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Hemi-Thioacetal Pummerer Reaction for the Synthesis of Gliovirin Benzylic Sulfide Models

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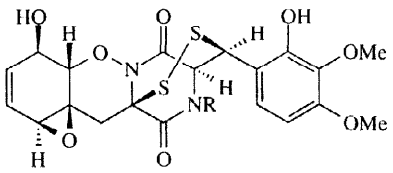
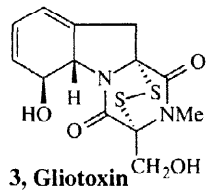
Abstract: The cyclic hemithioacetal sulfoxide **15** readily undergoes the Pummerer reaction in the presence of carbon nucleophiles to give substituted benzylic sulfides in excellent yields.

The structure of the unusual antibiotic gliovirin **1** was established in 1982 by X-ray crystallography.[1] Two years later the structure of the related antibiotic FA-2097 **2** was reported.[2] Gliovirin, and the related antibiotic gliotoxin **3,** are produced by P- and Q-strains, respectively of the fungus *Gliocladium virens* and are biosynthesized, in part, from L-phenylalanine.[3] While there are a substantial number of diketopiperazine-disulfide natural products, the disulfide functionality is usually attached to the adjacent amides as in, for example, gliotoxin **3**.[4] The only other example of the type of disulfide connection shown in **1** is found in aspirochlorine **4, Scheme 1**.[5]

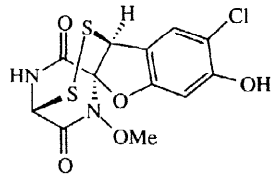
Scheme 1



1, Gliovirin (R = H)
2, FA-2097 (R = Me)



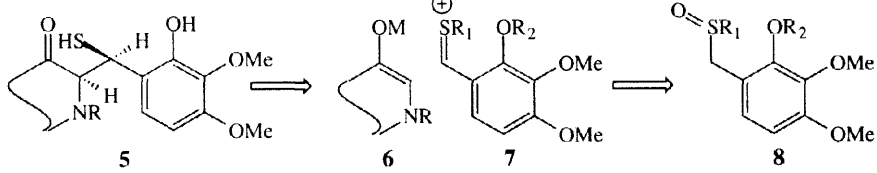
3, Gliotoxin



4, Aspirochlorine

The right-hand side of gliovirin can be dissected to the thiol **5**, which in principle, can be derived from trapping the sulfonium ion **7** with an enolate **6**. The sulfonium ion can be generated from the sulfoxide **8** by the classical Pummerer reaction, **Scheme 2**.[6]

Scheme 2



5 **6** **7** **8**

It was decided that an optimal choice of protecting groups R_1 and R_2 in **8** should be a cyclic version, and therefore **15, Scheme 3**, was chosen as the target. Selective demethylation of **9** by treatment with $AlCl_3$ gave **10**,[7] which was reduced with DIBAL-H to give **11**. Exposure of **11** to the standard Mitsunobu reaction

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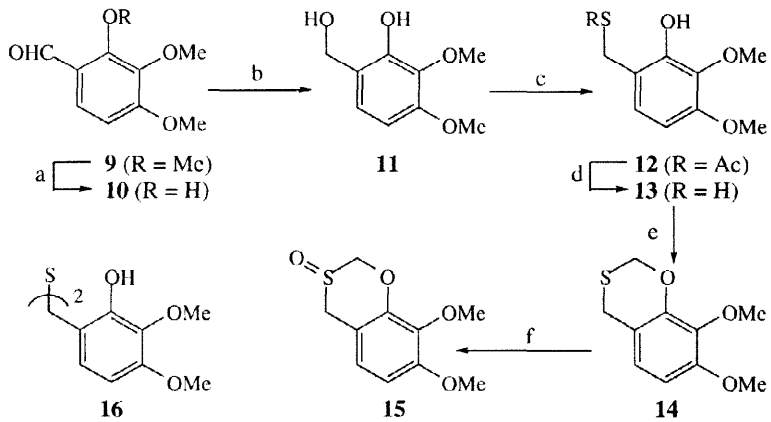
conditions with thioacetic acid as the nucleophile gave **12** (97%).[8] Hydrolysis of **12** under alkaline conditions resulted in **13**. All attempts to protect the thiol and adjacent hydroxyl group under acidic conditions, such as *p*-toluene sulfonic acid/2,2-dimethoxypropane, resulted in a complex mixture from which the only characterizable compound was the symmetrical sulfide **16**.[9] However, treatment of **13** with diiodomethane under phase transfer reaction conditions gave **14** (65%), which on oxidation with sodium periodate produced the required sulfoxide **15**.[10]

Scheme 3



Conditions:- a) $AlCl_3$/PhH/Δ 3h, **10** (100%). b) DIBAL/CH_2Cl_2/-78 °C 1h, **11** (98%). c) DEAD/PPh_3/AcSH/THF/0 °C, **12** (97%). d) NaOH/MeOH/H_2O, **13** (95%). e) CH_2I_2/$BnNEt_3Br$/NaOH/CH_2Cl_2/H_2O/25 °C 10 min, **14** (65%). f) $NaIO_4$/THF/H_2O, **15** (87%).

