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AN EFFICIENT SYNTHESIS OF d,l-GLIOVICTIN: CONSTRUCTION OF THE HYDROXYMETHYL MOIETY VIA A 3-FORMYL-2,5-PIPERAZINEDIONE

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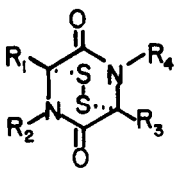
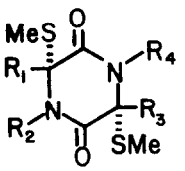
The epidithiapiperazinedione moiety (1), is common to the class of fungal metabolites[1] which includes the gliotoxins, sporidesmins, verticillins, aranotins, hyalodendrins and others. The cyclic disulfide of these metabolites is responsible for their potent antiviral and antibiotic properties. The corresponding bis-dethio(methylthio) derivatives (2) of these metabolites are also naturally occurring, but are of reduced toxicity.



1



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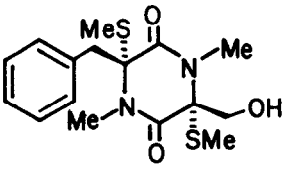
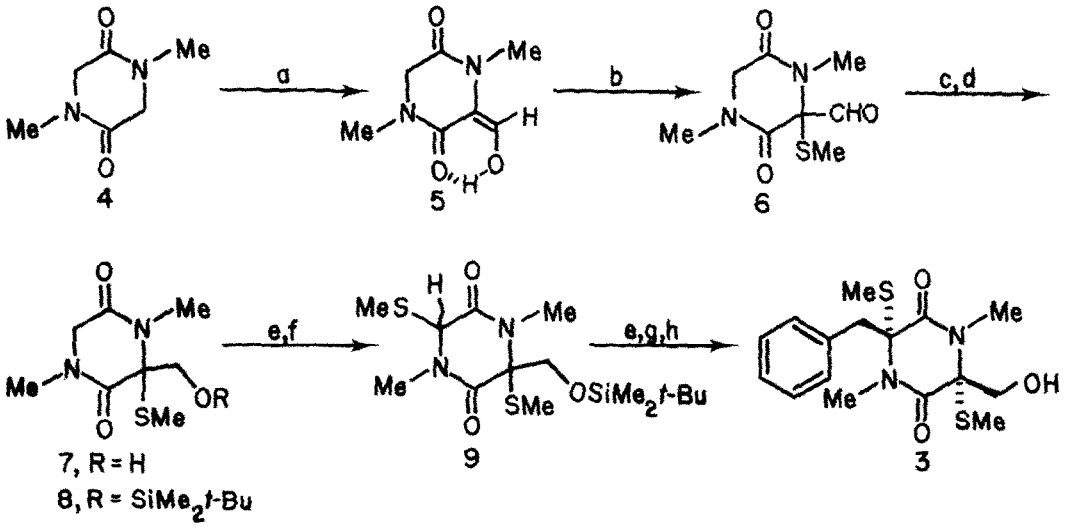


3

Introduction of sulfur into the 2,5-piperazinedione nucleus has been achieved[1] utilizing both nucleophilic and electrophilic sources of sulfur. As part of a program directed toward the synthesis of 1, we report the synthesis of the title compound 3,[2] via mild and selective introduction of electrophilic sulfur. The key element of our approach is the reduction of an α-methylthio carboxaldehyde (e.g., 6→7) formed by the efficient sulfenylation[3] of a 3-formyl-2,5-piperazinedione (e.g., 5→6). The hydroxymetnyl moiety (e.g., 7), present in numerous, naturally occurring epipolythia-2,5-piperazinediones, to date has been successfully constructed only via Kishi's elegant approaches.[4]

Treatment of sarcosine anhydride (4), and 2.0 eq. of sodium methoxide in THF (0°C), with 5.0 eq. of ethyl formate, afforded after two hrs. at reflux, the insoluble sodium salt of 5, which was filtered, washed with THF and acidified (1.0 eq. 1 N HCl). Removal of water *in vacuo* and trituration of the resulting white powder with CH_2Cl_2, gave pure enol 5[5,6] in 95% yield (recryst.$CHCl_3$, m.p. 143-145°C). Addition of 1.3 eq. CH_3SCl[7] to a THF solution of 5 and 1.1 eq. Et_3N at -100°C[8] produced, after filtration of insoluble $Et_3N{\cdot}HCl$, analytically pure

