The conversion of **8** to **9** was effected with the Tebbe reagent[9] (91%). Significantly for our purposes, the structural features in **9** effectively preclude possible prototropic isomerization of the vinyl ether double bond.[3] The thermal rearrangement of this intermediate (180 °C, 24 h, NaOH-washed Carius tubes) was consequently not plagued by this competing side reaction and delivered **11** together with its 4-methyl epimer in a ratio of 15:1 (34-60%). These isomers could be distinguished spectroscopically (NOE). Pure **11** exhibits an $[\alpha]_D$ of -2.7° (*c* 2.3, $CHCl_3$) at 19 °C. This stereochemical outcome is in agreement with dominant utilization by **9** of the chair transition state **10**.

With the structure and stereochemistry of **11** secure, attention was turned to regiospecific cyclopentannulation and installation of the four remaining stereogenic centers. Addition to **11** of the 4-bromo-2-butanone ethylene ketal Grignard reagent in the presence of $CuBr{\cdot}SMe_2$, direct O-silylation of the resulting enolate, phenylselenenylation (PhSeCl, THF, 0 °C), and oxidation (30% H_2O_2) generated **12** in 84% yield after acid hydrolysis. As a consequence of the conformation adopted by **12**, hydrogenation over platinum proceeded stereoselectively from the α-face. The mixture of **13** (42%) and **14** (48%, 9:1 mixture with its epimer) so produced was directly cyclized and then dehydrated (Scheme II). To arrive exclusively at **15** (62%), the initially formed **15**/**16** mixture was stirred for 1 week in the presence of methanolic K_2CO_3.

Well aware of the topography inherent to **15**, we reduced this ketone cleanly to **17** (95%) in order to take subsequent advantage of the known anti epoxidation mode to which 3-cyclooctenols are normally subject.[10] In the case of **17**, the exocyclic double bond responded analogously such that **18** was isolated at the 86% level from reaction with MCPBA. Swern oxidation led conventionally to **2** [mp, 135-137 °C; $[\alpha]^{19}_D$ = +138° (*c* 3.09, $CHCl_3$)]. Single-crystal X-ray analysis[11] of this ketone unambiguously confirmed its identity.

Presently work is underway to synthesize **1** from one or more of the intermediates or directly from **2**. It is already clear, however, that the availability of **11** should allow access to some interesting epoxybasmenones not available from natural sources for biological evaluation.

Acknowledgment. We thank the National Institutes of Health (Grants GM-30827 and CA-12115) for generous financial support and Dr. Judith C. Gallucci for the X-ray crystallographic analyses.

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Total Synthesis of Calicheamicinone: A Solution to the Problem of the Elusive Urethane

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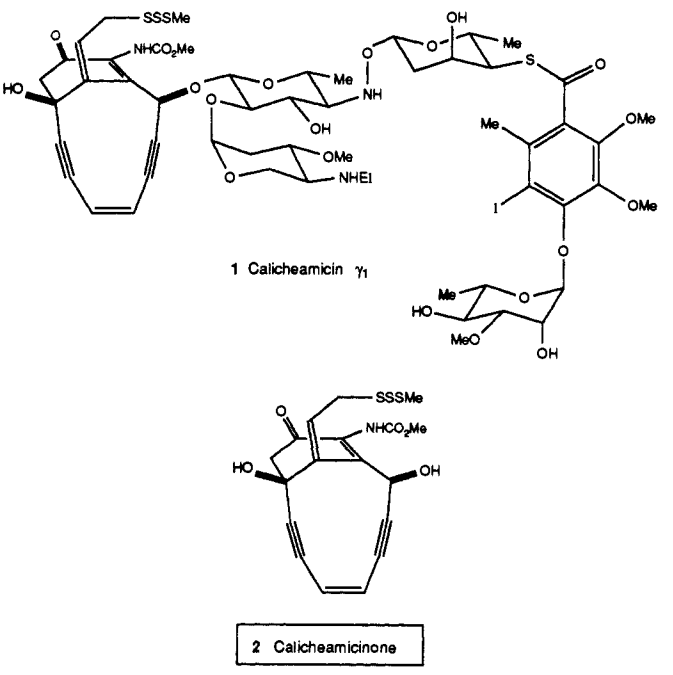
Received December 20, 1989
Revised Manuscript Received January 31, 1990

