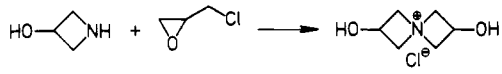
The sample of charamin used for the analytical studies has a minor impurity which could be removed by HPLC. This impurity was presumably an artifact since it could not be detected in the raw material. It was of no consequence with regard to the structure elucidation; however, it prohibited the determination of a reliable optical rotation value.

Charamin was synthesized (with concomitant formation of 1,3-dichloro-2-propanol) by the reaction of azetidin-3-ol, obtained by hydrogenolysis of 1-(diphenylmethyl)azetidin-3-ol,[11] with epichlorohydrin in analogy with the reported preparation of 1,1-diethyl-3-hydroxyazetidinium chloride.[10] The 500-MHz ^1H and ^{13}C NMR spectra of the



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natural and synthetic material were superimposable. The activity toward a natural bacteria population at a concentration of 4 μg/mL was about 60%. Work is in progress to optimize the synthetic procedure, to clarify the stereochemical identity (whether optical active or racemic) of the natural product, and to investigate the biological activity in more detail.

Experimental Section

The NMR measurements were obtained from a Bruker AM 500 spectrometer or a JEOL FX 90Q instrument. Samples were prepared in D_2O. IR spectra were recorded on a Perkin-Elmer 580 spectrometer and FAB mass spectra on a VG Masslab VG 20-250 Quadropole mass spectrometer fitted with a VG FAB source and probe. The primary beam of xenon atoms was produced from an ion gun operating at 1.0 mA, 8 kV.

Isolation of Charamin (3). Lyophilized *Chara globularis* (855 g dry weight) was extracted twice with petroleum ether (0.06% extract), three times with ethyl acetate (0.24% extract), and twice with water. All extractions were carried out at room temperature, and extractions with water were limited to 24 h in order to minimize any microbial growth during extraction. Lyophilization of the combined aqueous extracts left 51.84 g (6.1%) of crude material. The bioassay was performed in a standard procedure as follows: Filtered pond water (25 mL), 50 μL of test solution (2 mg/mL), and tritium-labeled glucose were incubated at 20 °C for 1 h. The bacteria were removed by filtration, and the activity was determined by scintillation counts. The activity was expressed relative to a control without test solution. The amount of [^{3}H]glucose added was adjusted to give a control sample with about 2000 cpm.

The crude material, which was mainly organic (C, 30.36%; H, 5.19; N, 5.16%; S; 1.09%; 26.65% combustion residue), reduced the tritium uptake to 12% and 21% on addition of 100 and 10 μL of test solution, respectively. Gel filtration (Sephadex G-25) did not significantly concentrate the active material. However, purification was achieved with cellulose chromatography (Avicel, Merck, 150 g) with 2-propanol/water (80:20) as eluent. Separation of 10 g of crude material afforded 249 mg, which after partition between water (5 mL), and chloroform (5 mL) left 71 mg of active material in the aqueous phase (reduction of tritium uptake to 20%). Repeated purification of this material by HPLC (RP-18, water/acetonitrile, 90:10 followed by 97:3) gave thymidine (0.03% of aqueous extract), deoxyuridine (0.07%), and the active material (0.4% of aqueous extract or 0.02% of dry plant material). Thymidine and deoxyuridine were identified by ^1H NMR, UV, and MS; all data were identical with the published values.

The active fraction had a minor impurity which affected the elemental analysis slightly. Calcd for $C_6H_{12}ClNO_2 \cdot 6H_2O$: C, 26.33; H, 8.78; N, 5.12; ionic Cl, 12.98. Found for charamin: C, 26.21; H, 6.75; N, 6.64; ionic Cl, 12.5.

