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Synthesis of 2,6-Dideoxy-4-S-Methyl-4-Thio-D-*ribo*-Hexopyranose, A Component of the Esperamicin Oligosaccharide

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Abstract: Two synthetic approaches to 2,6-dideoxy-4-S-methyl-4-thio-D-*ribo* pyranose, a component of the oligosaccharide of esperamicins are described. An asymmetric synthesis, starting from the propargylic alcohol dimer, relies on the Sharpless asymmetric epoxidation and the regio-selective opening of epoxy alcohols. The other synthesis is based on stereocontrolled transformations of a readily available sugar precursor, D-galactose.

INTRODUCTION

Esperamicins[1] and calicheamicins,[2] members of the ene-diyne class of antitumor antibiotics,[3] have attracted considerable attention due to their unusual structure and their ability to cleave DNA at a very low concentration.[4] Their mode of action, which involves hydrogen abstraction from the sugar backbone of DNA by a very reactive diyl radical is now well documented.[5] The oligosaccharide moiety of these compounds can act as a minor groove ligand of the duplex nucleic acid and is mainly responsible for the TC-rich site-selective cleavage of DNA observed with these antibiotics.[6] Recently, ^{1}H-NMR studies have been carried out on DNA-oligomer-calicheamicin γ_1^I complexes[7] and have provided direct evidence of the binding of the oligosaccharide moiety into the minor groove of DNA.

Many synthetic attempts to construct the ene-diyne aglycone[8] and the oligosaccharide[9] have been reported and the first total synthesis of a member of this class, calicheamicin γ_1^I, was completed in 1992.[10]

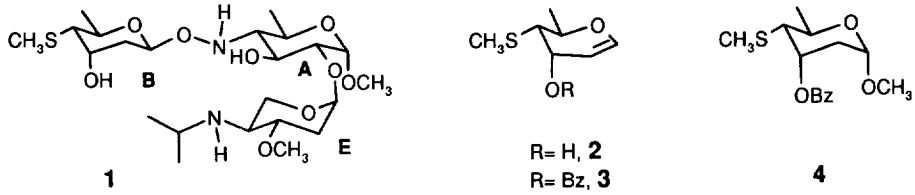


Figure 1

We have been particularly interested in the synthetic problems associated with the elaboration of **1**, the common trisaccharide of calicheamicins and esperamicins: namely the *N-O*-glycosidic linkage, the β-linked 2,6-dideoxy thiosugar (ring B) and the 2-deoxy-aminopentose (ring E). Our work began with the construction of ring A and the hydroxylamino glycosidic bond[11] and we now report our results for the elaboration of the thio sugar (ring B)[12] (Figure 1).

All reported synthetic approaches[9,13,14] to this rare sugar, 2,6-dideoxy-4-S-methyl-4-thio-D-*ribo*-hexopyranose have relied on stereocontrolled transformations of a suitable sugar precursor and could only deliver one enantiomer of the target depending on the availability of the starting sugar material. An asymmetric synthesis would allow much more flexibility for the preparation of this sugar and its analogues in either enantiomeric series.[40] We have focused our effort on the preparation of glycals **2** and **3**, good precursors for further glycosylation and elaboration of trisaccharide **1**. Moreover, we describe a very short and efficient synthesis of the methyl glycoside **4**, available in four steps from D-fucal.

ASYMMETRIC SYNTHESIS OF 2 AND 3

Propargylic alcohol dimer **5** was a good candidate as a suitable six-carbon precursor, which could be asymmetrically oxygenated using the Sharpless epoxidation after reduction of the triple bonds. Our retrosynthetic analysis of the title compound from the chiral epoxy alcohol **III** is summarized in Figure 2.

