Total Synthesis of the Unique Mycotoxin α-Cyclopiazonic Acid (αCA): An Unusual Dimethylzinc-Mediated Replacement of a Phenylthio Substituent by a Methyl Group and a Contrathermodynamic Raney Nickel Desulfurization Reaction

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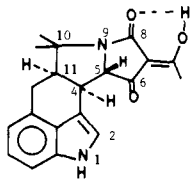
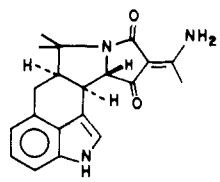
The structurally unique mycotoxin, α-cyclopiazonic acid (αCA), is produced by the fungus *Penicillium cyclopium* Westling,[1] which is found worldwide and is often isolated from stored grain and cereal products.[2] Several outbreaks of a disease have, in fact, been reported that occurred upon ingestion of feed contaminated with *P. cyclopium*.[3]

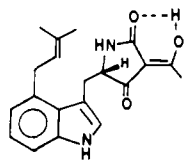
The structure of αCA was established by Holzapfel on the basis of chemical and physicochemical investigations.[1,4] Two other metabolites related structurally to αCA have been isolated more recently, cyclopiazonic acid imine and bissecodehydrocyclopiazonic acid (or β-cyclopiazonic acid).[5]



