **2c** by the general procedure gave **3c** as a colorless oil (72%). Cyclic sulfide **5a** was also isolated as a colorless oil (2.9%).

3c: IR (NaCl) 3051 (w), 2917 (w), 1490 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (q, 2 H, $SCH_2CH_2CH_2CH=$), 2.65–2.76 (m, 6 H, 3 SCH_2), 3.14–3.21 (m, 2 H, $=CCH_2CH_2$), 6.34 (t, 1 H, J = 8 Hz, CH=C), 7.24–7.36 (m, 3 H, meta and para H's of C_6H_5), 7.65 (d, 2 H, J = 7 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 29.3, 34.3, 37.5, 38.1, 127.1, 127.6, 127.9, 128.3, 134.3, 139.1, 140.2; MS m/z (relative intensity) 236 (M, 37), 208 (30), 175 (100), 121 (66); HRMS calcd for $C_{13}H_{16}S_2$ 236.0693, found 236.0687.

(*Z*)-2-Phenyl-1-thiacyclohex-2-ene (5a): IR (NaCl) 3058 (w), 2988 (w), 1680, (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02–2.04 (q, 2 H, $SCH_2CH_2CH_2CH=$), 2.36 (td, 2 H, J = 8, 5 Hz, $=CCH_2CH_2$), 3.00 (t, 2 H, SCH_2), 6.02 (t, 1 H, J = 4.5 Hz, CH=C), 7.24–7.35 (m, 3 H, meta and para H's of C_6H_5), 7.47 (d, 2 H, J = 8 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 24.9, 27.6, 119.2, 126.2, 127.7, 128.3, 132.8, 140.5; HRMS calcd for $C_{11}H_{12}S$ 176.0660, found 176.0651.

10-Phenyl-1,5-dithiacyclodec-9-ene (3d). Ring expansion of **2d** by the general procedure gave the two isomers *E*- and *Z*-**3d** as an approximately 7:1 mixture respectively (by NMR) in 98% total yield. They were partially separated by column chromatography as described in the general procedure.

***E*-3d**: IR (NaCl) 3058 (w), 2931 (w), 1673 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65–1.72 (m, 2 H, $SCH_2CH_2CH_2S$), 1.93–2.01 (m, 2 H, $=CCH_2CH_2$), 2.16–2.35 (m, 4 H, $SCH_2CH_2CH_2S$), 2.75–2.81 (m, 2 H, SCH_2), 3.06–3.09 (m, 2 H, $=CCH_2CH_2$), 6.41 (t, 1 H, J = 7 Hz, CH=C), 7.18–7.28 (m, 3 H, meta and para H's of C_6H_5), 7.43 (d, 2 H, J = 8 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 31.3, 31.5, 32.4, 32.6, 33.1, 127.4, 127.7, 127.8, 129.4, 129.9, 138.8; MS m/z (relative intensity) (GCMS) 250 (M^+, 69), 176 (100), 163 (20), 144 (39), 129 (53), 115 (84); HRMS calcd for $C_{14}H_{18}S_2$ 250.0850, found 250.0851.

***Z*-3d**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (t, J = 7 Hz, CH=C), 7.60 (d, ortho H's of C_6H_5); MS m/z (relative intensity) (GCMS) 250 (M^+, 79), 176 (100), 161 (18), 144 (36), 129 (47), 115 (76).

(*Z*)-10-Phenyl-1,4-dithiacyclodec-9-ene (*Z*-3e). Ring expansion of **2e** by the general procedure gave **3e** as a crystalline solid (54%) that was recrystallized from CH_2Cl_2/hexane for analysis: mp 88.5–90 °C; IR ($CHCl_3$) 3079, 2945, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58–1.66, 1.70–1.79 (2 m, 2 × 2 H, $CH_2CH_2CH_2S$), 2.43–2.46, 2.79–2.81 (s m, 2 × 2 H, SCH_2CH_2S), 2.60–2.75 (brd m, 2 H, $C=CHCH_2$), 3.00–3.30 (brd m, 2 H, $CH_2CH_2CH_2S$), 6.14 (t, 1 H, J = 8.3 Hz, C=CH), 7.25–7.33 (m, 3 H, meta and para H's of C_6H_5), 7.56 (d, 2 H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 24.4, 25.4, 26.4, 27.7, 35.0, 127.5, 127.7, 128.5, 136.1, 137.1, 139.5; MS m/z (relative intensity) 250 ($M^{\cdot+}$, 54), 222 (69), 189 (75), 158 (71), 129 (42), 121 (54), 115 (54), 101 (100); HRMS calcd for $C_{14}H_{18}S_2$ 250.0850, found 250.0845. Anal. Calcd for $C_{14}H_{18}S_2$: C, 67.15; H, 7.24. Found: C, 67.26; H, 7.34.