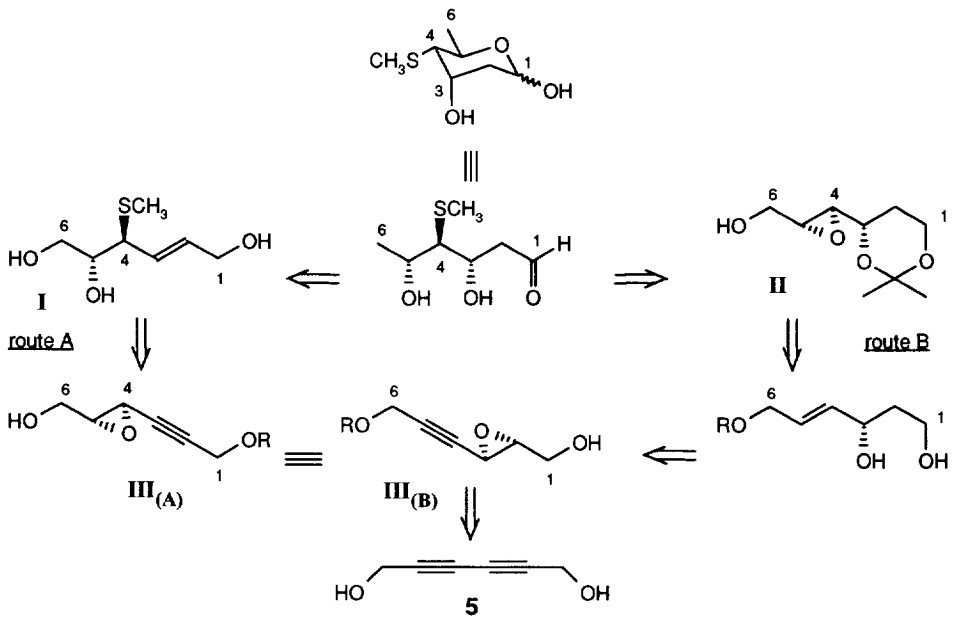


Figure 2

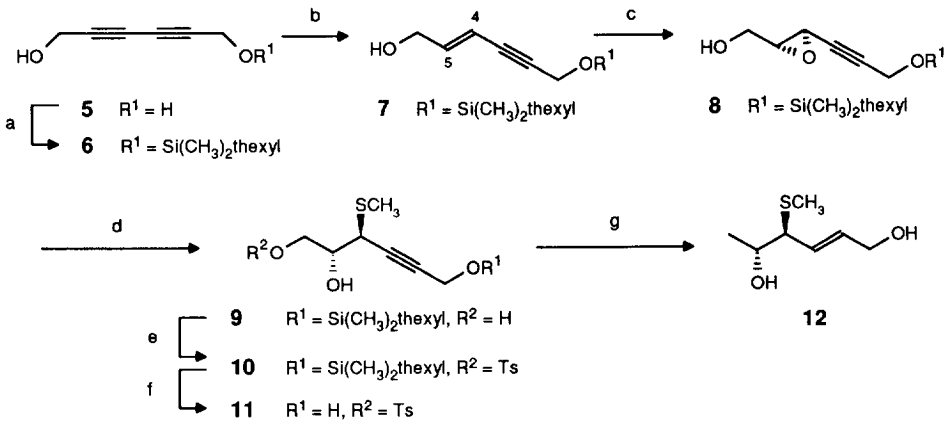
In route A, the sulfur atom was introduced before the C-1-C-3 functionalization (except for the Experimental Section and for the sake of clarity, only carbohydrate numbering has been used) taking advantage of the C-4 activation in epoxy alcohol $\mathbf{III_{(A)}}$ by the adjacent triple bond to control the epoxide opening. The major drawback of this route is that the somewhat sensitive sulfide functionality would have to be carried out from **I** to the end of the synthesis. In the other route (B), the step order was reversed and the sulfur atom was introduced after the C-3 oxygenation. In this case, it was necessary to devise a way to selectively reduce the epoxy alcohol $\mathbf{III_{(B)}}$ at the less reactive C-2 position to the 1,3 diol. Potential difficulties could also be expected for regioselective opening of epoxy alcohol **II** by the sulfur nucleophile at the sterically congested

C-4 position.

Both routes were explored and although we were able to solve every problem of selectivity along the sequence, only route A ultimately gave the target.

