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Asymmetric Synthesis of the Hydroxylamino Sugar of Calicheamicin

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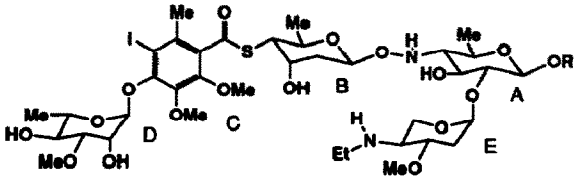
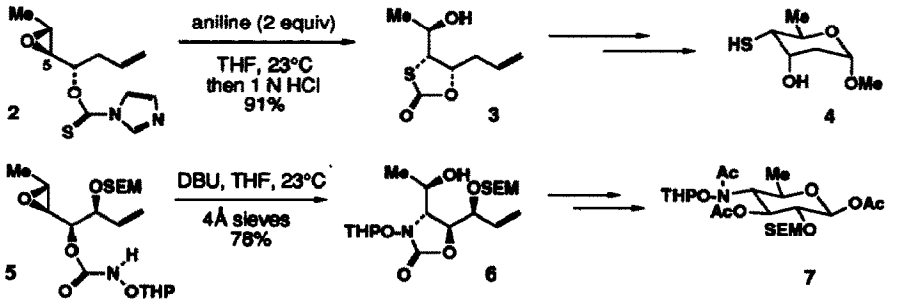
Abstract. A stereochemically general procedure for the conversion of 2,3-epoxyalcohols to *N*-alkoxy oxazolidinones via the DBU promoted cyclizations of 2,3-epoxy-*N*-alkoxyurethanes has been developed and applied to the first asymmetric synthesis of the calicheamicin hydroxylamino sugar, **7**.

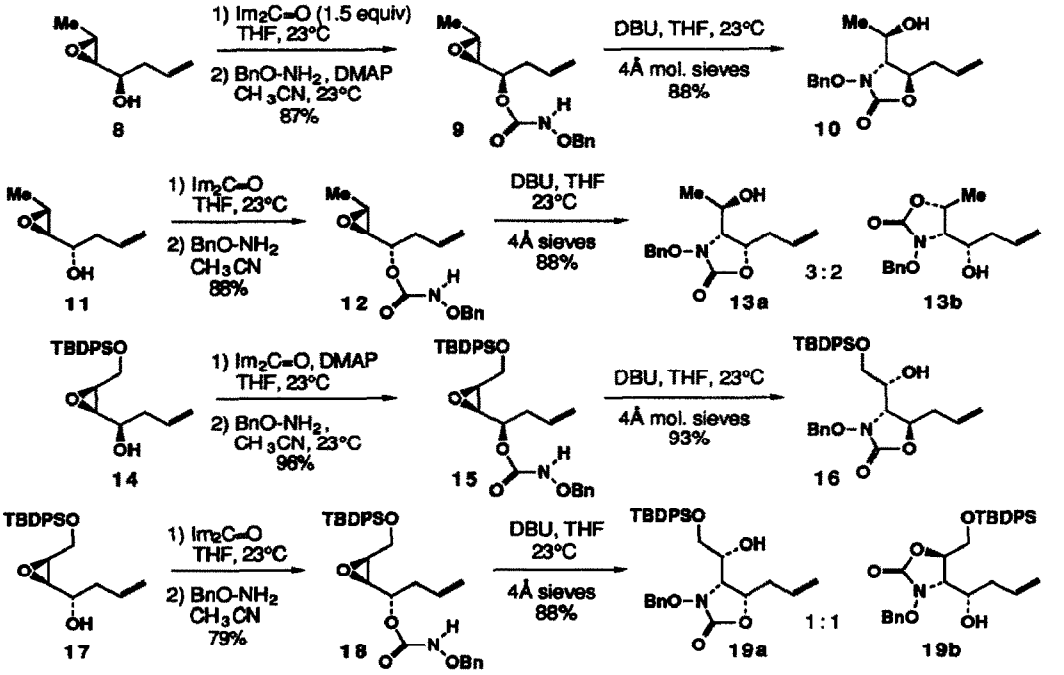
Aryl tetrasaccharide **1** has been identified as the major DNA binding and recognition substructure of calicheamicin, a potent double strand DNA-cleaving enediyne antibiotic that binds and cleaves DNA from within the minor groove.[1,2] Oligosaccharide **1** contains several novel structural elements that presumably contribute to the DNA recognition-binding properties,[2c,d,e,i] including the 2,4,6-trideoxy-4-thio sugar (B residue) and the hydroxylamino linkage connecting the A and B residues. In anticipation that conjugates of aryl tetrasaccharide **1** (R = H) or its stereoisomers can be used to increase the specificity of DNA binding of other therapeutic agents,[3] we have initiated a program focusing on the development of a stereochemically general synthesis of **1** (R = H). In the preceding communication we described a simple asymmetric synthesis of the thio sugar **4** involving neighboring group assisted delivery of a sulfur nucleophile to C(5) of the epoxyalcohol precursor (e.g., **2** → **3**).[4] We report herein an analogous and equally straightforward method for the synthesis of 4-hydroxylamino sugar **7** via the base catalyzed cyclizations of *N*-alkoxyurethane **5**.[5,6]