Scheme I



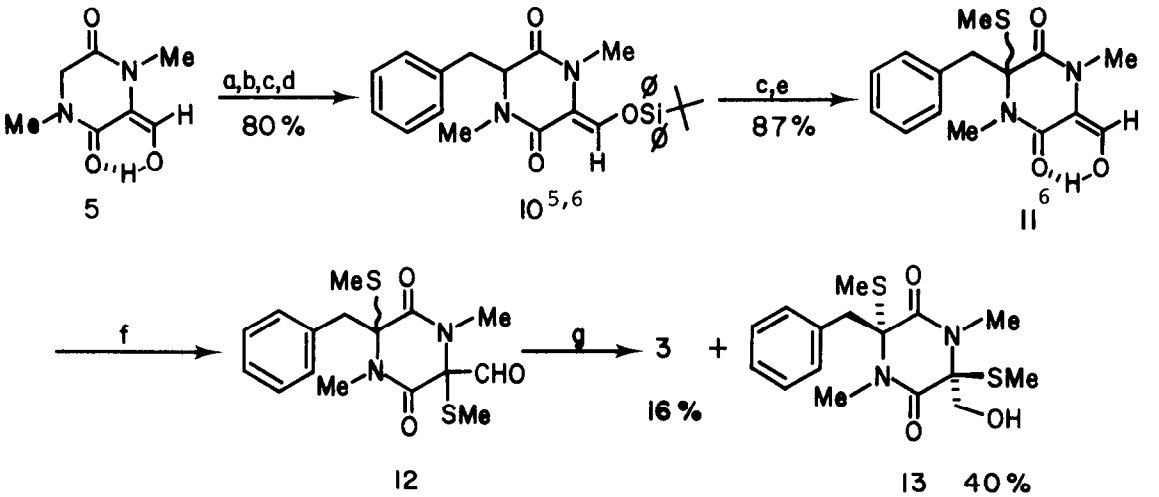
REAGENTS: a) HCOOEt, NaOMe, THF b) CH_3SCl, Et_3N, THF, -100°C c) LiAl(tert-BuO)$_3$H, THF, -78°C d) tert-butyldimethylsilyl chloride, imidazole, DMF e) LDA, THF, -78°C f) methyl disulfide, THF, -78°C g) benzyl bromide, THF, -78°C h) 2N HCl/MeOH, 1 hr., room temp.

methylthio carboxaldehyde 6[5,6] (quantitative yield, m.p. 98-100°C). Reduction of 6 with 1.5 eq. LiAl(tert-BuO)$_3$H in THF at -78°C afforded, after workup, the pure alcohol 7[5,6] in 92% yield (recryst. CH_2Cl_2/Et_2O/EtOAc, m.p. 104-106°C). The alcohol was cleanly protected as its tert-butyldimethylsilyl ether 8[6] in quantitative yield.

Stereoselective conversion of 8 to d,l-gliovictin (3), was achieved by introduction of the remaining thiomethyl and benzyl groups. Thus, sulfenylation of the enolate of 8 with methyl disulfide gave after chromatography (silica gel, EtOAc) a mixture of distereomers 9[6] (51% yield or 66% based on recovered 8). Benzylation of the enolate of 9 (see 14), deprotection and chromatography (silica gel, EtOAc) gave d,l-gliovictin in 85% yield (m.p. 118-120°C) which was indistinguishable from natural material[9] by ^{1}H NMR, IR, MS, TLC and combustion analysis.[10]

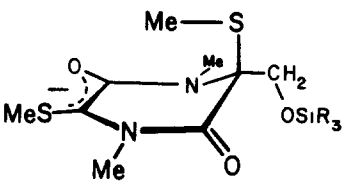
Analysis of crude 3 (Scheme 1) by HPLC (Porasil, CH_2Cl_2/EtOAc 1:1) revealed that less than 10% of diastereomeric material (see 13, Scheme 2) was formed in the benzylation step (9 → 3). Inspection of Dreiding or CPK molecular models of the enolate 14 indicates a preference for the conformation in which the bulky tert-butyldimethylsilyl group is held in a psuedoequatorial position and the methylthio group remains psuedoaxial. As shown in structure 14, the psuedoaxially disposed methylthio group can thereby shield one face of the enolate from electrophilic attack.[11]