Recently there has been discovered a growing collection of antibiotics bearing novel patterns of interactive unsaturation. The antimicrobial and antitumor properties of these compounds[1] follow from their capacity to cut double-stranded DNA.[2] Evidence has been accumulated that the effector species for DNA degradation in vitro are diyls arising from chemically induced Bergman type[3] bond reorganizations[4] of the unsaturated loci. In a suitable setting,

Scheme I



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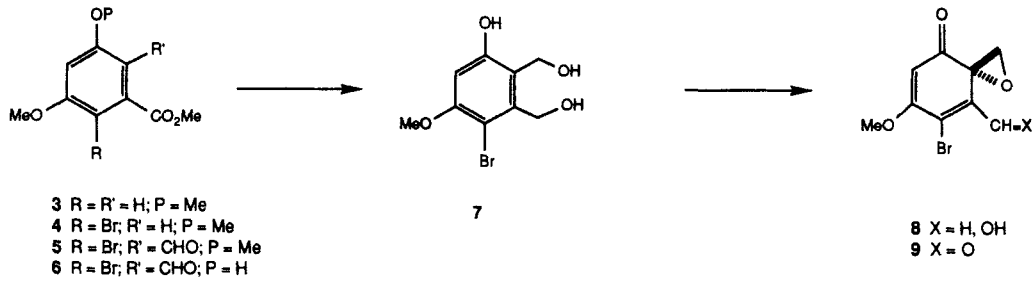
Scheme II