1, calicheamicin aryl tetrasaccharide



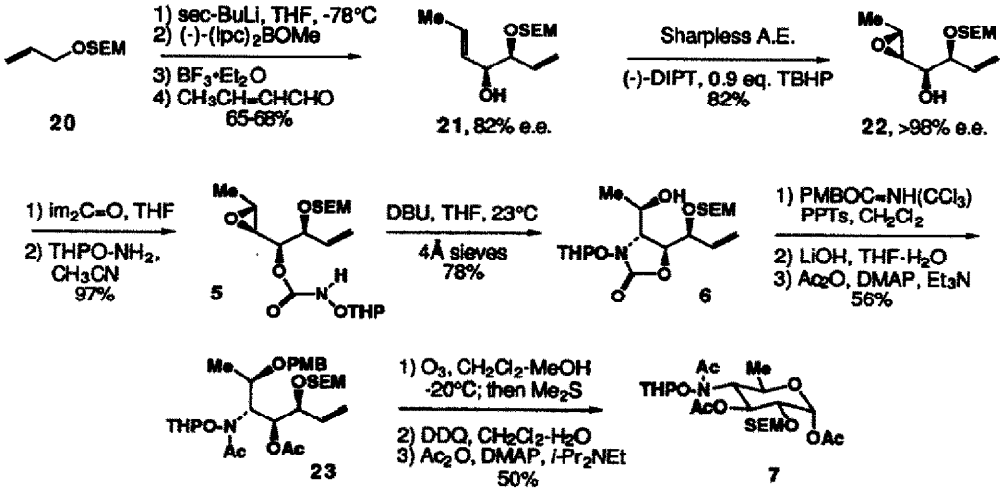
We originally planned to synthesize the requisite *N*-alkoxyurethanes (e.g., **5**) via the reaction of suitable 2,3-epoxyalcohols with an *N*-alkoxyisocyanate. However, in view of a report that methoxyisocyanate is stable only at temperatures below 90°K,[7] and because preliminary efforts to generate $PhCH_2ON{=}C{=}O$ in situ from the reaction of carbonyl diimidazole (CDI) and *O*-benzyl hydroxylamine were not encouraging, we developed a stepwise procedure illustrated by the conversion of **8** to **9**. Thus, treatment of epoxyalcohol **8**[6a] with 1.5 equiv. of CDI in THF followed by treatment of the intermediate acyl imidazolide with 3 equiv. of *O*-benzyl hydroxylamine[8] and catalytic DMAP in acetonitrile provided **9**[9] in 87% yield. This procedure was also applied to epoxyalcohols **11**,[4] **14**,[10] and **17**[10] which provided **12** (88% yield), **15** (96% yield) and **18** (79% yield), respectively. Cyclization of *O*-acyl hydroxamates **9**, **12**, **15** and **18** was accomplished by exposure to DBU in THF containing suspended 4 Å molecular sieves. If sieves were not included, hydrolysis of the *N*-(benzyloxy)oxazolidinones was observed in several cases. In this way, *N*-(benzyloxy)oxazolidinones **10**, **13**, **16** and **19** were obtained in 88-93% yield (69-89% for the three step sequence from the epoxyalcohol precursors). Single regioisomers were obtained in the cyclizations of **9** and **15** (*erythro* epoxy alcohol stereochemistry; the oxazolidinone products thus have *trans* configuration), but mixtures of acyl transfer isomers were obtained in the cyclizations of **12** and **18** derived from *threo* epoxyalcohols **11** and **17**. The primary cyclization products **13a** and **19a** in these cases have *cis* oxazolidinone stereochemistry and therefore are sensitive to acyl transfer. This is not a serious problem, however, since hydrolysis of these mixtures lead to a single hydroxylamine in each case.



