ortho-SH + meta-TMS), which may be explained by an increase in γ-shielding on P by S. In the third and fourth series, with the exception of **15** → **16**, hydrogen bonding in the phosphine oxides causes downfield ^{31}P shifts, which appear to be cumulative and in opposition to the γ-effect. In the case of **16**, combined steric effects due to the three trimethylsilyl groups apparently preclude the type of extensive hydrogen bonding found in **11**. None of the shift effects observed are explained by an electronic effect of the sulfur.[7]

Phosphine oxide **10** could be oxidized to 11-phenyl-11*H*-dibenzo[*cf*][1,2,5]dithiaphosphepin-11-oxide (**17**), a new heterocyclic ring system, by heating with dimethyl sulfoxide at 90 °C for 24 h. The novel coordination chemistry and other reactions of the various new compounds reported herein will be presented elsewhere.[8]

Acknowledgment. We gratefully acknowledge support from the National Science Foundation, the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, and Société Nationale Elf Aquitaine. Funding for the 300 MHz NMR facility was provided by the National Science Foundation.

Supplementary Material Available: ^{13}C NMR chemical shifts of **3** and **6**–**17** (1 page). Ordering information is given on any current masthead page.

(7) We thank one of the referees for bringing this interesting NMR effect to our attention.

(8) For example, novel molybdenum complexes of **6** and **14** have been prepared and characterized: Block, E.; Kang, H.; Ofori-Okai, G.; Zubieta, J., manuscript submitted for publication.

The Biosynthesis of Acivicin and 4-Hydroxyacivicin from N^{δ}-Hydroxyornithine

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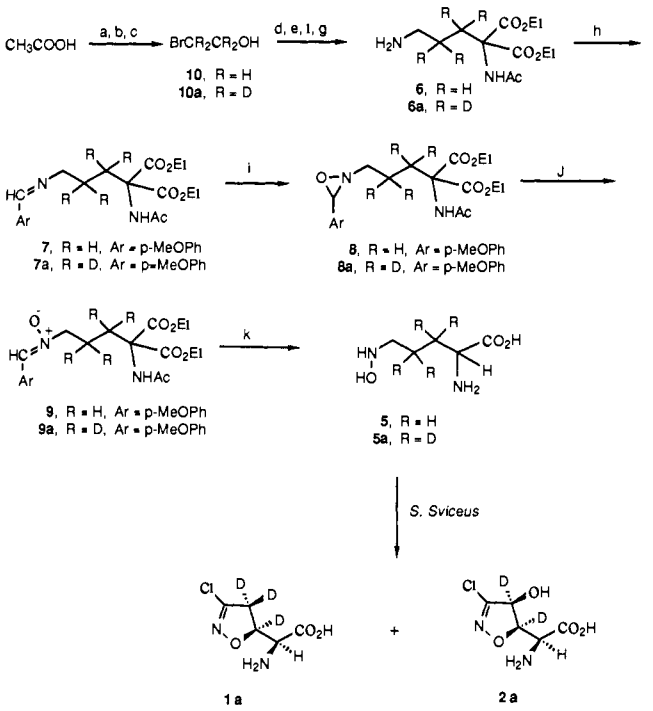
Acivicin (AT-125) (**1**)[1,2] and 4-hydroxyacivicin (**2**)[3] are produced from *Streptomyces sviceus*. Acivicin has potent anticancer activity[4] and has found use as an important tool for studying xenobiotic metabolism involving glutathione,[5] while **2** has approximately one-fifth the cytotoxic activity of **1**. The isoxazolidine ring upon which these structures are based occurs, at various levels of oxidation, in only a few other natural products: tricholomic acid,[6,7] ibotenic acid,[8–10] muscimol,[11] and cycloserine.[12–14] While

Scheme I



a: P, Br_2; b: C_2H_5OH / H^+; c: $LiAlH_4$; d: NaCN; e: TsCl / Py; f: diethyl acetamidomalonate, NH_3; g: PtO_2 / H_2; h: p-anisaldehyde, Et_3N; i: MPP; j: silica gel column; k: 6N HCl

cycloserine is derived from *O*-acetyl-L-serine and *N*-hydroxyurea,[15–17] we have reported[18] that ornithine (**3**) is the primary precursor of **1** and **2**, indicating a quite different biosynthesis.