The cyclic sulfide **(*Z*)-2-phenyl-1-thiacyclohept-2-ene (5b)** was also isolated as a minor product (2%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.62–1.69 (m, 2 H, $C=CHCH_2CH_2$), 2.02–2.10 (m, 2 H, SCH_2CH_2), 2.51–2.57 (m, 2 H, $C=CHCH_2$), 2.83–2.87 (m, 2 H, SCH_2), 6.42 (t, 1 H, J = 7.1 Hz, C=CH), 7.24–7.33, 7.56–7.59 (2 m, 3 and 2 H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 29.8, 32.3, 34.4, 127.3, 127.6, 128.1, 133.5, 136.3, 141.4; HRMS calcd for $C_{12}H_{14}S$ 190.0816, found 190.0821.

11-Phenyl-1,5-dithiacycloundec-10-ene (3f). Ring expansion of **2f** by the general procedure gave a mixture of the two isomers *E*- and *Z*-**3f**, which were poorly separable by flash column chromatography, in a ratio of approximately 1.5–4:1 (57% combined yield). The cyclic sulfide **5b** was also isolated (3%), identical with that isolated above.

***E*-3f**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.33–1.41 (m, 2 H, $C=CHCH_2CH_2CH_2CH_2$), 1.53–1.61 (m, 2 H, $C=CHCH_2CH_2CH_2CH_2$), 1.96–2.04 (m, 2 H, $SCH_2CH_2CH_2S$), 2.09–2.15 (m, 2 H, $C=CHCH_2CH_2CH_2CH_2$), 2.37–2.41 (m, 2 H, $C=CHCH_2CH_2CH_2CH_2S$), 2.62–2.66 (m, 2 H, $CH_2CH_2CH_2SC=C$), 2.97 (t, 2 H, J = 6.3 Hz, $CH_2SC=C$), 6.02 (t, 1 H, J = 7.2 Hz, C=CH), 7.15–7.36 (m, 5 H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.5, 29.4, 29.6, 29.9, 30.5, 32.7, 127.6, 127.9, 129.6, 129.8, 132.9, 139.1; MS m/z (relative intensity) (GCMS) 264 ($M^{\cdot+}$, 22), 189 (23), 158 ($M^{\cdot+}$ – $C_3H_6S_2$, 27), 129 (29), 115 (37), 106 ($C_3H_6S_2$, 100), 91 (23).

***Z*-3f**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.51–1.58 (m, 2 H, $C=CCH_2CH_2$), 1.63–1.79 (m, 4 H, $SCH_2CH_2CH_2S$ and $C=CCH_2CH_2CH_2$), 2.26–2.30 (m, 2 H, $C=CHCH_2CH_2CH_2CH_2S$), 2.59–2.73 (m, 6 H, $SCH_2CH_2CH_2S$ and $C=CCH_2$), 5.92 (t, 1 H, J = 7.7 Hz, C=CH), 7.18–7.29 (m, 3 H, meta and para H's of C_6H_5), 7.54 (d, 2 H, J = 7 Hz, ortho H's of C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 28.6, 29.2, 30.5, 30.8, 31.4, 32.1, 127.6, 127.8, 128.4, 135.8, 137.7, 139.9; MS m/z (relative intensity) (GCMS) 264 ($M^{\cdot+}$, 40), 189 (40), 158 ($M^{\cdot+}$ – $C_3H_6S_2$, 42), 129 (40), 115 (48), 106 ($C_3H_6S_2$, 100), 91 (30); IR (mixture) ($CHCl_3$) 3079, 3057, 2995, 2924, 2854, 1673, 1448 cm^{-1}; HRMS (mixture) calcd for $C_{15}H_{20}S_2$ 264.1006, found 264.0992.

Ring Expansion of 2-Methyl-2-(3′-chloropropyl)-1,3-dithiolane (2g). Ring expansion of **2g** by the general procedure gave the two isomers **3g** and **6g** as an approximately 20:1 mixture in 88% total yield. The two products were partially separated by column chromatography, as described in the general procedure, to give pure **3g** and a 1:1 mixture of **3g** and **6g**.

(*Z*)-8-Methyl-1,4-dithiacyclooct-7-ene (*Z*-3g): IR ($CHCl_3$) 2995, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (d, 3 H, J = 0.7 Hz, CH_3), 2.65–2.69 (m, 2 H, $=CCH_2CH_2$), 2.77–2.84 (m, 2 H, $=CCH_2CH_2$), 2.88 (s, 4 H, SCH_2CH_2), 6.07 (tq, 1 H, J = 8, 1 Hz, CH=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 31.7, 32.2, 33.6, 36.6, 130.6, 138.0; MS m/z (relative intensity) (GCMS) 160 ($M^{\cdot+}$, 22), 132 ($M^{\cdot+}$ – CH_2CH_2, 29), 100 (80), 99 (C_5H_7S, 100), 86 (53), 85 (61); HRMS calcd for $C_7H_{12}S_2$ 160.0380, found 160.0379.