It is noteworthy that the cyclizations of **9**, **12**, **15** and **18** occur under much milder conditions than analogous base promoted cyclizations of 2,3-epoxyurethanes,[6b] presumably due to the greater acidity of the *N*-alkoxyurethanes.[11] The epoxy *N*-alkoxyurethane cyclizations are also considerably milder than the bimolecular

couplings of glycosyl triflates and *O*-glycosyl hydroxylamines that Kahne and Danishefsky have used to construct the hydroxylamino linkage between the A and B residues of the calicheamicin-esperamicin core trisaccharide.[5b,c] Accordingly, we anticipate that the methodology reported herein can be used for the synthesis of the calicheamicin A-B glycosidic linkage if a suitable *O*-glycosyl hydroxylamine derivative is coupled with an appropriate acyl imidazolide intermediate. This possibility was explored in a synthesis of the protected calicheamicin hydroxylamino sugar **7** in which THP-ONH_2[12] was used as a surrogate for an *O*-glycosyl hydroxylamine.

The synthesis of **7** originates with an asymmetric syn-γ-alkoxyallylation of crotonaldehyde using the chiral allylborane generated from allyl SEM ether according to Brown's procedure.[13] Thus, metallation of **20** with 1.0 equiv. of *sec*-BuLi in THF at -78°C followed by sequential addition of 1.0 equiv. of (+)-$(Ipc)_2BOMe$ (prepared from (-)-α-pinene), 1.3 equiv. of $BF_3{\cdot}Et_2O$, and then 1.0 equiv. of crotonaldehyde provided **21** ($[\alpha]_D^{23}$ +59.7° (c = 8.7, $CHCl_3$)) in 65-68% yield. The enantiomeric purity of **21** was determined to be 82% e.e. by using the Mosher ester analysis.[14] The absolute stereochemical purity of this intermediate was improved by performing the subsequent Sharpless asymmetric epoxidation in the kinetic resolution mode.[15] Thus, by using TBHP (0.9 equiv.) as the limiting reagent, *erythro* epoxy alcohol **22** ($[\alpha]_D^{23}$ +40.3° (c = 9.2, $CDCl_3$)) was obtained in 82% yield and >98% e.e. (Mosher ester analysis). Treatment of **22** with 1.3 equiv. of CDI in THF followed by 1.5 equiv. of THP-ONH_2 in CH_3CN provided **5** ($[\alpha]_D^{23}$ +45.4° (c = 3.6, $CDCl_3$)) in 97% yield. Cyclization of **5** was smoothly accomplished by treatment with DBU in THF, thereby providing **6** ($[\alpha]_D^{23}$ +84.0° (c = 4.7, $CHCl_3$)) as a mixture of THP diastereomers in 78% yield. This mixture was separated chromatographically, and the more polar diastereomer (R_f 0.18, 40% EtOAc-hexane; the less polar THP anomer has R_f 0.25) was used in subsequent transformations. Protection of the free hydroxyl group as a *p*-methoxybenzyl (PMB) ether,[16] hydrolysis of the oxazolidinone (LiOH, THF-H_2O) and then peracetylation provided **23** ($[\alpha]_D^{23}$ +44.2° (c = 2.9, CCl_4)) in 56% yield. Finally, ozonolysis of the vinyl group, deprotection of the PMB ether, and acylation then completed the synthesis of **7** ($[\alpha]_D^{23}$ +60.3° (c = 1.2, $CHCl_3$)). The stereochemistry of **7** was easily established by ^1H NMR spectroscopy, which revealed $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 10.2 Hz, and $J_{4,5}$ = 10.5 Hz.



In summary, a stereochemically general procedure for the conversion of 2,3-epoxyalcohols to *N*-alkoxy-oxazolidinones via the DBU promoted cyclizations of *N*-alkoxyurethanes has been developed and applied to the first

asymmetric synthesis of the calicheamicin hydroxylamino sugar (7). These cyclization reactions proceed under exceptionally mild conditions and appear ideally suited for use in the synthesis of the calicheamicin ABE core trisaccharide. Additional progress towards this goal will be reported in due course.

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