We recognized that the first committed step toward the biosynthesis of **1** and **2** would most reasonably be hydroxylation of ornithine either at C-3 (the β-position) or at the terminal nitrogen (N^{δ}). Numerous naturally occurring β-hydroxyamino acids have been characterized,[19–25] but the formation of only one of these, *threo*-β-hydroxyaspartic acid, has been studied in detail.[26–29] β-Hydroxyornithine (**4**) has been synthesized a number of times,[30–32] but it has not yet been isolated as an authentic natural

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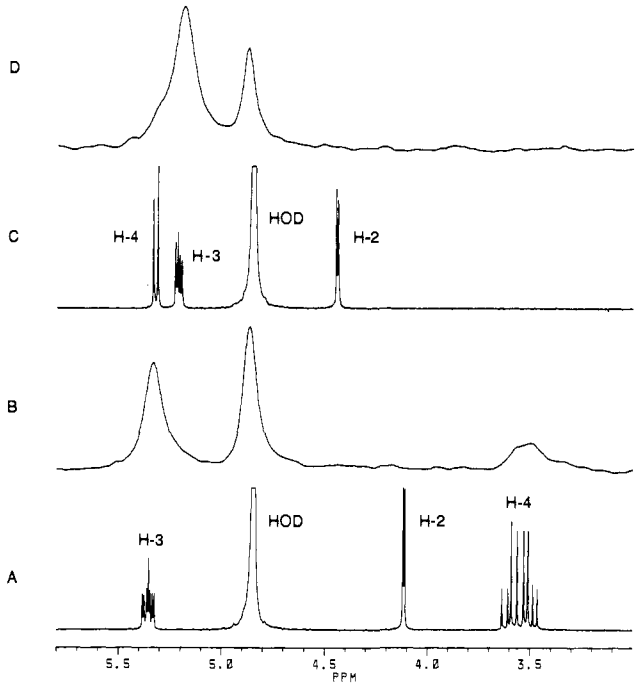
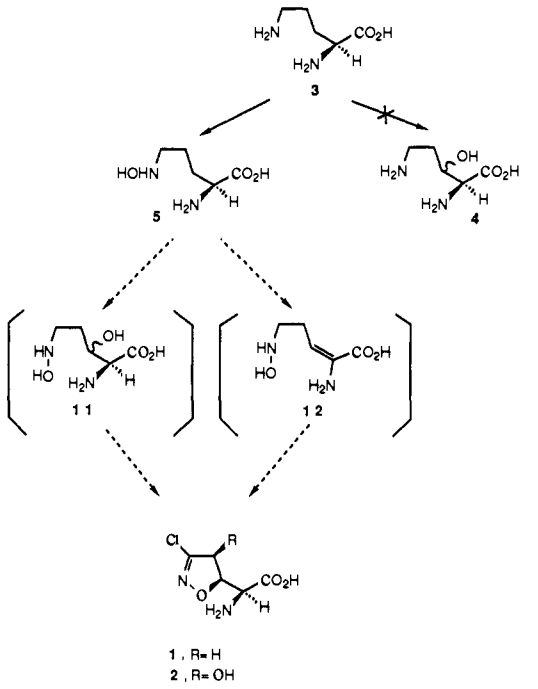


Figure 1. (A) 400-MHz ^{1}H NMR spectrum of **1** in D_2O with *t*-BuOH added for reference (sweep width, 6024.069 Hz; acquisition time, 1.360 s; number of scans, 32; 16 K data points. (B) 61.4-MHz ^{2}H NMR of **1a** in ^{2}H-depleted H_2O with 25 μL of *t*-BuOH added for chemical shift reference and deuterium quantitation (sweep width, 586.2 Hz; acquisition time, 1.7 s; number of scans, 16522; 2 K data points zero filled to 8 K; 2.0 Hz line broadening). (C) 400-MHz ^{1}H NMR spectrum of **2** in D_2O with *t*-BuOH (number of scans, 32). (D) 61.4-MHz ^{2}H NMR spectrum of **2a** (number of scans 4089).

product. Data from incorporation of deuterated ornithine indicated its possible involvement in the biosynthesis of **1** and **2**,[18] and it appeared that the conversion of ornithine to clavulanic acid[33] might involve **4**, as well. However, we have since tested both *erythro*- and *threo*-**4** and have found that it is not involved in acivicin and 4-hydroxyacivicin biosynthesis.[34,35]