α-cyclopiazonic acid



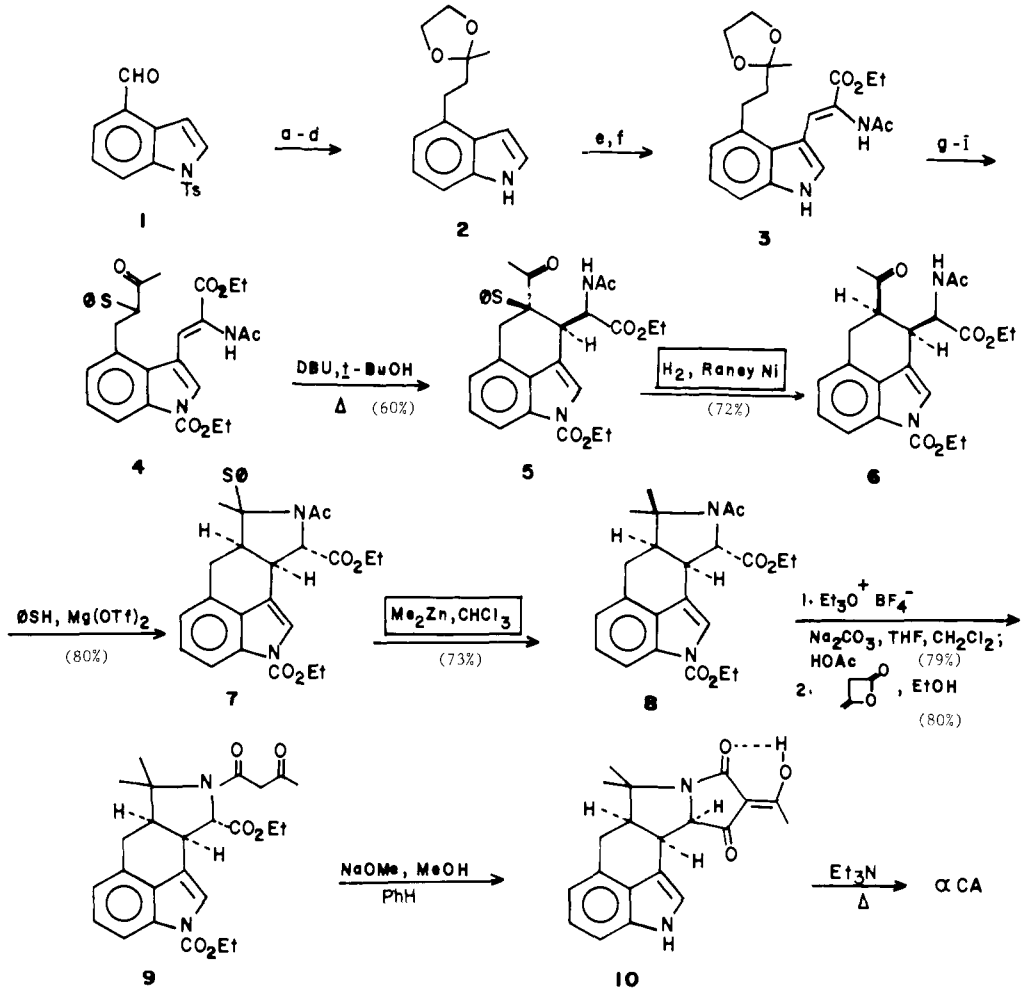
cyclopiazonic acid imine



β-cyclopiazonic acid

Of these three mycotoxins, only the simplest, β-cyclopiazonic acid, has been prepared by total synthesis.[6] Herein we report a route to αCA, a natural product which stands in a unique biogenetic relationship to the ergolines.[7] The readily available *N*-tosyl derivative of indole-4-carboxaldehyde (**1**)[8] was transformed to **3** by conventional methods.[9,10] The indole nitrogen of **3** was then carboethoxylated, the ketal cleaved, and the deprotected ketone α-sulfenylated via its thermodynamic enol silyl ether.[11] An intramolecular Michael reaction of **4** effected by DBU now led to the tricyclic material **5**. Interestingly, while an X-ray analysis of this tricyclic compound reveals that the two carbon appendages are trans, a subsequent Raney nickel desulfurization reaction leads almost exclusively to the cis product **6**.[12a,b] The "contrathermodynamic" nature[13] of this desulfurization reaction was revealed on stirring **6** with DBU, for complete epimerization to the trans compound (ii in ref 12) took place within 50 min at

Scheme I.[a] A Synthesis of α-Cyclopiazonic Acid



[a] (a) $CH_3COCH{=}PPh_3$, THF (95%); (b) H_2, Pd/C, MeOH-THF (94%); (c) $HO(CH_2)_2OH$, *p*-TsOH, PhH (99%); (d) 2 N KOH, MeOH (93%); (e) $POCl_3$, DMF, then NaOH (62%); (f) $AcNHCH(CO_2Et)CO_2H$, Ac_2O, pyr (78%); (g) $ClCO_2Et$, Et_3N (95%); (h) 10% HCl, THF (98%); (i) Me_3SiI, $HN(SiMe_3)_2$, then PhSCl (55%).

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room temperature. Intermediate **6** was treated in turn with magnesium triflate and thiophenol to effect D-ring formation with production of the α-phenylthio amide **7**.[14] On the basis of information garnered from our studies with the related trans compound,[15] **7** was exposed to excess dimethylzinc in chloroform. *Only with this organometallic reagent were we able to achieve selective replacement of the thio subsituent by methyl*! The mechanistic features of this new reaction and its extension to other sulfur-containing systems are under active study.

Having now overcome two major hurdles, creation of the proper cis relationship between the C-4 and C-11 side-chain appendages and installation of the gem-dimethyl grouping, we were ready to construct the fifth and last ring, the acyltetramic acid, a unit that may be responsible for the biological activity of αCA because of its ability to chelate trace metals. On the basis of prior methodology in the tetramic acid field,[16] we chose to accomplish this last ring forming step through an internal condensation between acetoacetamide and ester. The *N*-acetyl group of **8** was thus removed,[17] and the free amine reacted with diketene to provide the acetoacetamide **9**. Surprisingly, when this intermediate was exposed to methanolic sodium methoxide in benzene and the resulting enolate mixture brought to a pH of 4, iso-α-cyclopiazonic acid was isolated. The conversion of αCA to the iso compound has been reported by Holzapfel employing 0.3 N sodium hydroxide as base; however, after 10 h, the reaction mixture consisted primarily of αCA (ratio αCA:iso-αCA $\cong$ 1.5:1). Epimerization of the ester-bearing center may thus precede ring closure in the present instance. To complete the synthesis, the iso compound was isomerized with triethylamine in chloroform at 100 °C (sealed tube) to a 2.5:1 mixture of αCA and the iso compound. These could be separated by formamide–oxalic acid impregnated paper chromatography to provide the pure product.[1] The αCA obtained in this manner was identical with the natural product by UV, IR, NMR, and mass spectral analysis. In summary the synthesis scheme presented herein provides a fairly straightforward route to αCA which should prove valuable in analogue construction.[18] The zinc chemistry discovered in the context of this synthesis is unique and is certainly amenable to other important synthetic applications.[19,20]

Acknowledgment. We are indebted to the National Institutes of Health for their support of these investigations and to Professor C. W. Holzapfel and Dr. Richard Cole for samples of natural αCA. We also acknowledge Dr. Cole for his helpful discussions regarding the purification of αCA.

Registry No. 1, 79681-04-2; **2**, 92420-71-8; **3**, 92420-72-9; **4**, 92420-73-0; **5**, 92420-74-1; **6**, 92420-75-2; **7**, 92420-76-3; **8**, 92420-77-4; **9**, 92420-78-5; **10**, 92471-22-2; $AcNHCH(CO_2Et)CO_2H$, 54681-67-3; αCA, 83136-88-3; diketene, 674-82-8.

