Communications to the Editor

Total Synthesis of (+)-Gloeosporone: Assignment of Absolute Configuration[1]

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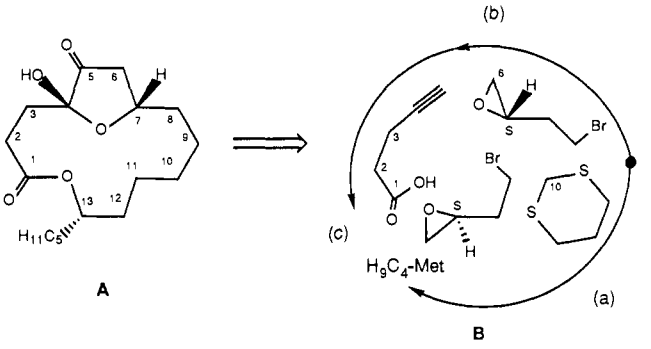
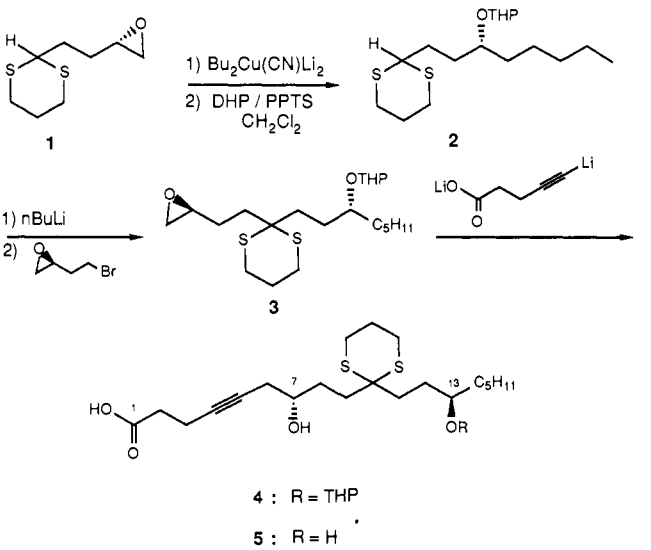
In 1982, Meyer[4] and co-workers reported the isolation of a germination self-inhibitor from the fungus *Colletotrichum gloeosporioides* which they called gloeosporone. Soon after isolation, they reported the structure, without regard to configuration, based solely on spectral data.[5] Later, attempted synthesis of gloeosporone led to the discovery that the proposed structure required revision.[6] A single-crystal X-ray structure analysis of gloeosporone was undertaken in 1986 which provided **A** (Scheme I).[7] The absolute configuration, however, was not determined at that time.[8] Presently, insufficient quantities of natural material are available[9] to test the generality of gloeosporone's activity as a fungistat, i.e., in various plant and mammalian systems. Therefore, our goals in synthesizing gloeosporone were twofold: to assign the absolute configuration as well as to provide ample quantities for biological testing. This would also allow for the investigation of the binding properties of gloeosporone. It has been suggested that gloeosporone may complex with certain metal ions and that their transport is involved in the inhibition of germination.[7]

Assuming that the hydroxy-1,2-diketo form of **A** would spontaneously cyclize to the correct C(4)-epimer,[7,8] and based on our previous experience with syntheses of enantiomerically pure macrolides,[10] we arrived at the retrosynthetic analysis presented in **B**. It involves the same building block for incorporation of both stereogenic centers: (*S*)-(+)-4-bromo-1,2-epoxybutane (from *S*-malic acid).[11] This would first be used for dithiane alkylation and attachment of the alkyl side chain with butyl cuprate (path a) followed by alkylation of the same dithiane moiety and completion of the carbon skeleton by epoxide ring opening with the acetylide anion of 4-pentynoic acid (path b). Finally, lactonization (path c) with inversion of configuration at C(13) would provide the macrocycle. Two conflicting synthetic transformations remained to complete the gloeosporone synthesis; these were reductive removal of the dithiane moiety and oxidation of the acetylene to the diketone function.[12]

Scheme I



Scheme II



Our synthesis began with the known epoxydithiane[14] **1** (Scheme II) from dithiane and the epoxy bromide shown in **B**. Next, the pentyl side chain was generated by using lithium butyl cyano cuprate[15] (1.5 equiv, THF, −20 °C). Protection of the newly generated secondary alcohol as the THP-ether [1.3 equiv of DHP, PPTS(catalyst), 4 h][16] gave **2** in 83% overall yield. Alkylation of the lithio derivative of **2** (1.1 equiv *n*-BuLi, THF, 5 h, −20 °C) with the epoxy bromide provided compound **3**. The C(1)–C(5) unit was introduced by reaction of the doubly deprotonated 4-pentynoic acid[17] with epoxide **3** (2.2 equiv *n*-BuLi, HMPT, 0 °C to room temperature, 24 h) to give, after removal of the THP group [HOAc/THF/H_2O (4:2:1), 50 °C],[18] diol acid **5** (45% from **2**) possessing the complete carbon skeleton of gloeosporone.