Exploration of route A: synthesis of 2 and 3.

Propargylic alcohol dimer **5**[15] was selectively protected as the monothexyldimethylsilyl ether **6**[16] (Scheme 1). Red-Al® reduction[17] of **6** to the E allylic alcohol **7** proceeded smoothly in 80% yield (E/Z >98/<2 $J_{4,5}$ 16.2 Hz) and catalytic Sharpless epoxidation,[18] with (-)-DET and titanium tetra-*tert*-butoxide gave 85% of epoxy alcohol **8** (ee = 95%).[19] When this reaction was run with the usual titanium tetraisopropoxide, some opening of the epoxide by the more nucleophilic isopropanol was observed, lowering the yield.



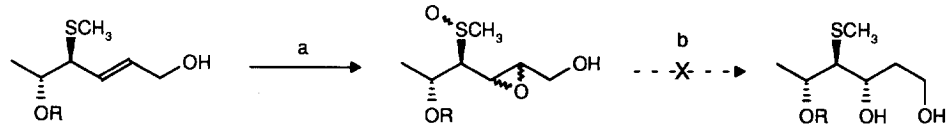
a: NaH, 0.75 eq. thexyl(Me)$_2$SiCl, THF, 1.5h., 80%; b: Red-Al®, THF, 0°C, 80%; c: Ti(OtBu)$_4$, (-)-DET, TBHP, Molecular sieves 4Å, -20°C, 12h., 85%, ee = 95%; d: MeSNa, MeOH, 0°C, 10 min., 82%; e: TsCl, DMAP, pyridine, CH_2Cl_2, 12h., 0°C, 85%; f: HCl, MeOH, 10 min., r.t., 85%; g: $LiAlH_4$, THF, r.t., 12h., 60%, ee>98%.

Scheme 1

Epoxide **8** was regio and stereospecifically opened at the C-4 position by sodium methanethiolate in dry methanol at 0°C to give diol **9** in 82% isolated yield. With the correct stereochemistry and substitution secured at C-4 and C-5, the C-6 position was deoxygenated with concomitant triple bond reduction. Thus, selective primary tosylation and silyl ether deprotection with acidic methanol provided diol **11** which was doubly reduced with LAH in THF at 0°C to diol **12** via the intermediate terminal epoxide. The stereochemistry of the new double bond was E without any of the geometrical Z isomer ($J_{2,3}$ 16 Hz). This product was recrystallized from toluene to enantiomerically pure[19] needles in 60% yield. Even more efficiently, refluxing tosylate **10** with 4 equiv. of LAH in THF provided the same diol **12** without erosion of selectivity or yield.

At this point, we needed to introduce the last stereocenter at C-3. This could be controlled by the primary hydroxyl group using the Sharpless epoxidation followed by a reductive C-2 selective opening. The secondary hydroxyl group could also direct an internal nucleophile in halogenocyclization reactions on the carbon-carbon double bond. Finally, allylic alcohol oxidation and cyclization of the unsaturated aldehyde would give other possibilities for the stereoselective C-3 oxygenation.

Sharpless asymmetric epoxidation of **12**, **13** or **14** needed more than one equiv. of titanium and was accompanied by sulfoxide formation (Scheme 2).[20] The reaction was very slow and the corresponding sulfone was also formed.