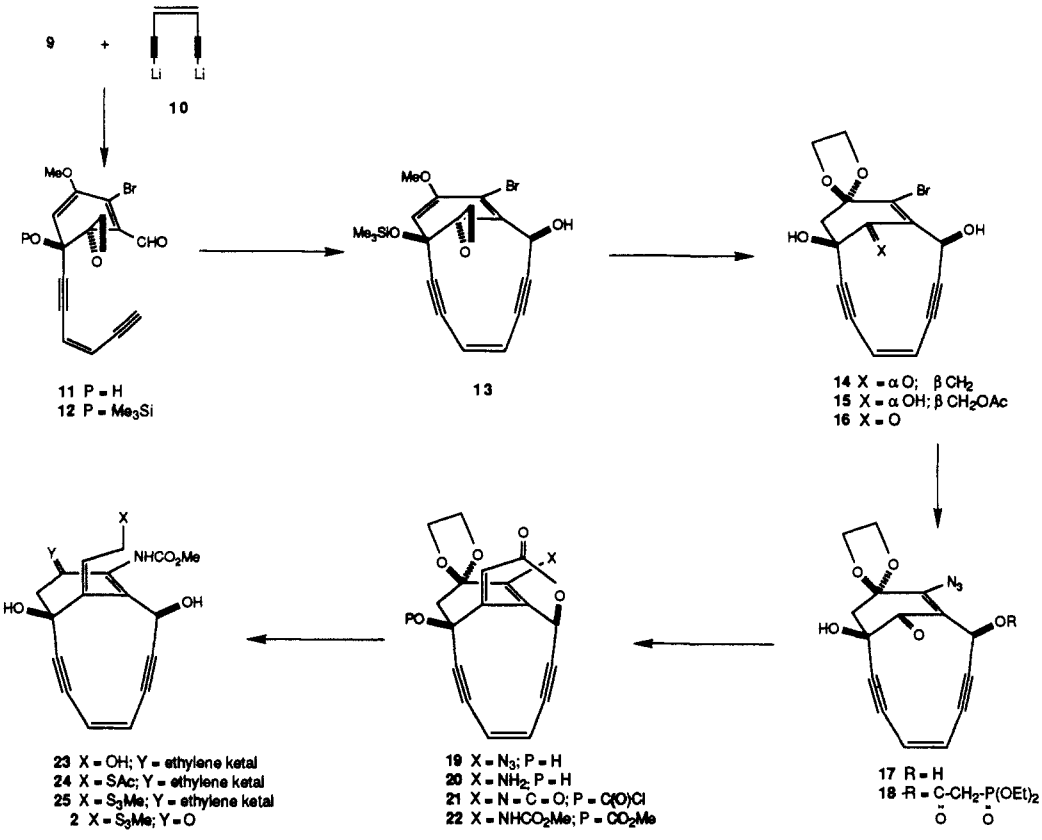


3 R = R' = H; P = Me
4 R = Br; R' = H; P = Me
5 R = Br; R' = CHO; P = Me
6 R = Br; R' = CHO; P = H

7

8 X = H, OH
9 X = O

Scheme III



11 P = H
12 P = Me_3Si

13

14 X = α O; β CH_2
15 X = α OH; β CH_2OAc
16 X = O

23 X = OH; Y = ethylene ketal
24 X = SAc; Y = ethylene ketal
25 X = S_3Me; Y = ethylene ketal
2 X = S_3Me; Y = O

19 X = N_3; P = H
20 X = NH_2; P = H
21 X = N = C = O; P = C(O)Cl
22 X = $NHCO_2Me$; P = CO_2Me

17 R = H
18 R = C-CH_2-P(OEt)$_2$
O O

such species have a proclivity for abstracting carbon-bound hydrogen atoms from deoxyribose units of oligonucleotides.[5] In some instances, the drug identifies sites for DNA degradation with remarkable sequence specificity.[6] The high in vitro potency of these compounds, their structural novelty, and their interesting mechanism of action have served to stimulate a large multidisciplinary effort addressed to their biology and chemistry. The eventual goal is that of developing cytotoxic agents that can be specifically directed to transformed or otherwise diseased cells.[7]

A fascinating example of such a drug is calicheamicin γ_1^{1a} (**1**). The aglycon moiety, with its poised enediyne linkage, is perceived as the source of latent chemical radiation.[8] The carbohydrate sector is seen to be the oligonucleotide recognition device.[6b] It would therefore be of great interest to study these functions independently. *However, at the present writing, there have been no reports of disengagement of the intact carbocyclic and carbohydrate sectors of calicheamicin (or esperamicin)*[1b] *by degradative means.* Thus, synthesis might be valuable in providing sharper insights into the functional subcomponents of the enediyne drugs. Moreover, the synthesis of either of the intact subunits (not to speak of the entire drug!) poses an obvious challenge to those who are sensitive to general issues of strategy and tactics in organic chemistry. Not surprisingly then, a great deal of fascinating science has already issued from synthetic undertakings in this area.[9]

Our laboratory has been involved in the enediyne problem at several levels. Early efforts led to the preparation of a functionalized core structure[10] and to the synthesis of systems with suitable functionality to actuate both diyl formation and DNA cleavage.[11a,b] *In this communication, we report the attainment*

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of an important goal in the field, i.e., the first total synthesis of the aglycon of 1 (i.e., calicheamicinone (2))[12] (Scheme I).

We drew from the general plan that was implemented in earlier work on simpler systems. However, it was necessary to provide the means to introduce the urethane function at the bridgehead double bond. The optimal timing for this installation emerged as a serious problem. The solution is described below.

Commercially available ester **3** (Scheme II) underwent regiospecific bromination (NBS, $CN_3C{\equiv}N$)[13] to afford **4**,[14] which upon formylation (Cl_2CHOMe; $TiCl_4$) gave **5**.[14] The aldehyde function was employed to direct regiospecific monodemethylation (via BCl_3), giving rise to the required phenol **6**[14] (65% from **3**). The sodium salt of **6** was subjected to reduction (DIBAH) to provide the unstable triol **7**, which, upon treatment with sodium periodate, afforded **8**.[15a] Upon oxidation of crude **8** with the Dess-Martin[15b] periodinane, there was obtained the spiroepoxy aldehyde **9**.[14] The yield for the three steps from **6** to **9** on large scale is ca. 40%.

The next phase of the effort involved insertion of the six-carbon enediyne bridge between the ketone and aldehyde functions. Dilithio enediyne **10**[16] was added to the ketone in the nominal presence of the aldehyde, using the logic of in situ protection as developed, in another context, in the pioneering research of Comins[17] (Scheme III). Reaction of **9** with **10** in the presence of lithium *N*-methylanilide afforded **11**. Silylation of the tertiary alcohol gave rise to **12**, which on cyclization (potassium 3-ethyl-3-pentoxide)[13,18] provided the core system **13**[14] (ca. 35-40% overall yield for the three steps from **9** on a 2-g scale). No stereoisomer of the secondary alcohol was observed. After considerable experimentation, it was found that the enol ether function was not suitable for the required subsequent manipulations. Accordingly, compound **13** was converted to ketal **14**[14] (CSA-ethylene glycol, 89% yield). Acetolysis of the epoxide (KOAc; AcOH; DMSO) led to crude **15**,[14] which upon deacylation (NH_3; MeOH) and oxidation (sodium periodate) gave rise to ketone-ketal **16**[14] (83% combined yield).

