Studies on the Synthesis of the Antitumor Agents Esperamicin A_1/Calicheamicin γ_1: Stereospecific Synthesis of the 12β-Hydroxybicyclo[7.3.1] Diynene Core Structure via a $Co_2(CO)_6$-Acetylene-Mediated Synclinal Aldol Reaction

Philip Magnus,* Hirokazo Annoura, and John Harling

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712

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Summary: Treatment of **11** with *n*-Bu_2BOTf/amine bases resulted in its stereospecific conversion into the 12β-hydroxybicyclo[7.3.1] diynene-$CO_2(CO)_6$ adduct **16**.

The key reaction in our approach to the synthesis of the potent antitumor compounds esperamicin/calicheamicin **1**[1] involves the use of the Pettit-Nicholas $Co_2(CO)_6$-propargyl cation chemistry to convert **2** into **3** (Scheme I).[2] While we have been able to introduce all of the functionality required for calicheamicin (C-1,2 double bond, C-2 nitrogen, C-3 oxygen, C-13 allylic trisulfide, and C-12 oxygen) into the cobalt-decomplexed substrate **4**, despite extensive experimentation we have not been able to successfully introduce the C-12 hydroxyl group by carrying out the Pettit-Nicholas reaction at the aldehyde oxidation level.[3] Scheme II shows a number of unsuccesful attempts to close the C-1, C-12 bond with a functional group at C-12. Even treatment of **9** with Me_3SiOTf/2,6-di-*tert*-butyl-4-methylpyridine (Pummerer reaction) only gave **3** (65%). Presumably, the PhS(O) group is activated by silylation (on oxygen) and then ionizes to the stabilized cation **2a** ($PhSOSiMe_3$ leaving group). The failure of the derivatives **5-9** to give **10** may be attributed to the lack of reactivity of **9a** (too stabilized). In support of this the keto aldehyde **11** was the major isolated product in all the attempts to convert **5-9** into **10**. Sulfonium and oxonium ions should be aligned antiperiplanar to the enol π-system, and this appears to be difficult to achieve (steric).[4] Furthermore, the product **10** may be unstable in respect to further ionization. Consequently, it was reasoned that a mild synclinal aldol reaction mediated by a boron enolate derivative might allow access to derivatives of **10**.[5] It should be noted that the other synthetic approaches to the esperamicins/calicheamicins arrive at 12-hydroxy bicyclo[7.3.1] diynene derivatives as a mixture of epimers at C-12.[1] Treatment of **12** with propargyl alcohol/$Pd(Ph_3P)_4$ (cat.)/CuI/*n*-$BuNH_2$ gave **13** (80%),[6] which was oxidized using Swern conditions to the unstable aldehyde **14** (Scheme III). Cobalt complexation gave **15** (92%)[7] and removal of the MEM protecting group using Me_2BBr-(THF/CH_2Cl_2)[8] gave the keto aldehyde **11** (73%). The yield of **11** was considerably decreased if THF was not added in this deprotection (30-35% of **11**). When **11** was treated with *n*-Bu_2BOTf/DABCO/NEt_3/CH_2Cl_2-THF the aldol product **16** was isolated as a single stereoisomer [45% after chromatography over silica gel (twice)] (Scheme IV). The 9-H to 12α-H proton-proton coupling is 1.59 Hz, which corresponds very closely to that observed in the natural products **1** (1.8 Hz). Surprisingly, when **16** was treated with I_2/THF/room temperature the aromatized diiodide **18** was isolated in 60% yield. This should be contrasted with **3**, which gave **4** (70%) with only small amounts of the iodide **19**. In contrast, when **16** was treated with *N*-methylmorpholine *N*-oxide/THF, *t*-BuOH/room temperature, the nonaromatized diynene **17** was isolated in 76% yield. Exposure of **17** to I_2/THF/room temperature did not give **18**. A plausible explanation for the aromatization of **16** to **18** might involve the hypoiodide **20**, which can deliver $I^\bullet$ to the adjacent triple bond to give **21** and initiate cycloaromatization to **19**. The above route to **17** was made more convergent by utilizing the modifications described by Kadow[9] in his adaptation of our original sequence.[2] Treatment of **22** with acetylene carboxaldehyde diethyl acetal under the usual coupling conditions gave **23** (68%) (Scheme V). Removal of the trimethylsilyl group with aqueous lithium hydroxide and treatment of the terminal acetylene with lithium bis(trimethylsilyl)amide generated the lithio derivative **24**, which was quenched with **25** to give **26** which undergoes silyl migration pro-