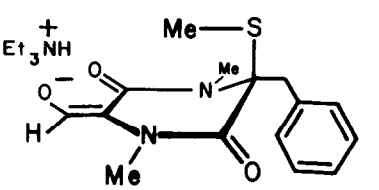
Scheme 2



REAGENTS: a) tert-BuOK, EtOH, THF b) tert-butyldiphenylsilyl chloride, DMF c) LDA, THF, -78°C d) benzyl bromide, THF, -78°C e) methyl disulfide, THF, -78°C f) CH_3SCl, Et_3N, THF, -100°C[8] g) $LiAl(tert\text{-}BuO)_3H$, THF, -78°C

Introduction of the thiomethyl groups in reverse order as depicted in Scheme 2 (cf. Scheme 1) led, with lower stereoselectivity, to a mixture of d,l-gliovictin (3) and its diastereomer, epi-gliovictin (13)[12] (separated on silica gel, 2% $MeOH/CH_2Cl_2$). The preponderance of diastereomer 13 produced in this sulfenylation/reduction sequence (Scheme 2, 11→ 12→ 13) may again reflect the shielding effect of a psuedoaxial thiomethyl group (cf. 15 and 14) during sulfenylation.





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4. a) T. Fukuyama, S. Nakatsuka and Y. Kishi, Tetrahedron Lett., 3393 (1976); b) Y. Kishi, T. Fukuyama and S. Nakatsuka, J. Amer. Chem. Soc., 95, 6490 (1973).
5. Satisfactory combustion analytical data were obtained for this compound.
6. Satisfactory spectroscopic data (^{1}H NMR, IR, MS) were obtained for this compound.
7. CH_3SCl was freshly prepared according to the procedure of H. Brintzinger, K. Pfannstiel, H. Koddebusch and K.E. Kling, Chem. Ber., 83, 87 (1950).
8. THF/liquid nitrogen slush bath provides a reaction temperature of -100°C.
9. Dr. George M. Strunz, Canadian Forestry Service.
10. Synthetic gliovictin: NMR, 90 MHz ($CDCl_3$) δ(Me_4Si): 1.54 (1H, exch., broad unsym. triplet, J_{ax}=7 Hz, J_{bx}=7.5 Hz); 2.14 (3H,s); 2.31 (3H,s); 3.04 (3H,s); 3.29 (3H,s); 3.15 (1H, 1/2 ABq, J=14 Hz); 3.75 (1H, 1/2 ABq, J=14 Hz); 3.14 (1H, dd, J_{ax}=7 Hz, J_{ab}=12 Hz);3.85 (1H, dd, J_{bx}=7.5 Hz, J_{ab}=12 Hz); 7.08-7.4 (5H, m). IR (KBr): 3380, 1660, 1636, 1499, 1373, 735, 700 cm^{-1}. Anal. calcd. for $C_{16}H_{22}N_2O_3S_2$: C, 54.21; H, 6.25; N, 7.90; S,18.09; found: C, 54.28; H, 6.31; N, 7.69; S, 18.31. Mass spectrum: M-1 at 353 (weak), m/e= 323.08629 ($C_{15}H_{19}N_2O_2S_2$, requires 323.08880), m/e= 307.11066 ($C_{15}H_{19}N_2O_3S$, requires 307.11164).
11. For a related observation, see ref. 4a and Ph.D. thesis, T. Fukuyama, Jan. 1977, Dept. of Chem., Harvard University, Cambridge, Mass.
12. Synthetic epi-gliovictin: NMR 90 MHz ($CDCl_3$) δ(Me_4Si): 1.13 (3H,s); 2.14 (3H,s); 3.06 (3H,s); 3.15 (1H, exch., broad s); 3.29 (3H,s); 3.20 (1H, 1/2 ABq, J=15 Hz); 3.74 (1H, 1/2 ABq, J=12 Hz); 3.83 (1H, 1/2 ABq, J=15 Hz); 4.16 (1H, 1/2 ABq, J=12 Hz); 7.17 (5H,s). IR (KBr): 3465, 3400, 1665, 1635, 1499, 1380, 755, 700 cm^{-1}. Anal. calcd. for $C_{16}H_{22}N_2O_3S_2$: C, 54.21; H, 6.25; N, 7.90, S, 18.09; found: C, 54.21; H, 6.33; N, 7.81; S, 17.93. Mass spectrum: m/e= 323.08844 ($C_{15}H_{19}N_2O_2S_2$, requires 323.08880), m/e= 307.11344 ($C_{15}H_{19}N_2O_3S$, requires 307.11164).

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