8-Methylene-1,4-dithiacyclooctane (6g): IR ($CHCl_3$) 2995, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81–1.91 (m, 2 H, $CH_2CH_2CH_2$), 2.66–2.67, 2.97–3.01 (2 m, 2 × 2 H, $CH_2CH_2CH_2$), 2.88–2.91, 3.13–3.16 (2 m, 2 × 2 H, SCH_2CH_2), 5.01, 5.18 (2 s, 2 × 1 H, $CH_2=C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 31.1, 31.9, 34.1, 36.7, 111.3, 144.9; MS m/z (relative intensity) (GCMS) 160 ($M^{\cdot+}$, 37), 132 ($M^{\cdot+}$ – CH_2CH_2, 77), 100 (C_5H_8S, 100), 99 (59), 85 (25).

Ring Expansion of 2-Methyl-2-(3′-chloropropyl)-1,3-dithiane (2h). Ring expansion of **2h** by the general procedure gave three isomeric products: *Z*- and *E*-**3h** and **6h**. Column chromatography gave *Z*-**3h** and **6h** as an inseparable mixture (63%) and a small amount of *E*-**3h**, mixed with *Z*-**3h**, **6h**, and starting **2h** (≈20% of products). The overall ratio of **6h**:*Z*-**3h**:*E*-**3h** was approximately 6:3:1.

9-Methylene-1,5-dithiacyclononane (6h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–1.90, 1.90–1.99 (2 m, 2 × 2 H, $SCH_2CH_2CH_2S$ and $CH_2CH_2CH_2$), 2.67–2.72 (m, 2 × 2 H, $CH_2CH_2CH_2$), 2.82–2.86, 3.11–3.15 (2 m, 2 × 2 H, $SCH_2CH_2CH_2S$), 5.14, 5.40 (2 s, 2 × 1 H, CH_2=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.0, 28.6, 29.4, 29.9, 31.3, 115.0, 144.4; MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 37), 132 ($M^{\cdot+} - C_3H_6$, 18), 113 (12), 106 ($C_3H_5S_2$, 10), 100 (C_5H_8S, 100), 99 (24), 85 (13), 67 (14).

(*Z*)-9-Methyl-1,5-dithiacyclonon-8-ene (*Z*-3h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77–1.83 (m, 2 H, $SCH_2CH_2CH_2S$), 2.09 (s, 3 H, CH_3), 2.57–2.62 (m, 2 H, =CCH_2CH_2), 2.76–2.80 (m, 2 H, =CCH_2CH_2), 2.90–3.00 (m, 4 H, $SCH_2CH_2CH_2S$), 5.70 (t, 1 H, *J* = 8 Hz, CH=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.1, 27.5, 28.1, 30.1, 32.3, 133.9, 134.9; MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 52), 127 (16), 113 (13), 106 ($C_3H_5S_2$, 27), 100 (77), 99 (C_5H_7S, 100), 85 (47), 71 (14); IR (mixture) ($CHCl_3$) 3086, 2995, 1602, 1441 cm^{-1}; HRMS (mixture) calcd for $C_8H_{14}S_2$ 174.0537, found 174.0537.

(*E*)-9-Methyl-1,5-dithiacyclonon-8-ene (*E*-3h): ^{1}H NMR (300 MHz, $CDCl_3$) (key signals observed) δ 1.97 (d, 3 H, *J* = 1 Hz, CH_3), 2.29–2.36 (m, 2 H, =CCH_2CH_2), 6.08 (tq, 1 H, *J* = 8, 1 Hz, CH=C); MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 90), 127 (49), 113 (39), 106 ($C_3H_5S_2$, 67), 100 (93), 99 (C_5H_7S, 100), 85 (81), 71 (39).

Acknowledgment. The authors thank Dr. Paul Ortiz de Montellano for his encouragement and National Institutes of Health Grant GM39552 for financial support. A reviewer is acknowledged for helpful suggestions.

