solved in 40 ml of methylene chloride and treated with 2.1 ml of THF containing 63 mg of 70% $HClO_4$ solution at room temperature for 1.5 hr. The reaction mixture was washed with saturated sodium chloride solution. The methylene chloride layers were dried over Na_2SO_4 and evaporated to dryness. The products were isolated by silica gel column chromatography, to give 63 mg of **9**[3] (R_1 = CH_3, R_2 = H) (mp (EtOAc) 127–128°, 65%).

In the preparation of 3,6-epidithio-1,3,4-trimethyl-6-hydroxymethyl-2,5-dione (**11**) (R_1 = CH_2OH, R_2 = CH_3) the monomethoxymethyl thioacetal **5**[3] (R_2 = CH_2OCH_3, R_3 = H) was prepared in 60% yield by the same procedure as above. The second alkylation with methyl iodide was again carried out under the same conditions to yield the methoxymethyl methyl thioacetal **10**[3] (R_2 = CH_2OCH_3, R_3 = CH_3) (mp 200–201°) in 76% yield.

The methoxymethyl methyl thioacetal **10**, 50 mg, was dissolved in 5 ml of methylene chloride and cooled with an ice bath. *m*-Chloroperbenzoic acid, 28 mg, was added portion-wise. After the reaction mixture had been kept at 0° for 10 min, 5 ml of BCl_3 was added at 0°. After 10 min the reaction mixture was evaporated under reduced pressure. The residue was dissolved in 5 ml of methanol and taken to dryness. The products were isolated by preparative tlc (silica gel) to afford 18 mg of **11**[3] (R_1 = CH_2OH, R_2 = CH_3) (mp-(EtOAc) 122–125°, 56%).

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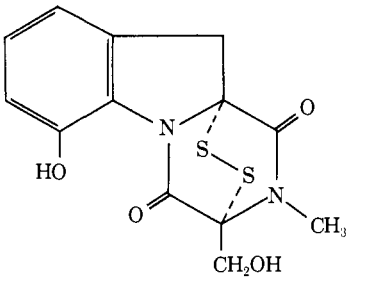
A Total Synthesis of Dehydrogliotoxin

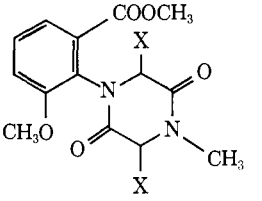
Sir:

Dehydrogliotoxin (**1**),[1] the dehydrogenation product of gliotoxin,[2] was found in surface cultures of an isolate of *Penicillium terlikowskii* and shown to inhibit the growth of *Bacillus subtilis* at concentrations similar to the inhibitory concentration of gliotoxin.[3] In this communication we report the first total synthesis of *d,l*-dehydrogliotoxin (**1**) based on the method described in the preceding paper.[4]

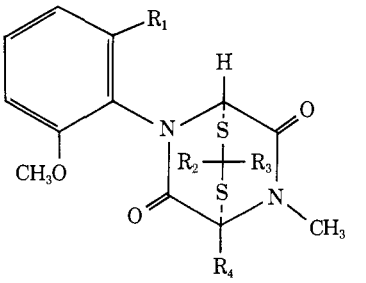
Heating 1-methylpiperazine-2,5-dione[5] with 2-iodo-3-methoxybenzoic acid[6] in nitrobenzene in the presence of cuprous iodide and potassium carbonate at 170° for 40 min, followed by esterification with diazomethane, afforded the diketopiperazine **2**[7] (mp 140–141°) in 50% yield. Oxidation of **2** with NBS benzoyl peroxide in carbon tetrachloride and work-up with potassium thioacetate in methylene chloride at room temperature gave



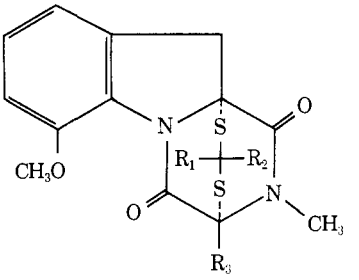
1, dehydrogliotoxin



2, X = H
3, X = SAc (1:1 cis and trans mixture)



