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A Stereochemically General Synthesis of Methyl 2,4,6-Trideoxy-4-methylthio-α-D-*ribo*-pyranoside, the Thio Sugar of Esperamicin A_1

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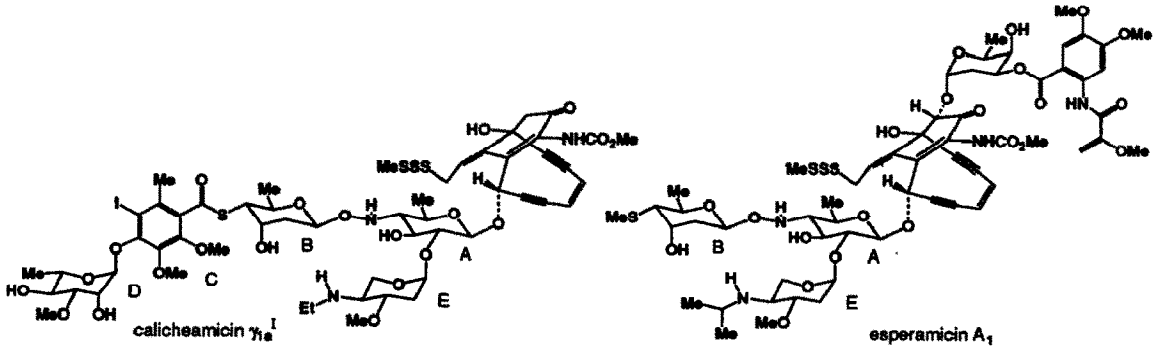
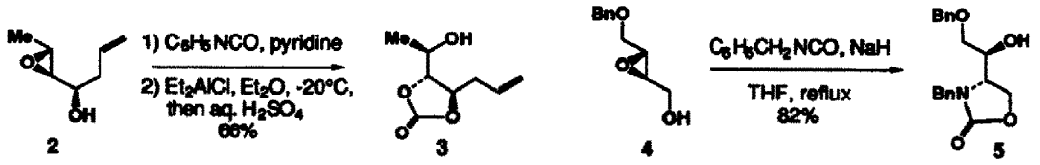
Abstract. A stereochemically general synthesis of methyl 2,4,6-trideoxy-4-methylthio-α-D-ribo-pyranoside (**1b**), the thio sugar isolated from esperamicin, is described. The synthesis involves the neighboring group assisted delivery of a sulfur nucleophile to C(5) of epoxyalcohol **6** via aniline promoted cyclization of thioimidazolide **7**.

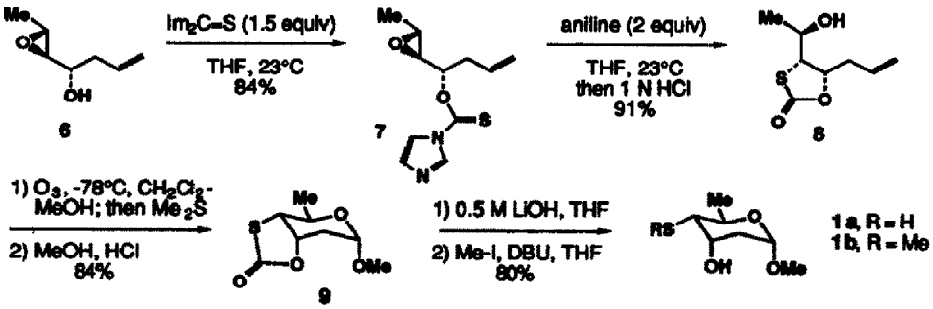
The enediyne antitumor antibiotics have attracted considerable attention owing to their potent biological activity and novel mechanism of action as double strand DNA cleaving agents.[1] The calicheamicins[2] and esperamicins[3] are of particular interest since they bind with high site selectivity in the DNA minor groove (calicheamicins > esperamicins), with the aryl tetrasaccharide unit of calicheamicin γ_1 serving as the major DNA recognition-binding domain.[4] Efforts are ongoing in several laboratories to understand the nature of the DNA-oligosaccharide interactions and to use the oligosaccharide-DNA recognition properties in the design and synthesis of novel, highly specific DNA binding agents.[1a,4d,e,i,5] We report herein an asymmetric synthesis of methyl 2,4,6-trideoxy-4-methylthio-α-D-*ribo*-pyranoside (**1b**), the esperamicin thio sugar, by a stereochemically general route that should be useful for the synthesis of analogs of the ABE core trisaccharide substructures.[6,7]