Lactonization was achieved by using the Mitsunobu[19] reaction (2 equiv of DEAD, 2 equiv of Ph_3P, benzene, 10 min, 59%) which provided macrolide **6** as the only detectable product. No ma-

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(2) Recipient of a Stipendium from the Fonds der Chemischen Industrie, Germany.
(3) American Cancer Society Post-Doctoral Fellow (1986–1987).
(4) Lax, A. R.; Templeton, G. E.; Meyer, W. L. *Phytopathology* **1982**, *74*, 503; **1985**, *75*, 386.
(5) Meyer, W. L.; Lax, A. R.; Templeton, G. E.; Brannon, M. J. *Tetrahedron Lett.* **1983**, *24*, 5059.
(6) (a) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (b) Meyer, W.; Schreiber, S. L., private communications.
(7) Meyer, W. L.; Schweizer, W. B.; Beck, A. K.; Scheifele, W.; Seebach, D.; Schreiber, S. L.; Kelly, S. E. *Helv. Chim. Acta* **1987**, *70*, 281.
(8) As expected, none of the hydroxy diketo form of A is present in solution as determined by NMR spectroscopy.[7]
(9) Only milligram quantities of gloeosporone were isolated from many liters of fungal broth making extensive activity studies impossible.
(10) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *Liebigs Ann. Chem.* **1986**, 1281.
(11) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.
(12) We were concerned with this general transformation in that a survey of the literature revealed success with use of RuO_4 only in simple systems.[13] Therefore, we have studied the viability of this reaction in many complex substrates, the results of which will be published elsewhere.
(13) Gopal, H.; Gordon, A. J. *Tetrahedron Lett.* **1971**, 2941. Carlson, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(14) Seuring, B.; Seebach, D. *Liebigs Ann. Chem.* **1978**, 2044.
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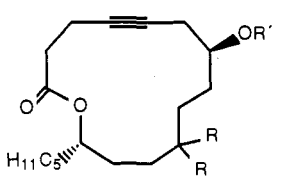
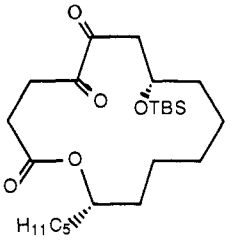
crodiolide from intermolecular esterification of the C(7)-hydroxyl group was observed.

Given that conventional methods for reductive removal of the dithiane (cf. Raney nickel) would also hydrogenate a triple bond and reduce a 1,2-diketone and, conversely, that oxidation of the acetylene could alter the dithiane (sulfoxide or sulfone formation), we chose the following two-step procedure for removal of the dithiane unit. Hydrolysis[20] of the dithiane of **6** (20 equiv of MeI, aqueous acetone, 60 °C, 4 h) provided ketone **7** which was con-





10

6 R,R = -S(CH$_2$)$_3$S- ; R′ = H
7 R,R = O ; R′ = H
8 R,R = H,H ; R′ = H
9 R,R = H,H ; R′ = TBS

verted to the tosylhydrazone [1.1 equiv of *p*-$CH_3C_6H_4SO_2NHNH_2$, *p*-TsOH, sulfolane/DMF (1:1), 100 °C, 15 min] and reduced (in one pot) with sodium cyanoborohydride[21] (4 equiv, 3 h, 100 °C, 35% of **8** from **6**). It was necessary to protect the C(7) hydroxyl [2 equiv of TBSCl, 2 equiv Et_3N, 4-PP (catalyst), DMF, 12 h, 88% of **9**][22] in order to oxidize the acetylene without competing ketone formation. Oxidation was then achieved without event by using sodium periodate (4.1 equiv) and catalytic ruthenium dioxide[13] [$CH_3CN/CCl_4/H_2O$ (2:2:3)] to give the brightly yellow dicarbonyl compound **10** (74%). Deprotection of the C(7)-hydroxyl [pyridine·$(HF)_x$, THF][23] caused slow disappearance of the yellow color with the expected formation of synthetic gloeosporone (80%), identical with the natural product (500 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, IR, MS, TLC (several solvent systems)).