4, R_1 = $COOCH_3$; R_4 = H;
R_2 or R_3 = H or *p*-$CH_3OC_6H_4$
(1 : 1 diastereomeric mixture)
5a, R_1 = CH_2Cl; R_2 = R_4 = H;
R_3 = *p*-$CH_3OC_6H_4$
b, R_1 = CH_2Cl; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = R_4 = H
8, R_1 = CH_2Cl; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = H; R_4 = CH_2OCH_3



6a, R_1 = R_3 = H; R_2 = *p*-$CH_3OC_6H_4$
7a, R_1 = H; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = CH_2OCH_3
b, R_1 = *p*-$CH_3OC_6H_4$; R_2 = H;
R_3 = CH_2OCH_3

the dithioacetate **3**[7] (mp 168–175°, *ca.* 1:1 mixture of cis and trans isomers). This cis–trans mixture of **3** was transformed into the anisaldehyde adduct **4**[7] (mp

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(3) G. Lowe, A. Taylor, and L. C. Vining, *J. Chem. Soc.*, 1799 (1966).
(4) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6490 (1973).
(5) P. A. Levene, L. W. Bass, A. Rothen, and R. E. Steiger, *J. Biol. Chem.*, **81**, 697 (1929).
(6) W. M. Stanley, E. McMahon, and R. Adams, *J. Amer. Chem. Soc.*, **55**, 706 (1933).

(7) Satisfactory analytical and spectroscopic data were obtained on this compound.

222–225°, *ca.* 1:1 diastereomeric mixture at the anisaldehyde residue) by treatments with methanolic hydrogen chloride at 50° and then anisaldehyde in methylene chloride containing a trace of boron trifluoride etherate at room temperature.[4] The overall yield from **2** to **4** was 45%. Compound **4** was converted to the 1:1 diastereomeric mixture of the chlorides **5a**[7,8] (mp 212–213°) and **5b**[7,9] [mp 119–120° (from benzene)] by the following four steps in 41% overall yield: (1) sodium hydroxide in aqueous dioxane at room temperature, (2) *N,N'*-carbonyldiimidazole in THF at room temperature, (3) lithium borohydride at 0°,[10] and (4) carbon tetrachloride and tri-*n*-octylphosphine at room temperature.

Treatment of the diastereomeric mixture (*ca.* 1:1) of the chlorides **5a** and **5b** in THF at −110° with butyllithium (1.1 equiv), followed by acetic acid work-up, gave the cyclized compound **6a**[7] [38%, mp 223–224°; $\delta_{ppm}^{CDCl_3}$ 3.15 (3 H, s), 3.75 (3 H, s), and 3.98 (3 H, s)] and recovered chloride **5b** (35%). This result can be explained, as the position of the carbanion formation is determined by the stereochemistry of the anisaldehyde residue and, therefore, only the diastereomeric chloride **5a** can be used for the cyclization.[4] Alkylation of **6a** with chloromethyl methyl ether (1.0 equiv of BuLi in THF at −78°) afforded the methoxymethyl derivative **7a**[7] [mp 172–173°; $\delta_{ppm}^{CDCl_3}$ 3.23 (3 H, s), 3.46 (3 H, s), 3.76 (3 H, s), and 4.01 (3 H, s)] in 61% yield.[11]

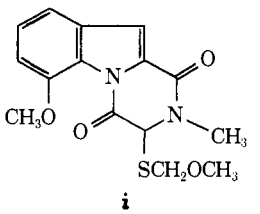
The chloride **5b**, recovered from the cyclization with butyllithium, can be utilized for the synthesis in two ways. One is to epimerize **5b** under acidic conditions to an equilibrium mixture with respect to the asymmetric center associated with the anisaldehyde residue; namely, treatment of **5b** with boron trifluoride etherate in boiling methylene chloride for 15 hr formed an equilibrium mixture of **5a** (3 parts) and **5b** (2 parts), which can be used for the cyclization with butyllithium. Thus, an overall yield from a mixture of **5a** and **5b** to **6a** went up 55% after two cycles of the equilibration. The second way is to use the monocarbanion of **5b** for alkylation with chloromethyl methyl ether first. Namely, the chloride **5b** was converted to the compound **8**[7] (mp 141–142°) in 49% yield under the standard conditions.[4] Addition of butyllithium (1.1 equiv) to **8** in THF at −78° generated the carbanion at the desired position, to yield the cyclized compound **7b**[7] [mp 228–229°; $\delta_{ppm}^{CDCl_3}$ 3.39 (3 H, s), 3.48 (3 H, s), 3.77 (3 H, s), and 3.94 (3 H, s)] in 80% yield. The cyclized compound **7b** is epimeric to **7a** at the anisaldehyde residue.

