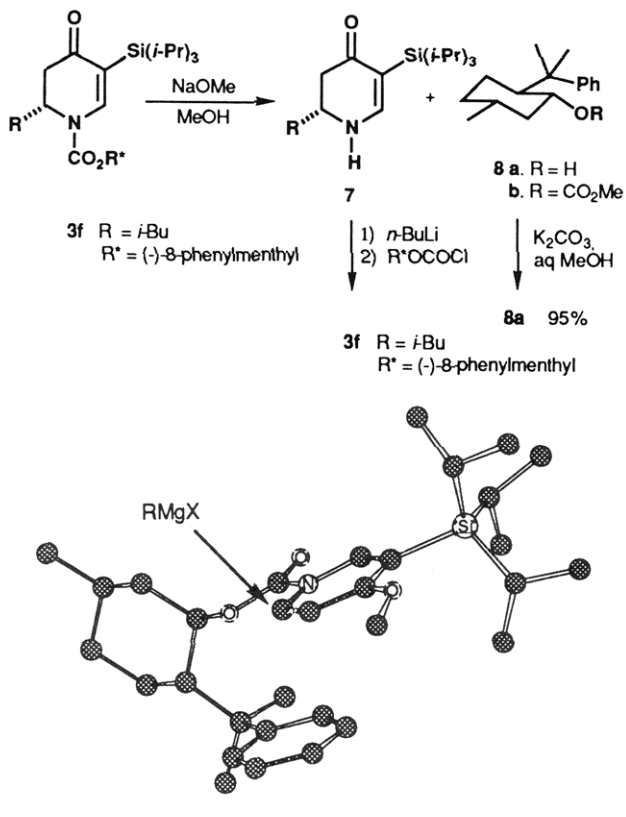
Scheme III



9

Figure 1. A working model derived from molecular mechanics (MMX).[12]

stereomers to the NMR spectrum of the 2-methyl derivative, which was subjected to X-ray single-crystal structure analysis. In all cases the dihydropyridones (**3**) prepared from (−)-8-phenylmenthyl chloroformate were crystalline compounds. Purification of the crude products by recrystallization can give high yields of diastereomerically pure dihydropyridones **3** (entries h and n).[10]

(10) All new compounds have been characterized by NMR and IR spectroscopy and elemental analysis.

The chiral auxiliary can be removed and recovered as shown in Scheme III. Treatment of recrystallized **3f** (R = *i*-Bu) (100% de) with sodium methoxide in methanol (4 equiv, reflux, 16 h) gave a 92% yield of dihydropyridone **7** [$[\alpha]^{23}_D$ +216.6° (*c* 1.34, $CHCl_3$); mp 150–152 °C (hexane)] and a mixture of **8a** and **8b** after radial preparative-layer chromatography. The mixture (**8a** and **8b**) was treated with K_2CO_3 in aqueous methanol (room temperature, 2 h) to give a 95% yield of (−)-8-phenylmenthol. The dihydropyridone **7**[11] was deprotonated with *n*-BuLi in THF (−78 °C, 15 min), and the resulting anion was added to (−)-8-phenylmenthyl chloroformate (THF, −78 °C to room temperature) to give **3f** (98%, 100% de), demonstrating that no racemization occurred on removal of the chiral auxiliary.

A working model that rationalizes the formation of **3f** as the major diastereomer is depicted in Figure 1. Attack by a Grignard reagent at C6 on the more accessible face of the pyridinium ring in **9** leads to the observed formation of diastereomer **3f** as the major product. It is not known at this time whether the in situ formed *N*-acyl salt exists mainly in the reaction medium as a nonequilibrating rotamer, i.e. **9**, or if equilibration between rotamers is occurring. Additional studies on the mechanism and scope of this novel asymmetric synthesis and its application toward the enantioselective synthesis of natural products will be reported in due course.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health and North Carolina State University.

Supplementary Material Available: Experimental details for the preparation of **3f** (R = Ph), physical data for compounds **3f** (R = Ph, Me), ORTEP plots of the X-ray structures, and crystal data of **3d** (R = Ph) and **3f** (R = Me) (7 pages). Ordering information is given on any current masthead page.