It was found that treatment of the TMS enol ether **17** with TMSOTf/2,6-lutidine at -78 °C followed by **15**, and warming the mixture to 25 °C resulted in the formation of **18** in excellent yield.[11] As partial proof of the structure of **18** it was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to give the β-elimination product **19**, **Scheme 4**.[12]

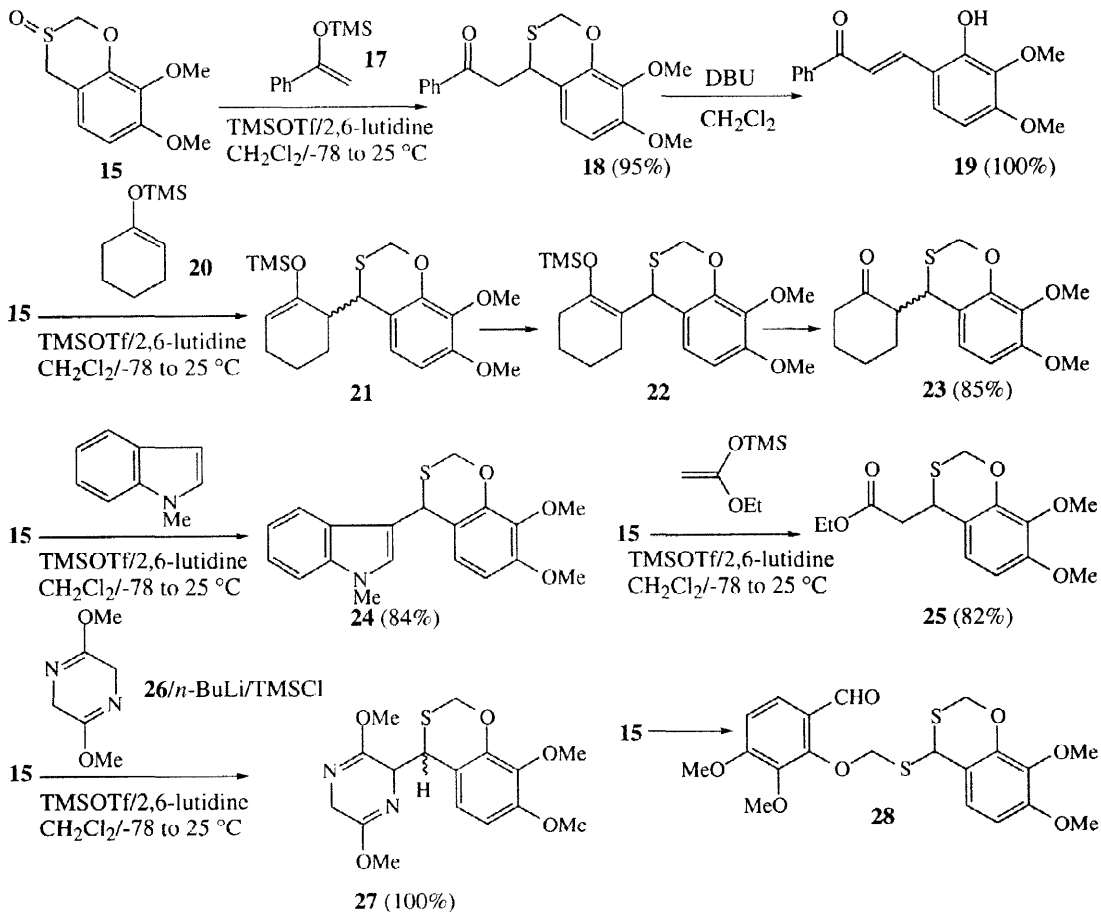
Interestingly, treatment of the enol ether **20** with **15** under the same reaction conditions as above, gave **21** (mixture of diastereomers), which on a silica gel column isomerized to give **22** (single compound). Hydrolysis (standing in $CDCl_3$) of **22** resulted in **23** (1:1 diastereomers). Similarly, both *N*-methylindole and the TMS ketene acetal derived from EtOAc reacted efficiently with **15** using the same conditions to give **24** and **25** respectively.

