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Two Syntheses of 2,4,6-Trideoxy-4-methylthio-D-*ribo*-pyranose

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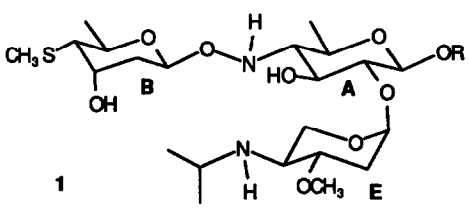
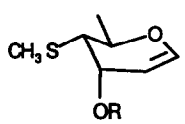
Abstract: *Two syntheses of 2,4,6-trideoxy-4-methylthio-D-*ribo*-pyranose, a component of the oligosaccharide of esperamicins are described: an asymmetric synthesis starting from the propargylic alcohol dimer and the stereocontrolled transformation of D-fucose .*

Esperamicins and calicheamicins are the most prominent members of the new class of the ene-diyne antitumor antibiotics[1]. They were shown to interact and cleave the DNA at very low concentration[2]. The oligosaccharidic component of these compounds, clearly involved in the recognition step and the selective binding of the antibiotic into the minor groove of the nucleic acid, is thought to be mainly responsible for the observed selective cleavage at TC-rich sites[2, 3]. There has been considerable work directed towards the understanding of the cleavage mechanism[4], the synthesis of the ene-diyne aglycone[5], and the elaboration of the very unusual oligosaccharide found in these compounds[6]. These synthetic efforts culminated in 1992 with the report of the first total synthesis of a member of this class, calicheamicin γ_1^I [7].

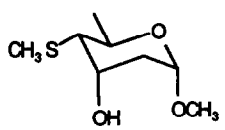
We were especially interested in the following problems associated with the contruction of **1**, the trisaccharide found in the esperamicins: a new *O-N*-glycosidic linkage, a β-linked 2,6-dideoxy thiosugar and a 2-deoxy aminopentose. We began our work with the elaboration of the central unit (ring A)[8] and we now report our results on the construction of the thiosugar (ring B).



1



R= H, **2a**
R= Bz, **2b**



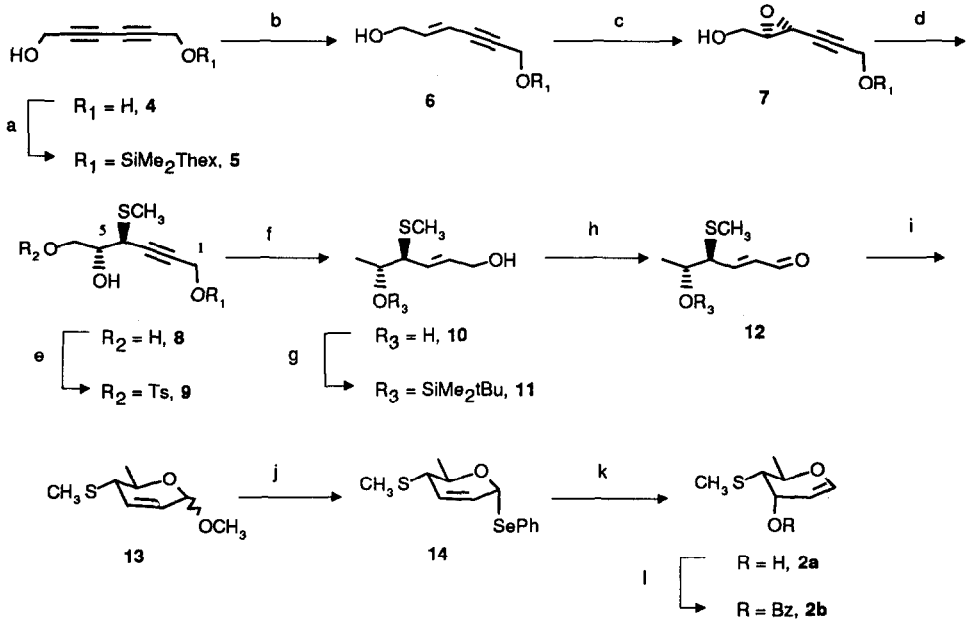
3

Synthetic approaches to this rare sugar, 2,4,6-trideoxy-4-methylthio-D-*ribo*-pyranose, have been recently reported by the groups of Danishefsky[9], Scharf[10] and Nicolaou[11]. All these syntheses relied on the stereocontrolled transformation of a suitable sugar precursor and could only deliver one enantiomer of the target, depending on the availability of the starting material. We thought that an asymmetric synthesis of this unit would be competitive, in length and overall efficiency, and would allow much more flexibility for the elaboration of the target, or analogs in an enantiomerically pure form. Our efforts were focused on the preparation of the glycals **2a** and **2b**, good precursors for further glycosylation. As an alternative, we disclose a short and efficient synthesis of the methyl glycoside **3** from fucose, commercially available in enantiomerically pure D and L forms.