(11) Optically active dihydropyridones of this type have been prepared from chiral imines and Danishefsky's diene. Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067; **1989**, *28*, 1068. Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. Also see: Danishefsky, S.; Kerwin, J. F. *Tetrahedron Lett.* **1982**, *23*, 3739.

(12) MMX version by K. E. Gilbert and J. J. Gajewski based on MM2 (Allinger, QCPE 395) and MMP1 Pi (Allinger, QCPE 318) modified by K. Steliou.

Installation of the Allylic Trisulfide Functionality of the Enediyne Antibiotics. Thiol-Induced Reductive Actuation of the Bergman Process

John N. Haseltine and Samuel J. Danishefsky*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

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Summary: The title compounds were synthesized through thiosulfenylation. Exposure of the trisulfides to benzyl mercaptan induced reductive cycloaromatization.

Prevailing theory concerning the mode of action of the enediyne antibiotics envisions initial noncovalent binding to double-stranded DNA.[1] It is further assumed that reductive cleavage of the allylic trisulfide initiates a cascade which generates a diyl species strategically disposed to effect cutting of the duplex DNA.[2,3] Recently we have simulated the diyl priming process by recourse to an allylic thioacetate trigger.[4] Actuation involved an S → O acetyl

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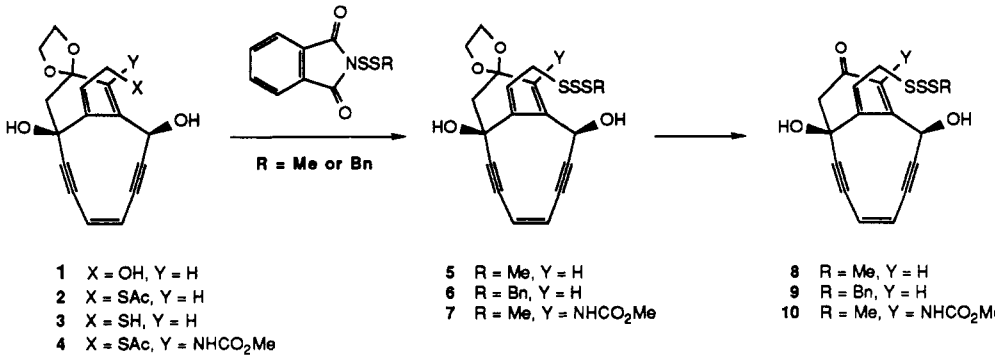
Scheme I

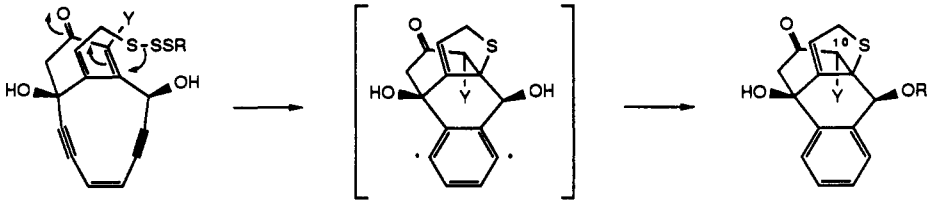


1 X = OH, Y = H
2 X = SAc, Y = H
3 X = SH, Y = H
4 X = SAc, Y = $NHCO_2Me$

5 R = Me, Y = H
6 R = Bn, Y = H
7 R = Me, Y = $NHCO_2Me$

8 R = Me, Y = H
9 R = Bn, Y = H
10 R = Me, Y = $NHCO_2Me$

Scheme II



8, 9, or 10

11 R = Y = H
12 R = Ac, Y = H
13 R = H, Y = $NHCO_2Me$

migration. Herein we describe for the first time the chemistry of systems which contain both structural elements, i.e., the bridgehead enone and the allylic trisulfide employed by the naturally occurring antibiotics.