13 R = Bn
14 R = $Si(CH_3)_2tBu$

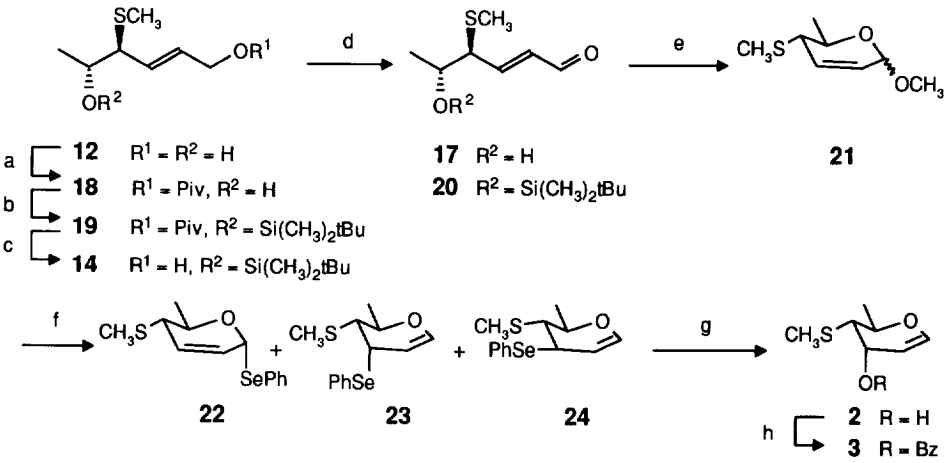
15 R = Bn
16 R = $Si(CH_3)_2tBu$

a: $Ti(OiPr)_4$, (-)-DET, TBHP, CH_2Cl_2, -20°C to 0°C. b: Red-Al®, THF, 0°C.

Scheme 2

Sulfoxide formation preceded epoxidation and the sulfoxide group severely deactivated the electrophilic attack on the double bond (inductive effect and bulkiness of the sulfoxide-titanium complex[20]). Although it was possible to isolate small amounts of epoxysulfoxides **15** and **16** (a mixture of diastereoisomers of unknown configuration) reduction of these products was unmanageable and gave complex mixtures in poor yields, hence this approach was not pursued.

Our attempts to use the secondary hydroxy group as an anchor point in halogenocyclization reactions[21] were also disappointing. Whatever nucleophile (carbonate,[21,22] carbamate[23] or phosphate[24]) or promoter (I_2, NIS or NBS) was used these reactions were plagued by sulfur participation and thiomethyl migration. Even though interesting results were obtained in some cases, they were not useful for the projected synthesis, thus the oxidation/cyclization route was explored (Scheme 3).



12 $R^1 = R^2 = H$
18 R^1 = Piv, $R^2 = H$
19 R^1 = Piv, $R^2 = Si(CH_3)_2tBu$
14 $R^1 = H$, $R^2 = Si(CH_3)_2tBu$

17 $R^2 = H$
20 $R^2 = Si(CH_3)_2tBu$

21

22 **23** **24**

2 R = H
3 R = Bz

a: 1 eq. $(CH_3)_3COCl$, pyridine, -10°C, 4h., 85%. b: 1.2 eq. $tBu(CH_3)_2SiCl$, imidazole, DMF, 40°C, 1.5h., 95%. c: 1 eq. K_2CO_3, CH_3OH, 40°C, 3 h., 95%. d: 40 eq. MnO_2, CH_2Cl_2, r.t., 1 h., 85%. e: 0.5 eq. PPTS, CH_3OH, reflux, 5 h., 75%. f: 1.1 eq. PhSeH, 1.0 eq. $BF_3.OEt_2$, CH_2Cl_2, -90°C, 5 h., 80%. g: 2 eq. mCPBA, 2.2 eq. Et_2NH, CH_2Cl_2, r.t., 12 h., 75%. h: 1.5 eq. BzCl, pyridine, CH_2Cl_2, r.t., 4 h., 90%.