N^δ-Hydroxyornithine (**5**) is the key biogenetic unit of most of the hydroxamate-type naturally occurring siderophores,[36-43] and a number of syntheses of **5** have been reported.[44-46] We have developed a new synthesis of **5** based on the methodology of Polonski and Chimiak,[47] as shown in Scheme I, that allowed the convenient introduction of deuterium labels at C-3 and C-4. Thus, (aminopropyl)acetamidomalonate **6**[48] was converted to imine **7**

Scheme II



with *p*-methoxybenzaldehyde, oxidized without purification to the oxaziridine **8** with monoperphthalic acid, and rearranged to nitrone **9** by silica gel chromatography. The yield from **6** was 32%. Hydrolysis of the nitrone with 6 N HCl directly afforded **5** in 62% yield. When [CD_3]acetic acid was brominated, esterified, and reduced with $LiAlD_4$, [1,1,2,3-$^2H_4$]bromoethanol (**10a**) was obtained, and this was readily converted to **6a** in three steps.[48] In the event, cyanide displacement in CH_3OH led to extensive hydrogen exchange so that **6a** was 100% deuterated at C-3 but only 10% deuterated at C-4 (calculated by ^{1}H NMR integration); nonetheless, this proved sufficient for our needs.

Deuterium-labeled **5a** (57.46 mg, label distribution as in **6a** above) was divided and fed to ten production broths (200 mL each in 1-L Erlenmeyer flasks) 48 h after inoculation with a seed culture of *S. sviceus*,[18] and an equal amount was fed 12 h later. After a total of 120 h the broths were worked up in standard fashion[18] to yield 8.0 mg of pure **1a** and 43.1 mg of pure **2a** (Scheme I). Each sample in deuterium-depleted water[49] was then analyzed by ^{2}H NMR at 61.4 MHz and both spectra revealed excellent enrichments at C-3 and C-4 (Figure 1, B and D). The H-3 and H-4 resonances of **1a** (δ 5.2 and 3.4, respectively) were well-resolved and allowed measurement of their individual enrichments (4.3 and 5.8%, respectively[50]). On the basis of the H-4 enrichment, a 2.0% incorporation of **5a** was calculated, and based on the deuterium enrichments of the **5a** fed, it was clear that, in addition to the deuterium that had been replaced by oxygen, 30% of the remaining deuterium at C-3 had been lost. This loss is consistent with that observed previously with [2,3,3-$^2H_3$]-ornithine.[18] The H-3 and H-4 resonances of **2a** at δ 5.2 and 5.3, respectively, could not be resolved in the ^{2}H NMR spectrum due to the broad line widths; however, if the same relative loss of deuterium from C-3 is assumed, the enrichments for H-4 and H-3 are 4.4 and 3.3%, respectively, and a 3.9% incorporation (based on H-4) of **5a** was obtained.

As shown in Scheme II, acivicin and 4-hydroxyacivicin are derived by initial oxidation of ornithine at the terminal nitrogen, rather than at C-3. The steps beyond **5** may involve either N^δ,3-dihydroxyornithine (**11**) or N^δ-hydroxydehydroornithine (**12**).

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These and other questions regarding this unusual pathway[18] are currently under investigation.

Acknowledgment. Dr. David Martin and Shirley Gerpheide of The Upjohn Co. are thanked for providing samples of acivicin and 4-hydroxyacivicin, slants of *Streptomyces sviceus*, and the design of the baffled flask used in fermentations. P. C. Prabhakaran and Rodger Kohnert are thanked for obtaining the ^2H NMR spectra. The work was supported by a grant from the Public Health Service GM 32110 to S.J.G. NMR spectra were obtained on a Bruker AM 400 spectrometer purchased in part by grants from the National Science Foundation (CHE-8216190) and from the M. J. Murdock Charitable Trust to Oregon State University.