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(3) For very recent examples of the stereoselective aldol reaction of $Co_2(CO)_6$-acetylene aldehyde complexes, see: Ju, J.; Reddy, B. B.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989**, *54*, 5426. Mukai, C.; Nagami, K.; Hanaoka, M. *Tetrahedron Lett.* **1989**, *30*, 5623 and 5627. For a comprehensive review of $Co_2(CO)_6$-complexed propargyl cations, see: Nicholas, K. M. *Acc. Chem. Res.* **1987**, 208. For the original report of the $Co_2(CO)_6$-propargyl cation chemistry, see: Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 3475.

(4) The newly formed C-1/C-2 bond in **3**/**16** is axial and the 12β-substituent (corresponding to an antiperiplanar aldol transition state) is equatorial. There is poor overlap between C-1 and C-12 in this orientation.

(5) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, *559*. Fenzl, W.; Koster, R. *Justus Liebigs Ann. Chem.* **1975**, 1322. Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 6120. Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585 and references therein pertaining to chiral boron reagents. For a comprehensive review on the aldol reaction, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3, pp 111-212. For a recent description of transition state geometry in the aldol reaction, see: Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.

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(7) The less sterically hindered triple bond is preferentially complexed with $Co_2(CO)_8$. A small amount (ca. 5%) of the other regioisomer is formed, along with <1% of the bis adduct. The desired adduct **15** is purified by chromatography over silica gel prior to use.

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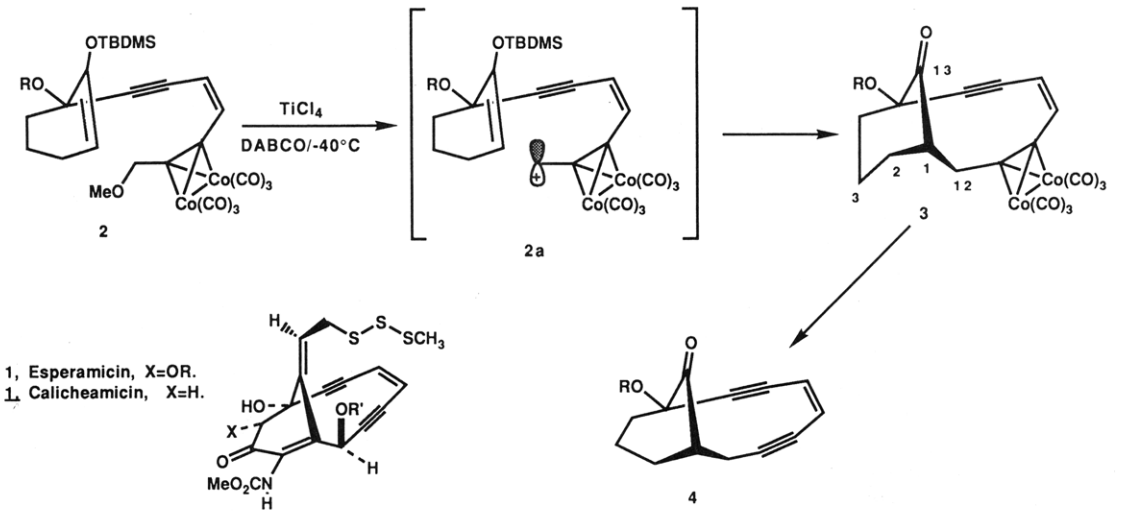
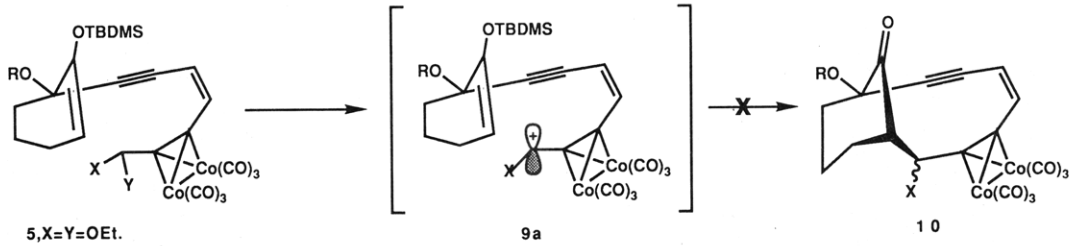
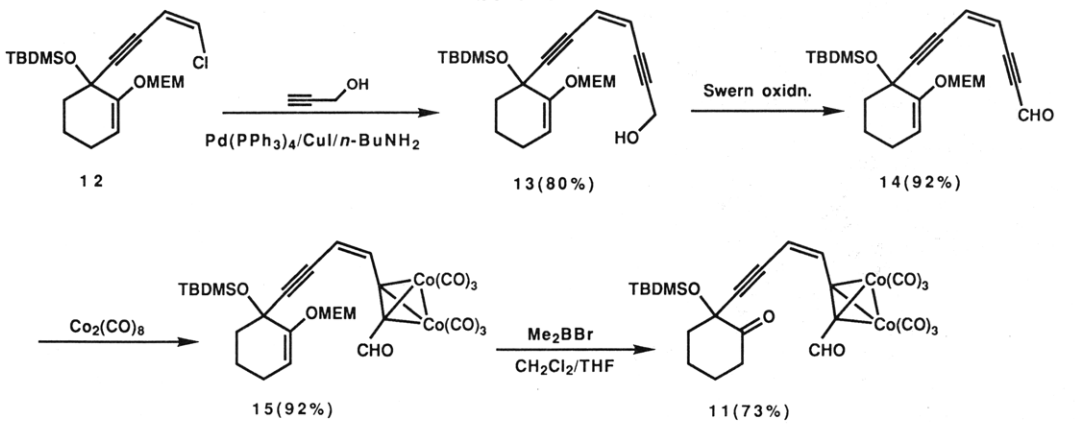
Scheme I (R = TBDMS)