The bridgehead enone presented a target of opportunity for the introduction of an azido function. *For this to be possible, the ketone at the one-carbon bridge had to provide adequate enolate stabilization to support an addition-elimination mechanism, a possibility presaged by the research of Magnus.*[9c] In the event, reaction of **16** with sodium azide in methanol afforded an 82% yield of **17**.[14] As matters transpired, this stage was still too early to actually unveil the urethane. First the secondary alcohol was acylated ($(EtO)_2P(O)CH_2COCl$; Py)[19] and the resultant ester **18**[14] subjected to intramolecular Emmons condensation[11b,20] to produce **19**[14] (50% from **17**).

The conjugation afforded by the conjugated lactone provided a sufficiently stable setting for the steps required to transform the azide to the methyl carbamate function. Reduction of **19** (H_2S-piperidine-methanol; 95% yield) led to the remarkably robust vinylamine **20**.[14] The latter, upon treatment with phosgene in pyridine, gave rise to a bis acylation product, **21**, and thence, upon treatment with methanol and pyridine, to the carbamate-carbonate **22**[14] in 80% overall yield. Treatment of **22** first with DIBAH (which results in deprotection of the tertiary alcohol and reduction of the lactone to a lactol) followed by sodium borohydride produced the alcohol **23**[14] in 43% overall yield. The first sulfur atom was installed by a Mitsunobu reaction on **23** (thiolacetic acid, triphenylphosphine, diisopropyl azodicarboxylate) to produce **24** (45% yield).[14,21] Treatment of thioacetate **24** with DIBAH resulted in deacetylation. The crude product was subjected to the action of phthalimidomethyl disulfide,[22] thereby leading to trisulfide **25**[14] (65% from **24**). Finally, the ketal linkage was cleaved through the action of CSA in aqueous THF at room temperature. There was thus obtained *dl*-calicheamicinone (**2**) as a powder in 65% yield. While there exists, to our knowledge, no reference sample of this compound (**2**),[12] the structure proposed here is firmly supported by infrared, NMR, and mass spectral determinations. Furthermore, the assignments are supported by the close similarity of these compounds with those of the desureido series, which were in turn supported by crystallographic determinations.[10,11]

With the feasibility of the "end game" reactions having been demonstrated, various intermediates in this effort emerge as possibilities for other syntheses, which might be more concise and which might produce only the relevant antipode. Research toward these goals is continuing in our laboratory.

Acknowledgment. This research was financially supported by PHS Grant CA28824. An MEC/Fulbright Fellowship to M.P.C. and an NIH Postdoctoral Fellowship (Grant CA08388-02) to R.S.C. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We acknowledge the work of D. Yamashita, N. Iwasawa, M. Chu Moyer, and J. Haseltine for contributions in related series or for optimization experiments in this synthesis.

Supplementary Material Available: NMR, IR, and mass spectral data for compounds **2**, **4-6**, **8**, **9**, **13-20**, and **22-25** (6 pages). Ordering information is given on any current masthead page.

(12) We suggest this name, which incorporates the standard suffix use to denote the aglycon substructure of the anthracycline antibiotics.
(13) These conditions were developed by Dr. Nobuharu Iwasawa.
(14) The structure assigned to each new compound is consistent with its infrared and 250-MHz ^1H NMR spectra, as well as parent ion identification by high-resolution mass spectroscopy and/or elemental analyses.
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Solid-State ^{199}Hg Nuclear Magnetic Resonance as a Probe of Coordination Number and Geometry in Hg(II) Complexes

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Received November 27, 1989

Although Hg(II) chemistry is dominated by linear, two-coordinate compounds, studies of Hg(II)-biopolymer complexes including Hg-substituted blue copper proteins[1] and the Hg(II) biosensor, MerR,[2] have revealed important primary bonding interactions with additional ligands.[3,4] Unfortunately, even for simple model compounds, vibrational,[5] electronic absorption,[6] and solution NMR[7] spectroscopic data are unable to clearly differentiate between Hg(II) thiolate complexes with primary coor-

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0002-7863/90/1512-3255$02.50/0