Asymmetric synthesis of 2a and 2b

Our strategy for the asymmetric synthesis of **2a** and **2b** relies on the enantioselective epoxidation of a suitable six-carbon synthon, which will be further stereospecifically transformed to **2a**. The complete synthetic sequence is summarized in Scheme 1.

Scheme 1



a: 1eq NaH, 0.75 eq $ThexMe_2SiCl$, THF, 0°C, 60%. b: 1.5 eq Red-Al, THF, 0°C, 80%. c: 0.24 eq (-)-DET, 0.2 eq $Ti(OtBu)_4$, 3 eq TBHP, 4A MS, CH_2Cl_2, -20°C, 85%. d: MeSNa, MeOH, 0°C, 95%. e: 1.1 eq TsCl, pyridine, DMAP, CH_2Cl_2, 0°C, 80%. f: 4 eq $LiAlH_4$, THF, reflux, 60%. g: 1.1 eq PivCl, pyridine, r.t., 85%; 1.1 eq $Me_2tBuSiCl$, imidazole, DMF, r.t., 95%; K_2CO_3, MeOH, 40°C, 80%. h: 40 eq MnO_2, CH_2Cl_2, 85%; i: 0.5 eq PPTS, MeOH, reflux, 75%. j: 1.1 eq PhSeH, 1.0 eq BF_3:Et_2O, CH_2Cl_2, -90°C. k: 2 eq MCPBA, 2.2 eq Et_2NH, CH_2Cl_2, 60% from **13**. l: 1.5 eq BzCl, pyridine, 95%.

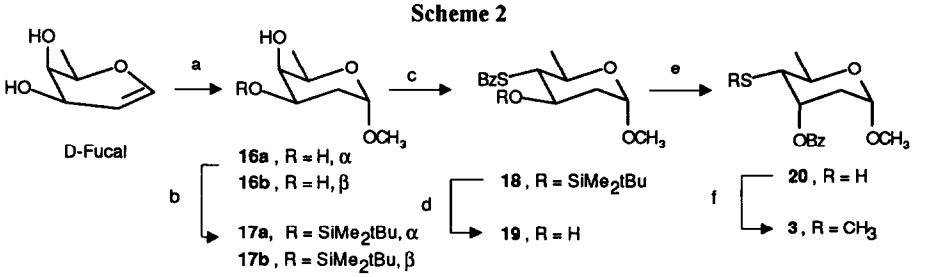
Propargylic alcohol dimer **4**[12], treated with sodium hydride[13] and 0.75 equiv. of thexyldimethylsilylchloride, gave the monoprotected diol **5** in 60% yield, (80% based on the silicon reagent), which was reduced with Red-Al at 0°C[14] to the E-allylic alcohol **6** in 80% yield, (E/Z >98/<2, $J_{H4\text{-}H5}$ = 16.2 Hz). Compound **6** was epoxidized under catalytic asymmetric Sharpless conditions[15], using (-)-DET and titanium tetra-*tert*-butoxide to the epoxy alcohol **7** in 85% yield. ^{1}H-NMR analysis of the Mosher ester of **7** showed a 95% enantiomeric excess for this product. Regiospecific nucleophilic opening of the epoxide at the activated propargylic position with sodium methanethiolate in anhydrous methanol at 0°C gave the diol **8** in 95% yield, securing the right stereochemistry at C-4 and C-5, (carbohydrate numbering, see Scheme 1). Selective primary tosylation afforded **9** in 80% yield. Although **9** could be deprotected with TBAF in THF and then doubly reduced with an excess of LAH in THF at room temperature to give **10**, the same transformation could be carried out more conveniently in one pot using an excess of LAH in refluxing THF to deprotect *in situ* the silyl ether before the reduction of the propargylic alcohol. Of special importance for this asymmetric synthesis, **10** was obtained as enantiomerically pure white needles after recristallization in toluene, (60% yield, mp = 67°C, E/Z >98/<2, $J_{H2\text{-}H3}$ = 16 Hz). Direct selective oxidation of the allylic alcohol with MnO_2 proved