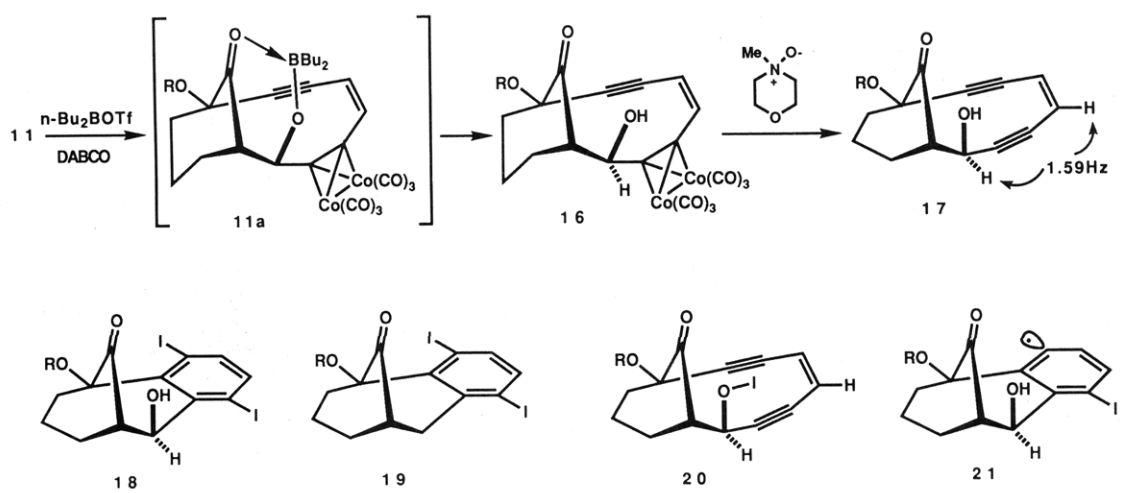
Scheme II



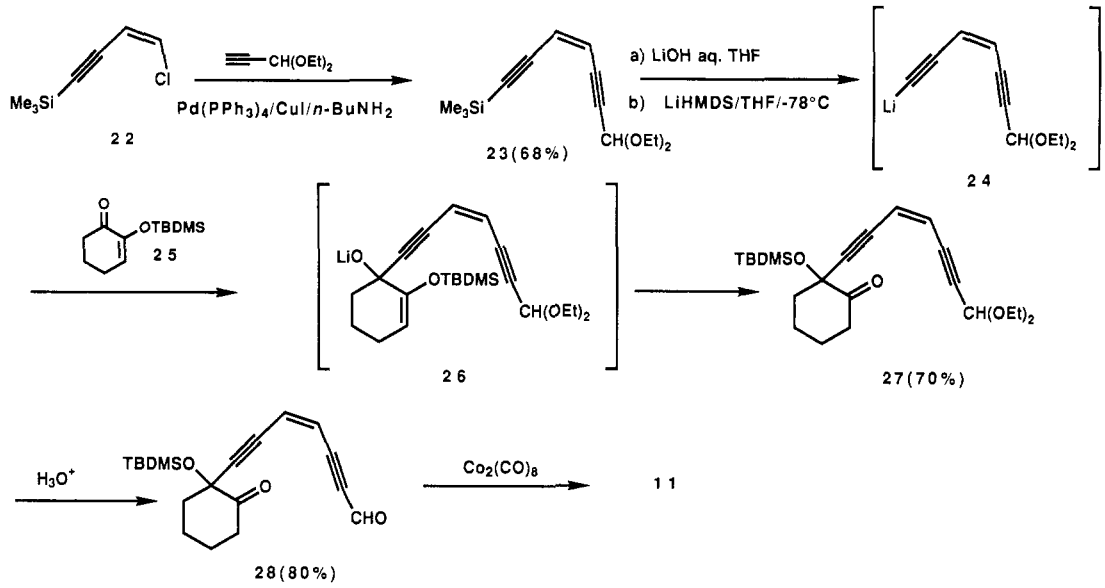
Scheme III



Scheme IV



Scheme V



viding **27** (70%). Hydrolysis of **27** with trifluoroacetic acid/chloroform gave **28** (80%) which was converted directly into **11** (90%) by treatment with dicobalt octacarbonyl. This route allows access to 12β-hydroxybicyclo[7.3.1] diynene **17** in eight steps from *cis*-dichloroethylene and trimethylacetylene in an overall yield of 14% (unoptimized). The synclinal aldol mediated stereospecific synthesis of the 12β-hydroxybicyclo[7.3.1] diynene system **17** should allow the examination of bridgehead enol chemistry (C-1, C-13) in the presence of the 12β-substituent.

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Supplementary Material Available: Spectral data for compounds **11** and **13–18** (1 page). Ordering information is given on any current masthead page.

Articles

1-Hydroxy-3-amino-2-piperidone (δ-*N*-Hydroxycycloornithine) Derivatives: Key Intermediates for the Synthesis of Hydroxamate-Based Siderophores

Teodozyj Kolasa and Marvin J. Miller*

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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Several routes for the synthesis of δ-*N*-(benzyloxy)cycloornithine (**2**) from glutamic acid derived starting materials are described. Efficient methods were developed for the synthesis of glutamic acid γ-semialdehyde and δ-hydroxynorvaline derivatives as key substrates for preparation of δ-*N*-hydroxyornithine analogues. Thus, the best approaches to the synthesis of **2** were: (1) reductive cyclization of an *N*-hydroxysuccinimide ester of the *O*-benzyloxime **4** of α-amino-protected glutamic acid γ-semialdehyde **5** and (2) cyclization of the *N*-(benzyloxy)amide of δ-bromonorvaline (**7**).

Introduction

The pseudomonads represent a diversified group of Gram-negative bacteria widely distributed in the soil. The fluorescent pseudomonads which belong to group 1, according to their genetic homology, release yellow-green flourescent pigments when grown under iron-deficient conditions. These pigments are the siderophores of the fluorescent pseudomonads and are called pyoverdines[1-4] or pseudobactins[5-9] and serve as a biological source of iron for these bacteria.

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