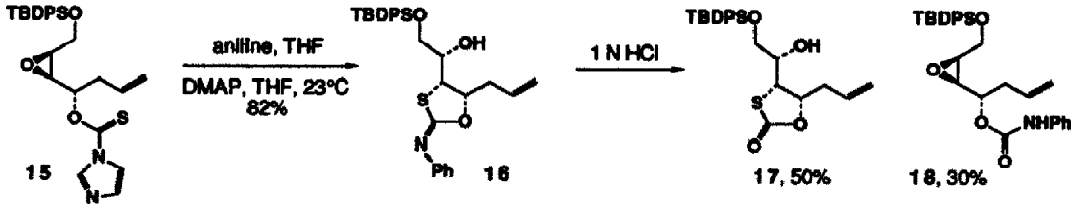
With the exception of the recent work of Beau,[7d] all previous syntheses of the thio sugar components of calicheamicin and esperamicin have utilized carbohydrate starting materials.[7] Our strategy called for the development of a stereochemically general synthesis of **1** from acyclic precursors, since this would facilitate the synthesis of analogs of the core ABE trisaccharide for use in DNA binding studies. In previous work on the synthesis of 2,6-dideoxyhexoses and amino sugars, we developed highly stereoselective procedures for the neighboring group assisted delivery of oxygen and nitrogen nucleophiles to C(2) of epoxyalcohol derivatives (e.g., **2** → **3** and **4** → **5**).[8] We recognized that this strategy would be applicable to the synthesis of **1** if a procedure for the delivery of a sulfur nucleophile to C(5) of epoxyalcohol **6** could be devised.



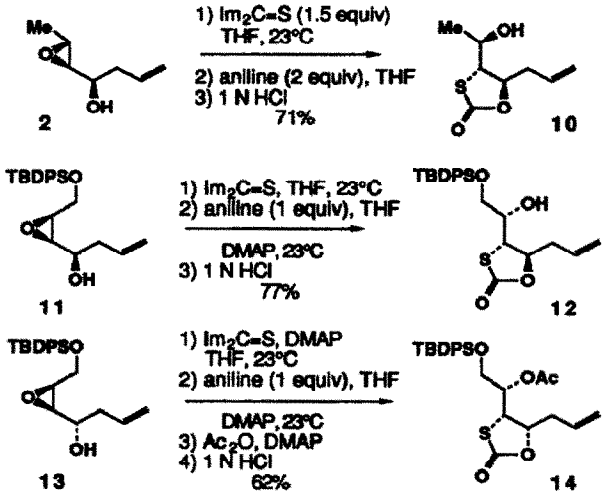
Toward this end, epoxyalcohol **6**[9,10] was treated with thiocarbonyl diimidazole (1.5 equiv.) in THF at 23°C to give imidazolide **7** ($[\alpha]_D$ +1.1° (c 0.89, $CHCl_3$)) in 84% yield.[11] Cyclization to the thiocarbonate **8** ($[\alpha]_D$ +2.2° (c 0.48, $CHCl_3$)) was smoothly accomplished by treating **7** with aniline (2 equiv.) in THF followed by hydrolysis of the intermediate iminocarbonate with 1N HCl. Ozonolysis of **8** in 1 : 1 CH_2Cl_2-MeOH at -78°C (Me_2S workup) followed by methyl glycoside formation (MeOH, HCl) provided **9** as a ca. 1 : 1 mixture of β ($[\alpha]_D$ -30° (c 1.4, $CHCl_3$)) and α ($[\alpha]_D$ +161° (c 0.61, $CHCl_3$), lit.[7b] $[\alpha]_D$ +107.3° (c 1.23, $CHCl_3$)) anomers in 84% overall yield. As a proof of structure, **9α** was elaborated to the esperamicin degradation product **1b** ($[\alpha]_D$ +220° (c 0.3, $CHCl_3$); lit.[7d] $[\alpha]_D$ +218° (c 1.0, $CHCl_3$); lit.[7a] $[\alpha]_D$ +270° (c 0.61, $CHCl_3$); m.p. 57.5-58.5°C, lit.[7a] m.p. 53-54°C) by treatment with 0.5 M aq. LiOH in THF followed by methylation of the thiol **1a** by using MeI (1.0 equiv.) and DBU in THF. The spectroscopic properties of **9α** and **1b** were in complete agreement with literature values.[7a,b,d]