to be very difficult to control due to the instability of the reaction product and it was necessary to protect the secondary hydroxyl prior to oxidation. This was done by sequencial treatment with pivaloyl chloride (85%), *tert*-butyldimethylsilylchloride (95%) and potassium carbonate in methanol (80%). MnO_2 oxidation of the silylated allylic alcohol **11** afforded an 85% yield of the unsaturated aldehyde **12**. Desilylation[16], E to Z isomerization[17] and cyclization were carried out in one operation by refluxing **12** with pyridinium *p*-toluene sulfonate in methanol and afforded a 4:1 mixture of the volatile α and β anomers of **13** in 75% yield. Treatment of this mixture at -90°C with phenylselenol and $BF_3.OEt_2$ provided the α-phenylselenoglycoside **14**, contaminated with the regioisomers at position 3 (total yield 80%, 13:2:1 α-selenoglycoside: 3-equatorial selenoether: 3-axial selenoether). A rigorous temperature control is critical for the success of this transformation. The mixture of seleno compounds was then selectively oxidized at the selenium at 0°C with *m*-chloroperbenzoic acid and diethylamine was added to promote the [2,3] sigmatropic rearrangement of the intermediate phenylselenoxide to the known[9] glycal **2a**, which gave, after hydrolysis, an overall yield of 60% from **13** to **2a**[18]. ($[\alpha]_D^{20}$ = +215, c = 1, chloroform; lit.[9], $[\alpha]_D^{25}$ = +170, c = 1.8, chloroform). Benzoylation provided **2b** in 95% yield, thus completing the synthesis.

Synthesis of 3 from D-fucose

The synthesis of **3** from D-fucose relies on the inversion of configuration at positions 3 and 4 of the starting sugar via triflates. The sulfur atom, introduced first at position 4, carries the nucleophile for the second intramolecular displacement. The sequence is summarized in Scheme 2.

Scheme 2



a: 0.02 eq Camphorsulphonic acid, MeOH, r.t., 90%. b: 1.5 eq Bu_2SnO, toluene, reflux, then 2 eq NBu_4Br, 1.2 eq $tBuMe_2SiCl$, 80°C, 85%. c: 1.1 eq Tf_2O, pyridine, CH_2Cl_2, 0°C, then 5 eq BzSK, DMF, 0°C, 80%. d: HCl, MeOH, r.t., 85%. e: 1.1 eq Tf_2O, pyridine, CH_2Cl_2, 0°C, then H_2O, r.t., 50%. f: 5 eq MeI, 1.1 eq DBU, THF, r.t., 90%.

Acidic methanolysis of D-fucal, available in 63% overall yield from the commercial D-fucose by a modification of known procedures[19], furnished an unseparable mixture of methyl 2-deoxy-α,β-glycosides **16** in 85% yield. (α/β ratio 8.5:1). Selective silylation at position 3, using the stannylene methodology[20] gave **17a** (85%) and the β-anomer **17b** (10%). Triflate formation on **17a**, (J_{H4-H5} = 1 Hz, J_{H4-H3} = 3 Hz) was achieved with triflic anhydride and pyridine at 0°C and the intermediate was reacted, without purification, with an excess of potassium thiobenzoate in dry DMF to yield 80% of the D-*arabino* product **18**, ($J_{H4-H5} = J_{H4-H3}$ = 11 Hz). Alcohol **19**, obtained in 85% yield by desilylation of **18** in methanolic HCl, led directly to the benzoate thiol **20** in 50% yield after hydrolysis. The overall result of this step, inversion at position 3 with a concomitant S to O shift of the benzoate ester, is easily explained by an intramolecular displacement of the transient 3-*O*-triflate by the carboxyl oxygen of the neighboring benzoate[21], followed by a regioselective opening of the tetrahedral intermediate ion pair by water. Methylation with iodomethane and DBU gave the target **3** in 90% yield[22].

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References and notes

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18. Considering step *j* (PhSeH treatment) and based on the overall yield from **13** to **2a**, the [2,3] rearrangement of the anomeric phenylselenoxide is indeed a high yielding procedure (>90% yield).
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22. All new compounds gave satisfactory microanalytical and/or spectral data.
Selected data for **3**: $[\alpha]_D^{20}$ = +218, (c = 1.0, $CHCl_3$). ^1H NMR, ($CDCl_3$), δ, (ppm): 1.43, d, $J_{H5\text{-}H6}$ = 6.5 Hz, 3H, *H6*; 2.02, dt, $J_{H2ax\text{-}H2eq}$ = 15.5 Hz, $J_{H2ax\text{-}H3}$ = $J_{H2ax\text{-}H1}$ = 4 Hz, 1H, *H2ax*; 2.16, s, 3H,*SMe*; 2.27, ddd, $J_{H2ax\text{-}H2eq}$ = 15.5 Hz, $J_{H2eq\text{-}H3}$ = 3 Hz, $J_{H2eq\text{-}H1}$ = 1 Hz, 1H, *H2eq*; 2.60, dd, $J_{H4\text{-}H5}$ = 10.5 Hz, $J_{H4\text{-}H3}$ = 3 Hz, 1H, *H4*; 3.35, s, 3H, *OMe;* 4.29, dq, $J_{H5\text{-}H6}$ = 6.5 Hz, $J_{H5\text{-}H4}$ = 10.5 Hz, 1H, *H5*; 4.37, dd, $J_{H1\text{-}H2ax}$ = 4 Hz, $J_{H1\text{-}H2e}$ = 1 Hz, 1H, *H1*; 5.48, m, 1H, *H3*.

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