Synthesis of Charamin (3). Preparation of the hydrochloride of azetidin-3-ol was performed in accordance with ref 11. The ^{13}C NMR spectrum exhibited signals at 63.7 (CH) and 57.5 (CH_2) ppm and ^1H NMR showed complex multiplets from 3.84–4.34 and 4.56–4.86 ppm, the latter multiplet superimposed on the intense HOD resonance. The IR spectrum (KBr) had strong absorptions at 3390, 3210, and 3015 cm^{-1} and medium strong bands at 1625, 1433, 1300, 1240, 1158, and 1085 cm^{-1}. A sample of the free amine was prepared by addition of potassium hydroxide (three pellets) to 4.6 mmol of hydrochloride dissolved in a small amount of water. Wet amine was then obtained by vacuum distillation (30 °C) into a reaction flask cooled in N_2 liquid. The reaction was performed by addition of epichlorohydrin (4 mmol) and stirring for 1 day at room temperature. ^{13}C NMR of the residue left by evaporation reveals the product to be a mixture of 1,3-dichloro-2-propanol (72.5 and 47.9 ppm) and charamin. Preparative HPLC on a RP-8 column with acetonitrile/water (10:90) with a refractive index detector yielded 65 mg (10%) of charamin. The synthetic product exhibited ^1H and ^{13}C data identical with those of the natural product and FAB MS gave the 4-azoniaspiro[3.3]heptane-2,6-diol cation at m/z 130.08 (calcd for $C_6H_{12}NO_2$, m/z 130.06).

Acknowledgment. We are indebted to The Carlsberg Foundation, The Danish Natural Science Research Council, The NOVO Research Foundation, and The Thomas B. Thriges Foundation for financial support.

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3-Ferrocenyl-2*H*-thiete and 3-Ferrocenyl-2*H*-thiete 1,1-Dioxide

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Previous attempts to prepare transition-metal complexes of thietes (thiacyclobutenes), as distinct from preparing thietes with an organometallic substituent, resulted in ring opening to give complexes of the rare α,β-unsaturated thioaldehydes (enethials).[1] We report here the synthesis of a thiete substituted by a ferrocenyl group, a stable species in which the thiacyclobutene ring is intact. The synthesis involves an enamine derived from 3-acetylferrocene. Ferrocenyl enamines are uncommon, the examples **1** and **2** being prepared by special methods.[2,3] Treatment of ferrocenyl ketones with amines in the presence of aluminum chloride[4] or titanium tetrachloride[5] gave iminium salts with secondary amines and imines with primary amines; no mention was made of enamine formation. Acetylferrocene did not react with the dimethylamine–aluminum chloride complex[4] but gave enamine **3** on treatment with aniline–DMF–$POCl_3$.[3]

The original procedure of White and Weingarten[6] for the preparation of enamines, which involved addition of titanium tetrachloride to a solution of amine and ketone

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(2) Mueller-Westerhoff, U. *Tetrahedron Lett.* **1972**, 4639.

(3) Boev, V. I.; Dombrovskii, A. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1984**, *54*, 1439.

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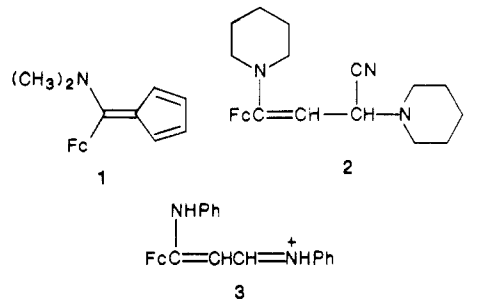
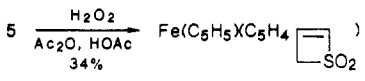


in benzene, when applied to acetylferrocene led only to a purple oil and no detectable amount of enamine. Reasoning that this result might be caused by formation of a stable titanium complex[7] with the relatively basic acetyl group, we avoided that complication by slowly adding the acetylferrocene to a mixture of titanium tetrachloride and dimethylamine in benzene. Under these conditions, in which an amine–titanium complex was presumably involved, an 89% yield of the enamine 4 was obtained.