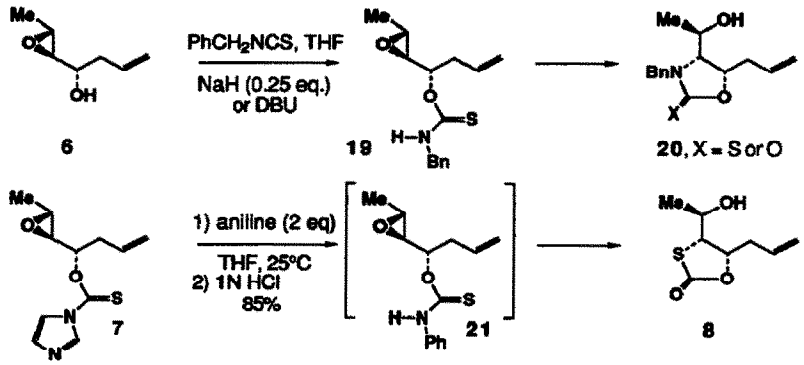
The stereochemical generality of this epoxide ring opening sequence was demonstrated by the conversions of epoxyalcohols **2**,[8a] **11**[12] and **13**[12] to thiocarbonates **10**, **12**, and **14**, respectively. The only reaction that proved problematic was the cyclization of thioimidazolide **15** (prepared from **13** in 98% yield). While the conversion of **15** to **16** (82%) proceeded smoothly with 1 equiv. of aniline and catalytic DMAP, hydrolysis of **16** provided a mixture of **17** (50%) and epoxyurethane **18** (30%). Fortunately, this problem could be suppressed by acylating **16** before the hydrolysis step, thereby allowing acetate **14** to be prepared in 62% overall yield from **13**. Similar problems were not encountered with any of the other epoxyalcohol substrates used in this study.



While neighboring group assisted cyclization reactions of thiourethanes are well known,[13] we are unaware of any previous examples of the use of a thiocarbonyl group for the intramolecular opening of an epoxide. However, one example of the intramolecular ring opening reaction of an epoxyalcohol with NaH and CS_2 was



reported while our work was in progress.[14] In that case, a xanthate functioned as the source of the nucleophilic sulfur atom. Our original plan was to perform the cyclization of epoxyalcohol **6** to thiocarbonate **8** by treatment of **6** with an isothiocyanate, by analogy to our cyclizations of epoxyalcohols to urethanes (c.f., **4** → **5**).[8] However, treatment of **6** with benzyl isothiocyanate in toluene at 80°C for 4 days in the presence of Hünig's base gave essentially no reaction (80% recovery of **6**). Use of stronger bases such as DBU or NaH in THF, or use of acylation catalysts such as DMAP, gave a mixture of **20** (X = S and O; ≤25% yield) in which the nitrogen atom of the intermediate thiourethane **19** opened the epoxide. The reaction of the Bu_3Sn-ether of **6** with PhNCS and DMAP provided a product analogous to **16** but in only 11% yield.[15] The cyclization via **7** described above is successful presumably because the intermediate phenyl thiourethane **21** is formed under very mild conditions with no further opportunity for condensation of **21** or the cyclization product with additional isothiocyanate.[15]



In summary, a stereochemically general procedure has been developed for the conversion of 2,3-epoxyalcohols to thiocarbonates and an asymmetric synthesis of the esperamicin thio sugar (**1b**) has been achieved. Additional studies on the synthesis of the calicheamicin/esperamicin oligosaccharides will be reported in due course.

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9. Epoxyalcohol **6** ($[\alpha]_D$ +17.5° (c 0.12, $CHCl_3$)) was prepared in 66% yield by Mitsunobu inversion of **2** (prepared via Sharpless kinetic resolution-asymmetric epoxidation as described in ref. 8a) using p-$NO_2C_6H_4CO_2H$, Ph_3P and $EtO_2CN{=}NCO_2Et$ in toluene followed by cleavage of the p-nitrobenzoate with catalytic NaOMe in MeOH.
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