(1) Holzapfel, C. W. *Tetrahedron* **1968**, *24*, 2101. Steyn, P. S.; Wessels, P. L. *Tetrahedron Lett.* **1978**, 4707.
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(4) Holzapfel, C. W.; Schabort, J. C. *S. Afr. J. Chem.* **1977**, *30*, 233.
(5) Holzapfel, C. W.; Hutchison, R. D.; Wilkins, D. C. *Tetrahedron* **1970**, *26*, 5239.
(6) Holzapfel, C. W.; Gildenhuys, P. J. *S. Afr. J. Chem.* **1977**, *30*, 125.
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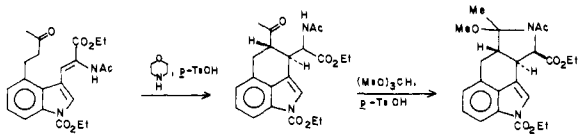
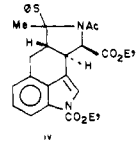
(8) Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 3350.
(9) Smith, G. F. *J. Chem. Soc.* **1954**, 3842.
(10) Hellmann, H.; Teichmann, K.; Lingens, F. *Chem. Ber.* **1958**, *91*, 2417. Hengartner, V.; Valentine, D.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741. The *E*/*Z* nature of the amidoacrylate group of **3** and **4** has not yet been rigorously determined.
(11) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(12) (a) The introduction and subsequent removal of the sulfur substituent was crucial to the control of the relative stereochemistry between C-4 and C-11, for cyclization of the keto amide ii prepared from i led to the product



iii possessing a trans-C,D-ring fusion. Accordingly, epimerization at C-11 does not precede D-ring closure, a feature that we had counted on at the outset of our work on αCA. The assignment of trans stereochemistry to iii is based on ^{1}H NMR analysis ($J_{4,11}$ = 11.9 Hz) as well as a single-crystal X-ray analysis. (b) Further experimentation has revealed that the tricyclic compound corresponding to **5** but containing a cis disposition of the carbon appendages is formed in the Michael reaction as well (~1:1). This compound is also converted to **6** (but at faster rate!) upon Raney nickel hydrogenolysis.
(13) van Tamelen, E. E.; Grant, E. A. *J. Am. Chem. Soc.* **1954**, *81*, 2160. Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356.
(14) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
(15) The α-methoxy amide iii[12] could be converted to the corresponding α-phenylthioamide iv on reaction with magnesium triflate and thiophenol.



Both iii and iv were treated with a wide variety of methyl metallics in an effort to replace the exocyclic-heteroatom substituent by methyl. Dimethylzinc was the only reagent capable of bringing about the desired transformation, and this reagent worked only with iv.
(16) Harris, S. A.; Fischer, L. V.; Folkers, K. *J. Med. Chem.* **1965**, *8*, 447. Yuki, H.; Kariya, K.; Hashimoto, Y. *Chem. Pharm. Bull.* **1967**, *15*, 727. Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 4225.
(17) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265.
(18) For a recent report concerning synthetic studies directed toward αCA, see: Somei, M.; Tokutake, S.; Kaneko, C. *Chem. Pharm. Bull.* **1983**, *31*, 2153.
(19) The structures of all of the materials reported herein are supported by satisfactory ^{1}H NMR, IR, high-resolution mass spectral data, and elemental analysis. Experimental procedures will be provided in a full paper to be published at a later date.
(20) Phenylthio glycosides are transformed, for example, to *C*-glycosides in high yield by using organozinc reagents. Ritter, A., unpublished results.

Copper(I) and Silver(I) Diiridium Polyhydrides

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In the course of our study of chemical oxidation (e.g., Ag^+) of transition-metal polyhydrides, we have isolated adducts of the related oxidant (electrophile) Cu^+.[1] It is known that one-electron oxidation of the 18-electron species $M(CO)_2(P\sim P)_2$ (M = Cr, Mo, W)[2] and $MX(CO)_3P_2$[3] (M = Mn and Re) greatly enhances the rate of (intramolecular) isomerization. Since *fac*- and *mer*-$IrH_3(PMe_2Ph)_3$ comprise a stereoisomeric pair whose thermal equilibrium (~70:30 in benzene) is established only slowly at 25 °C, we have used these polyhydrides to probe the degree to which our proposed "redox intermediates" mimic the behavior expected of true Ir(IV) radical cations (e.g., Cu^+ catalysis of eq 1).

$$fac\text{-}IrH_3P_3 \overset{Cu^+}{\underset{?}{\rightleftharpoons}} mer\text{-}IrH_3P_3 \qquad (1)$$

(1) Rhodes, L. J.; Zubkowski, J. D.; Folting, K.; Huffman, J. C.; Caulton, K. G. *Inorg. Chem.* **1982**, *21*, 4185-4192.
(2) Bond, A. M.; Grabaric, B. S.; Jackowski, J. J. *Inorg. Chem.* **1978**, *17*, 2153 and references therein.
(3) Bond, A. M.; Colton, R.; McDonald, M. E. *Inorg. Chem.* **1978**, *17*, 284i and references therein.

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