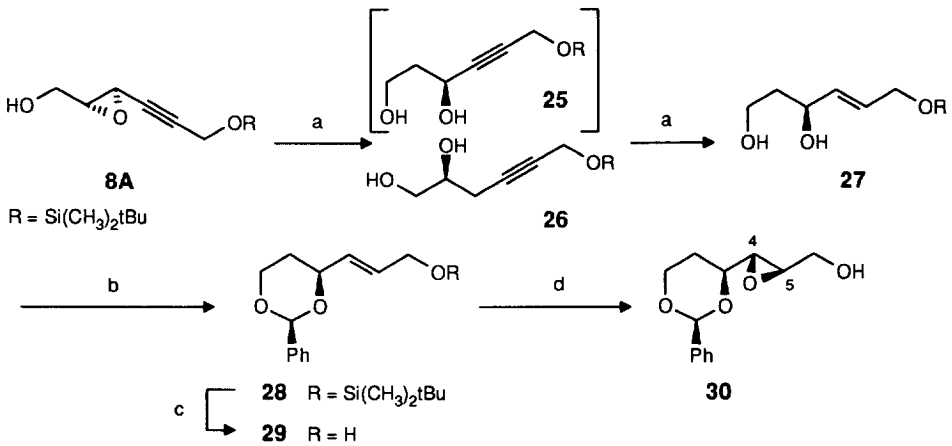
Scheme 3

Selective allylic oxidation of the diol **12** with manganese dioxide gave the expected hydroxy aldehyde **17** in only a moderate yield (50%). This product was very unstable and was thus difficult to isolate from the reaction mixture. Much better results were obtained on the protected derivative **14**, available from **12** by a standard three-step sequence: selective primary protection, secondary hydroxyl silylation and pivalate hydrolysis. MnO_2 oxidation of **14** gave an 85% yield of the unsaturated aldehyde **20**. Desilylation, E to Z isomerization[25] and cyclization were carried out in one step. Refluxing **20** with pyridinium *para*toluene sulfonate in anhydrous methanol furnished the volatile methyl glycoside **21** as a 4:1 mixture of the α- and β-anomers in 75% yield.

The C-3 axial hydroxyl group could now be introduced by a [2,3] sigmatropic rearrangement of an anomeric selenoxide.[26] Although this is reminiscent of Danishefsky's work,[14] we capitalized on the fact that selective selenium oxidation should be possible in the presence of the sulfur atom to provide a shorter route to the rearranged product. Treatment of **21** (anomeric mixture) in methylene chloride with phenylselenol and boron trifluoride etherate[27] at -90°C for 5 h gave **22**, contaminated with the axial and equatorial 3-seleno ethers **23** and **24** (yield, 80%; selectivity, **22/23/24**, 13:2:1). Careful temperature control is crucial for the success of this reaction. At -78°C, the selectivity was only 7.5:1.5:1. Selective selenium oxidation was readily accomplished with MCPBA in the presence of diethylamine to promote the [2,3] sigmatropic rearrangement of the intermediate selenoxide to the known[14] glycal **2**, obtained in a 60% overall yield from **21**. Based on the amount of **22** in the mixture of stereo compounds, the sigmatropic rearrangement proceeded in 92% yield. Benzoylation of **2** gave the protected glycal **3**, thus completing the synthesis.

Exploration of route B

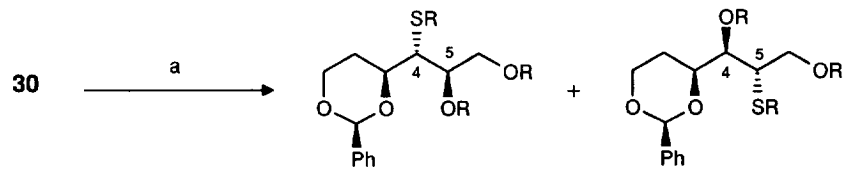
In the light of the high reactivity displayed by the methyl sulfide functionality during the synthesis, we briefly explored route B (see figure 2), that is C-3 oxygenation before sulfur introduction.



a: Red-Al®, DME, 0°C, 50%. b: 1.1 eq. dimethoxytoluene, 0.2 eq. CSA, DMF, r.t., 4 h. c: NBu_4F, THF, r.t., 3 h., 90% from **27**. d: 0.24 eq. (-)-DET, 0.2 eq. $Ti(OtBu)_4$, TBHP, CH_2Cl_2, -20°C, 12 h., 95%.