Scheme I outlines the remaining steps in the synthesis of 3-ferrocenyl-2*H*-thiete (7). The procedures in the scheme were developed previously for the preparation of stable 3-arylthietes.[1b] 3-Ferrocenyl-2*H*-thiete is stable for several days at room temperature and may be kept for a long time at 0 °C without decomposition. The sulfone derivative 8 of the new thiete is obtained by a Cope elimination from the *N*,*N*-dimethylamino sulfone 5.



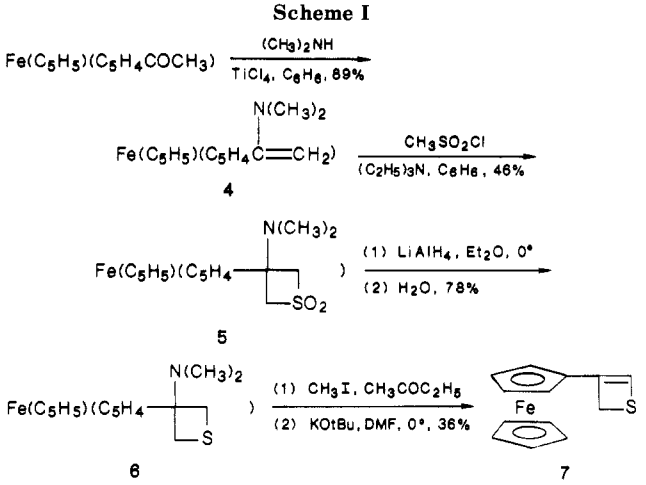
Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian T-60 spectrometer, and carbon-13 NMR spectra were obtained on a Varian CFT-20 spectrometer. Infrared spectra were taken on a Perkin-Elmer 710B spectrometer. Mass spectra were obtained on a Finnegan 4000 spectrometer. Elemental analyses were done by Microanalysis, Inc., Wilmington, DE.

3-Ferrocenyl-3-(*N*,*N*-dimethylamino)-2*H*-thiete 1,1-Dioxide (5). Titanium tetrachloride (12.5 g, 0.066 mol) in dry, degassed benzene (50 mL) was added with stirring during 90 min to a solution of anhydrous dimethylamine (59.0 g, 1.32 mol) in dry benzene (300 mL) cooled in an ice–salt bath in an atmosphere of nitrogen. Acetylferrocene (30.0 g, 0.132 mol) in dry benzene (200 mL) was added during 1 h to this mixture. The reaction mixture was allowed to stand overnight under nitrogen and filtered under nitrogen and the benzene removed under reduced pressure to yield an orange-brown oil (30.0 g, 0.120 mol, 89%): ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 6 H), 4.0–4.7 (m, 11 H); IR (thin film) 3100 (s), 2950 (m), 1680 (s), 1580 (m), 1340 (m) cm^{-1}. The *N*,*N*-dimethyl-*N*-(1-ferrocenylvinyl)amine (4) was used without further purification.

Methanesulfonyl chloride (13.5 g, 0.120 mol) in dry benzene (50 mL) was added over a 1-h period to a mixture of the crude enamine 4 (30.0 g, 0.120 mol) in dry benzene (200 mL) and triethylamine (35.7 g, 0.350 mol) under nitrogen and cooled in an ice–salt bath. The reaction mixture was stirred overnight. Diethyl ether (200 mL) and water (200 mL) were added, and the mixture was stirred for 10 min. (Product may precipitate at this point.) The ether–benzene layer was separated and dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give an orange-yellow solid, 5, which was recrystallized from ethanol (18.2 g, 0.055 mol, 46.0%): mp 145 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H), 4.0–4.9 (m, 13 H): IR (KBr) 1350 (m), 1300 (s), 1210 (s), 1150 (m), 1130 (s), 1050 (m), 1010 (m), 820 (m) cm^{-1}.