Application of the above procedure using an α-amino acid anion equivalent was examined. Treatment of **26**[13] with *n*-BuLi/THF/TMSCl followed by **15** and TMSOTf/2,6-lutidine at -78 to 25 °C gave the adduct **27** in quantitative yield as a 1:1 mixture of diastereomers. Attempts to trap the sulfonium ion derived from **15** with β-dialkylaminoketene acetals (glycine equivalents) were unsuccessful. The only product isolated from such reactions was the bis-adduct **28**.[14] Indeed, treatment of **15** with TMSOTf/2,6-lutidine at -78 to 25 °C, followed by aqueous work-up gave a mixture of **28**, **10** and starting material.

Representative procedure: Trimethylsilyl trifluoromethanesulfonate (120 mg, 530 μmol, 96 μL) was added to a stirred solution of EtOAc (43 mg, 480 μmol, 47 μL) and 2,6-lutidine (57 mg, 530 μmol, 62 μL) in dry dichloromethane (5 mL) at room temperature under argon. The solution was stirred at room temperature for 30 min, cooled to -78 °C, and 2,6-lutidine (52 mg, 480 μmol, 56 μL) and trimethylsilyl

trifluoromethanesulfonate (110 mg, 480 μmol, 90 μL) were then added to the stirred solution of silyl ketene acetal at -78 °C, followed by a solution of the **15** (22 mg, 96 μmol) in dry dichloromethane (3 mL) dropwise over 1 min. The solution was stirred at -78 °C for 30 min and then at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), washed with aqueous NH_4Cl (5 mL), extracted into EtOAc (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. The oil was purified by flash column chromatography over silica gel eluting with Et_2O/hexanes (1:1) to give **25** (23 mg, 82 %) as a colorless oil.

Scheme 4



The ability of **15** to participate in Pummerer chemistry without fragmentation to the *o*-quinomethide **13a**[9] is noteworthy.

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References and Footnotes

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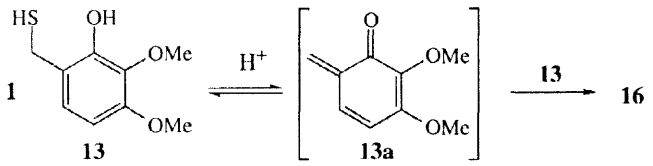
9. Presumably, the formation of **16** results from **13** undergoing acid catalyzed elimination of H_2S to give the *o*-quinomethide intermediate **13a**, which will conjugatively add **13** to give **16**, **Eqn 1**.

Eqn 1



10. δ_H (300 MHz, $CDCl_3$) 6.82 (1H, d, *J* = 8.6 Hz), 6.65 (1H, d, *J* = 8.6 Hz), 5.02 (1H, dd, *J* = 10.9 and 1.5 Hz), 4.94 (1H, d, *J* = 10.9 Hz), 4.03 (2H, app. q, *J* = 14.8 Hz), 3.88 (3H, s), 3.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 153.6, 146.6, 125.7, 122.9, 107.2, 105.4, 80.0, 61.3, 56.3, 49.0; υ_{max} (film) 1023 cm^{-1}; *m/z* (CI) 229.
11. δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, *J* = 7.4 Hz), 7.63-7.46 (3H, m), 6.86 (1H, d, *J* = 8.8 Hz), 6.56 (1H, d, *J* = 8.8 Hz), 5.34 (1H, dd, *J* = 11.6 and 1.0 Hz), 5.26 (1H, d, *J* = 11.6 Hz), 4.71 (1H, dd, *J* = 9.6 and 3.8 Hz), 3.89-3.77 (7H, m), 3.53 (1H, dd, *J* = 17.7 and 4.0 Hz); δ_C (75 MHz, $CDCl_3$) 196.6, 152.3, 147.9, 138.3, 136.8, 133.6, 128.8, 128.2, 123.9, 117.2, 105.2, 64.7, 61.0, 56.1, 47.9, 33.7; υ_{max} (film) 1682 cm^{-1}; *m/z* (CI) 331.
12. δ_H (300 MHz, $CDCl_3$) 8.05-8.02 (2H, m), 7.95 (1H, d, *J* = 15.7 Hz), 7.74 (1H, d, *J* = 15.7 Hz), 7.57-7.47 (3H, m), 7.28 (1H, d, *J* = 8.7 Hz), 6.54 (1H, d, *J* = 8.8 Hz), 3.94 (3H, s), 3.92 (3H, s); δ_C (75 MHz, $CDCl_3$) 191.3, 154.0, 149.9, 140.8, 138.8, 135.6, 132.5, 128.6, 126.3, 121.6, 115.8, 104,3, 61.1, 56.0; υ_{max} (film) 3554, 1654 cm^{-1}.
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14. While the ^1H NMR/IR data is in agreement with the assigned structure for **28**, it should be viewed as a tentative proposal.