Magnus and co-workers had communicated their efforts pertinent to the preparation of a [7.3.1] enediyne skeleton bearing the trisulfide group but lacking a bridgehead Michael acceptor.[5] In this work, convenient recourse was made to the phthalimido disulfide reagents of a type originally developed by Harpp and others.[6] However, the preparation of the allylic trisulfide was complicated by the formation of significant amounts of disulfide.[5] We also used the Harpp reagents, initially for the generation of des-ureido aglycon prototypes, and subsequently in the first total synthesis of the calicheamicin aglycon.[7] The present paper describes the elaboration of allylic trisulfides in the des-ureido series and provides the first demonstration of activating the Bergman[8] cascade via the trisulfide trigger in the aglycon series.

Thioacetate **2**, previously obtained from the corresponding primary mesylate,[4] has subsequently been prepared directly in 50–60% yield from triol **1** using the conditions of Volante (DIAD, PPh_3, HSAc).[9] Deacylation (DIBAL, CH_2Cl_2, −78 °C) followed by treatment with methyl phthalimido disulfide (CH_2Cl_2, THF, room temperature)[5] or benzyl phthalimido disulfide[6a] gave the corresponding alkyl trisulfides, **5**[10] and **6**,[10] in 84 and 61% yields, respectively. Deprotection of the bridgehead enone in the presence of the trisulfide moiety was approached with some concern. However, in the event exposure of **5** and **6** to the action of camphorsulfonic acid in THF/H_2O at room temperature provided the derivative enones **8**[10] and **9** in quantitative yield. The calicheamicin aglycone, **10** was obtained in similar fashion from **4** as previously described.[7]

Interestingly, the syntheses of trisulfides **5**, **6**, and **7** are apparently not complicated by formation of any corresponding disulfide. The factors responsible for the difference between our findings and those reported by Magnus have not been fully clarified. It might be that subtle differences in the nature of the substrate undergoing thiylation determine the course of cleavage of the Harpp disulfides. Alternatively the difference might arise from the method in which the reagents are prepared and used.[11]

With these allylic trisulfides in hand, it was of interest to study their ability to potentiate the diyl-forming cascade. Treatment of either **8** or **9** with benzyl mercaptan, triethylamine, and 1,4-cyclohexadiene in methanol for 2 h at room temperature resulted in the formation, in each instance, of an approximately 50% yield of cycloaromatized tetracycle **11**.[10] In addition to routine characterization, the structure of **11** was corroborated through acetylation of the secondary alcohol (Ac_2O, pyridine, room temperature) to provide the previously identified ester **12**.[4] Similarly, the cycloaromatization of **10** with the intact urethane afforded a 16% yield of **13** (wherein the stereochemistry at C_{10} has not been rigorously determined.[12]

In summary we have demonstrated the clean introduction of the trisulfide trigger in extensively functionalized versions of the calicheamicin/esperamicin antibiotics. Moreover, thiol-induced cleavage in these systems (a model for the possible action of glutathione) initiates the cascade which culminates in Bergman cyclization. Thus, the urethane functionality is not crucial for the activation cascade.

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(10) The structure of this compound is consistent with its infrared and 250-MHz ^1H NMR spectra as well as parent identification by high-resolution mass spectroscopy.
(11) A detailed procedure for the preparation of methyl phthalimido disulfide is provided in the supplementary material.
(12) ^1H NMR data in hand are consistent with a structural assignment for **13** in which the urethane function is of the α configuration. The same stereochemistry has been suggested for the Bergman product derived from calicheamicin γ_1^I. See: Ellestad, G. A.; Hamann, P. R.; Zein, N.; Morton, G. O.; Siegel, M. M.; Pastel, M.; Borders, D. B.; McGahren, W. J. *Tetrahedron Lett.* **1989**, *30*, 3033.

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Supplementary Material Available: Experimental procedure for the preparation of methyl phthalimido disulfide and spectral data (IR, ^{1}H NMR, and MS) for compounds **3**, **5**, **6**, **8**, **9**, **11**, and **13** (8 pages). Ordering information is given on any current masthead page.