The optical rotation $[\alpha]_D$ of synthetic gloeosporone was +52° (c = 0.71, $CHCl_3$)[24] with mp 117-118 °C, whereas $[\alpha]_D$ = -14° (c = 0.28 $CHCl_3$) and mp 108-110 °C were reported for the natural material.[25] With the absolute configuration derived from (*S*)-(+)-4-bromo-1,2-epoxybutane, the synthetic compound can be specified as 4*R*,7*S*,13*S* as shown in **A**.[25]

In conclusion, the first total synthesis of (+)-gloeosporone has been achieved in eleven steps from readily available starting materials and in 4.2% overall yield.[26]

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(20) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.
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(23) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.
(24) The optical rotation in acid free $CHCl_3$ was found to be +58° (c 0.48) and in benzene, $[\alpha]_D$ = +79° (c 0.40).
(25) Upon purification of a very small sample of natural gloeosporone, the optical rotation increased to -30° (c 0.08, $CHCl_3$). Given the low concentration, we can only use this value as an indication that natural gloeosporone is levorotatory (we thank W. L. Meyer, University of Arkansas, for a sample of natural gloeosporone). Thus, the synthetic sample described here should be the enantiomer of the natural product. Since the submission of this communication, we have also prepared (-)-gloeosporone from (*R*)-malic acid. The optical rotation was found to be -61° (c 0.34, acid free $CHCl_3$) and $[\alpha]_D$ = -72° (c 0.34, benzene). Activity studies of both enantiomers are underway and will be reported in due course.
(26) All new compounds were characterized by 300 MHz ^{1}H NMR, IR, MS and, when stability allowed, elemental analysis to ±0.3%.

Phototropic Molecules. 1. Phase Transfer As a Method for Detecting Transient Species

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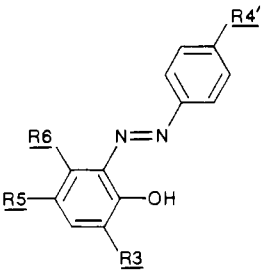
A light-induced large temporary change in the pK_a of an acid would have many practical uses. These include light-switched acid catalysis, light-powdered proton transport through a membrane, etc. The most obvious way of accomplishing this is to make use of the discovery[1] that the pK's of the photoexcited states of compounds such as phenols or anilines differ enormously from the pK's of these molecules in the ground states. Unfortunately, attempts to utilize these light-induced changes in acidity for chemical purposes[2] are likely to fail because the lifetimes of these photoexcited states are too short to effect an appreciable change in the pH of the solution.[3] What is needed is a reversible change in the pK_a of a species which is longer lived than an electronic excited state but sufficiently short lived to enable one to have many on/off cycles in a reasonably short time period.

While there are sophisticated methods for measuring the pK's of excited states and the lifetimes of excited states, it would be useful to have a simple method for measuring temporary light-induced changes in pK's, whilst simultaneously making certain that these temporary species are sufficiently long lived to pass through membranes or to engage in other chemical work. This paper describes such a procedure and applies it to the measurement of the pK_a's of three azophenols.



	R3	R5	R6	R4′
1 2-hydroxy-5-methylazobenzene	H	CH_3	H	H
2 2-hydroxy-3,5,6-trichloro-4′-methylazobenzene	Cl	Cl	Cl	CH_3
3 2-hydroxy-5,4′-dinitroazobenzene	H	NO_2	H	NO_2

trans-2-Hydroxyazobenzenes are known to have a diminished acidity which is due to the hydrogen bond between the phenolic hydroxyl and an azo nitrogen.[4] In the cis configuration the hydrogen bond is lost, and the acidity of the phenol is consequently enhanced. The thermal cis → trans reversion of *o*- and *p*-hydroxyazobenzenes and aminoazobenzenes is very fast.[5] Is the lifetime of the more acidic *cis*-azophenol long enough to effect useful chemical work, and is this enhanced acidity detectable by conventional chemical techniques?

A 50-mL solution of azophenol **1**, 4.56 × 10^{-5} M in toluene was stirred with 50 mL of 1.0 N aqueous NaOH in a 200-mL,

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