Supplementary Material Available: ^{1}H and ^{13}C spectra (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Facile Synthesis of Tepoxalin, 5-(4-Chlorophenyl)-*N*-hydroxy-1-(4-methoxyphenyl)-*N*-methyl-1*H*-pyrazole-3-propanamide

William V. Murray* and Susan K. Hadden

The R. W. Johnson Pharmaceutical Research Institute, P.O. Box 300, Route 202, Raritan, New Jersey 08869-0602

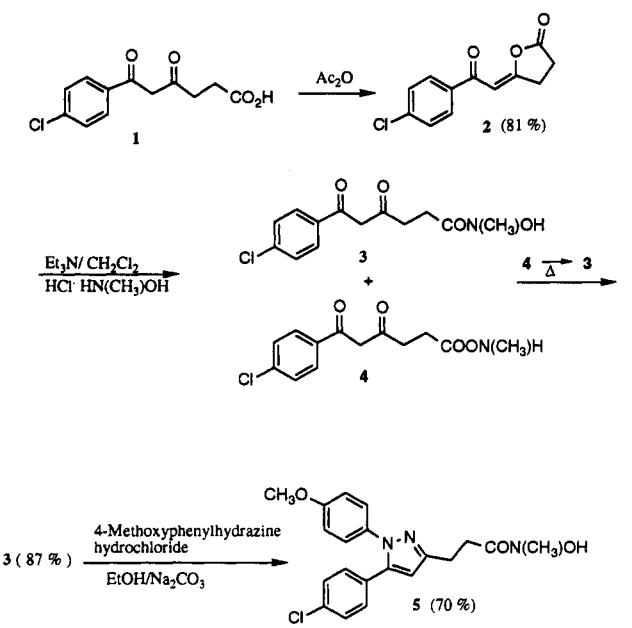
Received June 29, 1992

Tepoxalin (**5**)[1] is a potent inhibitor of both the cyclooxygenase and lipoxygenase pathways of the arachidonic acid cascade. We have previously described a highly efficient regioselective synthesis of this compound.[2] Due to toxicity considerations it became desirable to synthesize tepoxalin without using methylene chloride or oxalyl chloride in the last step. Herein we report a high-yield synthesis of tepoxalin which meets this objective.

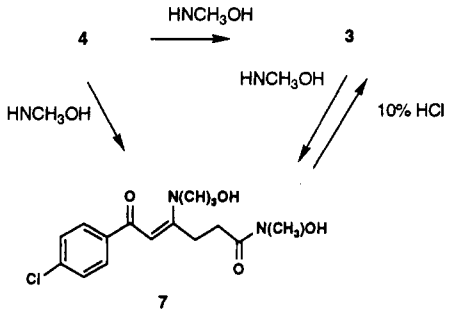
Results and Discussion

The synthesis of tepoxalin is outlined in Scheme I. The starting 6-(4-chlorophenyl)-4,6-dioxohexanoic acid (**1**) was previously synthesized in our laboratories.[2,3] When **1** was treated with acetic anhydride at 100 °C the enol lactone **2** was produced in 81% yield.[4] Compound **2** was added

Scheme I



Scheme II



to *N*-methylhydroxylamine hydrochloride in methylene chloride containing triethylamine, initially forming a mixture of the N- and O-acetylated *N*-methylhydroxylamines. Stirring at room temperature with excess *N*-methylhydroxylamine converts the O-acylated compound **4** to the N-acylated compound **3** in 87% yield.

During the course of performing this reaction we noticed that a portion of **3** was isolated from the aqueous acid portion of our workup. We surmised that some intermediate to **3** was being extracted into the acid phase and hydrolyzed in the aqueous phase to **3**. We felt that the extracted compound was likely to be **7**. By direct chromatography of the concentrated reaction mixture we were able to isolate a small quantity of a compound whose spectral properties (notably the UV absorbance at 322 nm) were consistent with **7**.[5] Furthermore this compound could be converted to **3** by dissolving it in 10% HCl (Scheme II). We can envision a number of mechanisms by which **4** can be converted to **3**. Scheme III outlines a mechanism where **4** closes to an internal vinylogous amide **6**. The six-membered ring can then be opened by excess *N*-methylhydroxylamine to afford **7** which is then hydrolyzed to **3** during acidic workup. In an attempt to isolate **6**, we dissolved **4** in methylene chloride and allowed it to stand at room temperature overnight. With no additional *N*-methylhydroxylamine present we found 70% of **4** had been converted to **3**. An alternative mechanism is shown in Scheme IV where **4** is converted to **3** through the in-

(1) (a) Wachter, M.; Ferro, M. U.S. Patent 4,826,868, 1989. (b) Robinson, C. *Drugs Future* **1990**, *15* (9), 202 and references therein.
(2) Murray, W.; Wachter, M., Barton, D., Forrero-Kelly, Y. *Synthesis* **1991**, 18.
(3) Murray, W.; Wachter, M. *J. Org. Chem.* **1990**, *55*, 3424.
(4) Hori, K.; Takaishi, N., *Bull. Chem. Soc. Jpn.* **1988**, *61* (5), 1791.
(5) Ostercamp, D. *J. Org. Chem.* **1965**, *30* (4), 1169 and references therein.

0022-3263/92/1957-6662$03.00/0