(8) About the assignment of the stereochemistry of **5a** and **5b**, see ref 4. Pure **5a** was isolated by crystallization of the about 3:2 diastereomeric mixture of **5a** and **5b** from hot ethyl acetate.

(9) Pure **5b** was obtained from the material recovered in the cyclization with butyllithium on the mixture of **5a** and **5b**.

(10) The intermediate at this stage (R = CH_2OH in the structure **4**) could be prepared directly from **4** by lithium aluminum hydride reduction in THF at 0°, but the yield by a one-step procedure was lower.

(11) One of the by-products was **i**.



i

Finally, the compounds **7a** and **7b** were converted to *d,l*-dehydrogliotoxin (**1**) by treatment with *m*-chloroperbenzoic acid in methylene chloride and then boron trichloride in methylene chloride at 0°. *d,l*-Dehydrogliotoxin (**1**)[7] (mp 177–178°; M^+ (found) 324.0251, (cald) 324.0238) was isolated by preparative tlc (silica gel) in 20% yield and identified as authentic dehydrogliotoxin (**1**)[3,12] by comparison with nmr,[13] ir, uv, and mass[13] spectra and tlc behavior.

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(12) We are indebted to Dr. Safe, National Research Council of Canada, Halifax, and Drs. Nagarajan and Neuss, Eli Lilly and Co., for their generous gifts of natural gliotoxin.

(13) We thank Drs. Dudek and Balaram, Harvard University, for the measurement of the exact mass spectrum and the FT-nmr spectrum.

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A Total Synthesis of Sporidesmin A

Sir:

Sporidesmins are toxic metabolites of *Pithomyces chartarum*, which cause the serious disease in sheep known as "facial eczema" in New Zealand. Successful isolation and structure determination of seven different sporidesmins, A through G, were carried out by Taylor and his coworkers.[1] In this communication we report a formal stereospecific total synthesis of sporidesmin A (**1**), the major metabolite of *Pithomyces*.

The diketopiperazine moiety of the sporidesmins was synthesized in the following way. Treatment of 1,6-dimethylpiperazine-2,5-dione[2] with chloromethyl methyl ether in *tert*-butyl alcohol containing potassium *tert*-butoxide (1.2 equiv) at room temperature gave 1,6-dimethyl-4-methoxymethylpiperazine-2,5-dione **2**[3a] (mp 46–48°) in 70% yield. Bromination of **2** by NBS benzoyl peroxide in carbon tetrachloride, followed by potassium thioacetate work-up in methylene chloride at room temperature, afforded the thioacetate **3**[3a] (mp 83–84°) in 74% yield. The thioacetate **3** was converted into the thioacetal **4**[3a] (mp 132–142°, *ca.* 1:2 syn and anti mixture with respect to the anisaldehyde and methoxymethyl residues) by treatment with hydrogen chloride in methanol at 50° and then the trithiane derivative[4] of anisaldehyde in boiling methylene chloride containing boron trifluoride etherate. The reaction with the trithiane probably involves a carbonium ion

(1) Sporidesmins. Parts I to XIII. The latest report: S. Safe and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 472 (1972).

(2) L. Birkofer, A. Ritter, and P. Neuhausen, *Justus Liebigs Ann. Chem.*, **659**, 190 (1962).

(3) (a) Satisfactory analytical and spectroscopic data were obtained on this compound. (b) Satisfactory spectroscopic data were obtained on this compound.

(4) E. Baumann and E. Fromm, *Chem. Ber.*, **24**, 1441 (1891).