Scheme I



3-Ferrocenyl-2*H*-thiete (7). Lithium aluminum hydride (2.84 g, 0.075 mol) was added under nitrogen to a solution of amino sulfone 5 (10.0 g, 0.03 mol) in dry diethyl ether (500 mL) and cooled in an ice–salt bath over a 2-h period followed by stirring for 2 h. Slow addition of water (5 mL), 20% aqueous sodium hydroxide (5 mL), and water (10 mL) hydrolyzed the lithium salts and unreacted lithium aluminum hydride. The residue was filtered and washed with methylene chloride (200 mL). The combined filtrate and methylene chloride wash solution was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give a yellow solid, 6 (7.0 g, 0.023 mol, 77.6%): mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 6 H), 3.8–4.5 (m, 13 H); IR (KBr) 1400 (w), 1300 (w), 1250 (w), 1180 (w), 1040 (w), 1000 (w), 800 (m) cm^{-1}.

Methyl iodide (3.3 g, 0.023 mol) was added to a cold (0 °C) solution of aminothietane 6 (7.0 g, 0.023 mol) in dry methyl ethyl ketone (45 mL). The reaction mixture was cooled in a freezer at −30 °C overnight. Upon addition of diethyl ether (40 mL), an orange-yellow methiodide salt precipitated (5.3 g, 0.012 mol, 52.0%): mp 60–61 °C; IR (KBr) 1460 (s), 1280 (m), 1200 (w), 1100 (m), 990 (m), 950 (s), 800 (s) cm^{-1}. The salt decomposed in the deuteriated NMR solvents, *N*,*N*-dimethylformamide, or dimethyl sulfoxide.

Potassium *tert*-butoxide (2.0 g, 0.018 mol) in dry dimethylformamide (20 mL) was added to a stirred cold (−30 °C) solution of methiodide (4.3 g, 0.0097 mol) in dry dimethylformamide (20 mL) under nitrogen over a period of 30 min. The reaction was warmed to 0 °C and poured into ice–cold water (100 mL) and diethyl ether (100 mL). The ether layer was washed with 5% aqueous hydrochloric acid (4 × 50 mL) and dried over anhydrous magnesium sulfate. Removal of the ether afforded the orange ferrocenylthiete 7 (0.90 g, 0.0035 mol, 36%): mp 85 °C; ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 2 H), 4.3 (s, 9 H), 6.4 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 134.8, 123.6, 80.5, 69.4, 69.2, 68.2, 36.2; IR (KBr) 1400 (m), 1240 (m), 1090 (s), 1010 (s), 990 (s), 800 (s), 770 (s) cm^{-1}; MS, *m*/*e* (relative intensity) 256 (M^+, 100), 255 (2), 191 ($M - C_5H_5$, 39), 121 (C_5H_5Fe, 9.8), 56 (Fe, 12). Anal. Calcd for $C_{13}H_{12}FeS$: C, 60.98, H, 4.69. Found: C, 60.66, H, 4.63.

3-Ferrocenyl-2*H*-thiete 1,1-Dioxide (8). 3-(*N*,*N*-Dimethylamino)-3-ferrocenyl thietane 1,1-dioxide (5) (6.0 g, 0.018 mol) in glacial acetic acid (10 mL)–acetic anhydride (10 mL), cooled in an ice–salt bath, was treated with aqueous hydrogen peroxide (4 g, 30%) added over a period of 10 min. After the reaction mixture was stirred for 2 h at 0 °C and for 16 h at room temperature, it was cooled to 0 °C and made basic by addition of aqueous 20% sodium hydroxide. The solvents were removed, and the residue was treated with chloroform (75 mL) and filtered. Removal of the chloroform gave the sulfone as an orange, crystalline solid that was recrystallized from chloroform–pentane (1.8 g, 0.0062 mol, 34%): mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 1 H), 4.66 (s, 2 H), 4.49, 4.26 (2 s, 9 H); ^{13}C NMR ($CDCl_3$) δ 149.4, 132.9, 72.2, 71.6, 70.8, 70.2, 68.8; IR (KBr) 1590 (m), 1310 (s), 1290 (s), 1220 (s), 1150 (s), cm^{-1}. Anal. Calcd for $C_{13}H_{12}FeO_2S$: C, 54.19; H, 4.20. Found: C, 54.05; H, 4.25.

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