Intramolecular $S_{N'}$ Cleavage of Allylic Ethers by Enolate Anions

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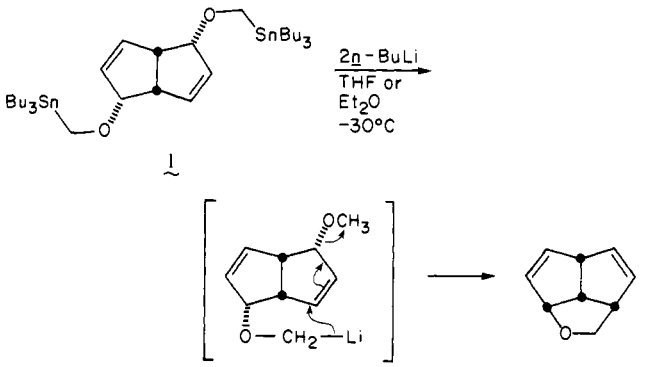
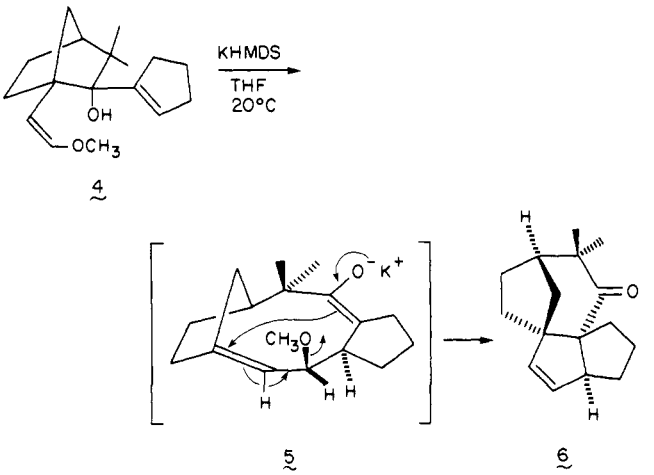
A fundamental property of allylic systems relates to their ability to engage nucleophiles in $S_{N'}$ reaction. Extensive theoretical[2] and experimental investigations[3] over many years attest to the significance attached to the phenomenon. Despite the wide-ranging nature of these studies, however, no attention has been purposefully directed to bimolecular nucleophilic substitution of allyl alkyl ethers, perhaps because of a predetermination that these systems would prove as inert toward displacement as dialkyl ethers. One interesting example known to us is due to Farnum and Monego who showed that dimetalation of **1** proceeds with subsequent proton abstraction from solvent to give **2**, which then experiences intramolecular $S_{N'}$ displacement of methoxide.[4]



1 2 3

As part of ongoing investigations of anionic oxy-Cope rearrangements,[5,6] our research groups have independently examined the ability of medium-ring enolates to undergo transannular cyclization concomitant with $S_{N'}$ displacement of a methoxyl leaving group. The result is rapid and efficient construction of structurally intricate polycyclic systems.

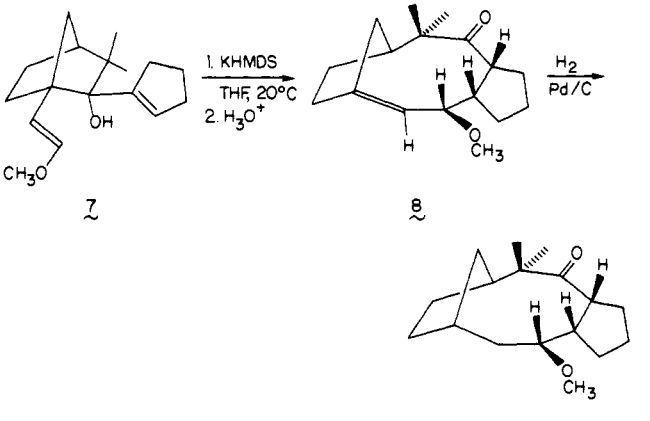
For example, when alcohol **4**[7] was stirred in anhydrous tetrahydrofuran solution with 1.1 equiv of potassium hexamethyldisilazide at 20 °C for 4 days, smooth conversion to ketone **6** was



4 5 6

observed. Chromatographically purified material, isolated in 51% yield, crystallized as colorless, rectangular plates well suited to X-ray analysis.[8] The suggested pathway to the product diquinane involves initial [3,3]sigmatropic electron reorganization via a chair-like transition state to generate **5**. This process establishes three stereocenters and the double bond geometry. The β-configuration of the methoxyl-substituted carbon results in proper alignment of the C–OCH_3 bond with the flanking π orbital, thereby allowing for the onset of the intramolecular $S_{N'}$ ring closure.

Support for this mechanistic analysis was gained by subjecting **7** to comparable ring expansion. In this instance, **8** was produced efficiently (88%) after only 5.5 h at room temperature. Since crystals of **8** of suitable quality could not be grown, saturation



7 8

9

of its double bond was undertaken. The structure of **9** was subsequently established by crystallographic methods to be as shown.[8] These data indicate the **7** → **8** conversion to be mediated by an

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(7) Details relating to the synthesis of this compound will appear elsewhere.
(8) We thank Dr. J. C. Gallucci of the Ohio State University Crystallographic Facility for these analyses.

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