α-Lithioamine Synthetic Equivalents: Syntheses of Diastereoisomers from the Boc Piperidines

Peter Beak* and Won Koo Lee

Department of Chemistry, University of Illinois at Champaign—Urbana, Urbana, Illinois 61801

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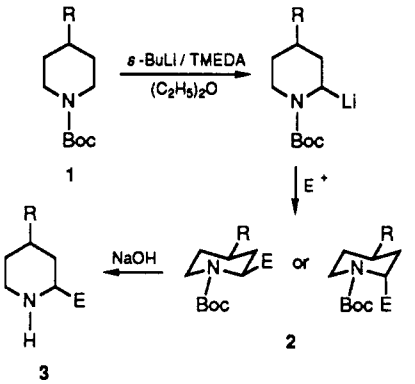
Summary: The α′-lithiations and electrophilic substitutions of selected Boc piperidines provide single or separable diastereoisomeric 2-substituted, 2,4-disubstituted, and 2,4,6-trisubstituted Boc piperidines which are readily hydrolyzed to the substituted piperidines.

Previous studies of the formation of α′-lithioamine synthetic equivalents from secondary amines have shown that piperidines provide an informative and demanding test of the methodology.[1-4] We have recently reported that the *tert*-butoxycarbonyl (Boc) group is an effective activating group for directing α′-lithiation of piperidines.[2] In this paper we provide preliminary results which show that diastereomeric 2-substituted, 2,4-disubstituted, and 2,4,6-trisubstituted piperidines can be prepared readily by this approach.

The reactions we have carried out are shown for the general conversions of **1** to **2** to **3**, with the specific reactants shown as **4**–**23** and the separated products shown as **7**, **9**, **11**, and **12**–**42** in Table I. Structures are shown in the first column for reactants for the lithiation–substitution step while reactants for the hydrolysis step are designated by compound number. The stereochemistries are assigned to the products on the basis of ^{1}H NMR spectra which distinguish the alternatives by molecular symmetry and/or characteristic coupling constants of the C_2 and C_6 protons to the adjacent methylene group. The assignments to the erythro:threo isomer pairs, including **26** and **27**, are based on the larger couplings found between the C_2 and exocyclic protons for the threo isomer in established systems.[5] The assignments were confirmed for **28** by direct comparison of the corresponding benzamides with authentic material, for the amino alcohols **38** (*dl*-conhydrine), **39** (*dl*-β-conhydrine), and **12** by comparison with literature physical properties and for **40** by an X-ray structure determination.[5]

As shown in the table, lithiation of the Boc piperidines followed by reactions with aldehydes provides mixtures of readily separable erythro and threo isomers in which the threo isomer is often in a cyclized form. The substituents for the monosubstituted systems **12**, **14**, **16**, and **19** are shown as equatorial because the proton at C_2 in **12** can be assigned as axial based on its couplings to the adjacent methylene of 5 and 12 Hz. Axial disposition of the methyl group in **6** is consistent with coupling constants of 2 and 3 Hz between the C_2 and the adjacent methylene protons and with $A_{1,3}$ strain.[6] The conformations assigned to **41** and **42** are made to be consistent with those of the monosubstituted systems.



The stereochemistries of the products from **4**–**6** and **8** are consistent with equatorial α′-lithiation followed by retention on electrophilic substitution as previously reported.[1] The formations of both diastereoisomers on reactions with aldehydes and the beneficial effect of a substituent on the piperidine ring on the yields of the alkylation reaction are also consistent with experience with the piperidine amides and formamidines.[1,7] However, the axial substitutions in the formations of the trans 2,6-substituted isomers from the 2,4-disubstituted systems **7** and **9** are different from the previous pattern.[8]

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(8) Meyers and co-workers obtained the *cis*-2,6-dimethyl product from the 4-*tert*-butylpiperidine formamidine by analogous chemistry.[1d] The fact that the stereochemistry is influenced by the directing group on nitrogen provides another approach for stereochemical control with this methodology.

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