Scheme 4

Selective intramolecular reduction[28] of epoxy alcohol **8A**[39] to the 1,3 diol **25** was complicated by severe competition from the intermolecular reduction at the activated propargylic position to the 1,2-diol **26** (Scheme 4). Compound **25** was further reduced in the medium to the E allylic alcohol **27** ($J_{4,5}$ 15.8 Hz). The best results were obtained by a very slow addition of Red-Al® to a 0.2 M solution of **8A** in DME at 0°C.[29] Opening selectivity, determined on the crude mixture, was 4:1 and a 50% isolated yield of the doubly reduced product **27** was obtained after chromatography. Protection of the 1,3-diol as a benzylidene acetal (only one diastereoisomer) and fluoride removal of the primary silyl protecting group gave the allylic alcohol **29** in a 90% yield. Asymmetric catalytic Sharpless epoxidation[18] with (-)DET and Ti(O*t*Bu)$_4$ provided epoxide **30** (95% yield, de = 91%). This product could be obtained enantiomerically pure after recrystallization from toluene (mp 94°C ee > 98%).[19] At this point, we needed to introduce selectively the sulfur nucleophile at the more congested C-4 position to set up the correct stereochemistry and substitution of all chiral centers. Titanium mediated opening[30] of **30** with various sulfur nucleophiles was investigated (Scheme 5). It appeared that selectivity was highly dependent on the nature of the promoter and the structure of the nucleophile. The best conditions were with titanium tetra *tert*-butoxide and thiol acetic acid in CH_2Cl_2 at 0°C. In this case, the C-4 versus C-5 opening, selectivity was 20 to 1. Titanium *tert*-butoxide is superior to titanium isopropoxide, certainly for steric reasons, and the choice of the nucleophile is crucial. Under the very same conditions, sodium methyl thiolate gave a 2 to 3 ratio of C-4/C-5 opened products.



31 R = Ac **32** R = Ac

33 R = H **34** R = H

a: 1.5 eq. Ti(OtBu)$_4$, 5 eq. RSH, CH_2Cl_2, 0°C, 5h.

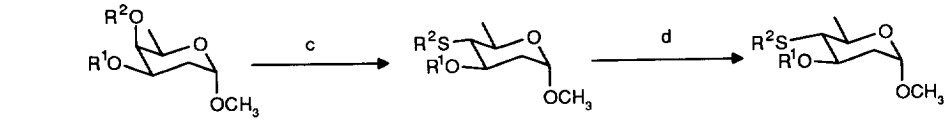
Scheme 5

We observed a complete S to O scrambling of the acetate group in the basic medium of the reaction and the crude mixture of opened products was acetylated before purification and analysis. This is a very serious limitation of this route as it was not possible to use any nucleophile other than thiol acetic acid. It was therefore necessary to peracetylate the complex mixture of products before purification. Unfortunately, we were not able to optimize the deacetylation step and the yield of pure deprotected thiol **33** never exceeded 40%. Although it has been possible to secure efficiently all asymmetric centers with good selectivity, this route did not seem competitive with the previous one, not only in the number of steps but in the overall yield, thus it was not further investigated.

In conclusion, the propargylic alcohol dimer proved to be a very valuable starting material, easily and selectively elaborated to polyfunctional products with high regio- and stereocontrol. The synthesis is only moderately efficient, (14 steps, 4% overall yield), but highly flexible. Advanced intermediates, like **8** or **30**, are available rapidly in either enantiomerically pure form and could be elaborated to chiral fragments potentially useful for other synthetic objectives.

SYNTHESIS FROM D-GALACTOSE

As an alternative, a more efficient synthesis of **4** from a sugar precursor was developed using methyl 2,6-dideoxy-α-D-*lyxo*-hexopyranoside **35**[31] as the key intermediate. Configurational inversion at positions 3 and 4 were needed: the sulfur atom would be introduced first at C-4 and carry the internal nucleophile for the second inversion at C-3. Compound **35** was readily prepared by acidic methanolysis of D-fucal[32] or photochemical deoxygenation of methyl 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-α-D-*galacto*-hexopyranoside followed by acidic hydrolysis.[33] Boths methods gave an 8.5:1 α:β-anomeric mixture. Although the α anomer could be purified by chromatography, anomers were more readily separated after selective silylation at position 3 with the stannylene methodology.[34] Triflic anhydride treatment of **36** provided triflate **37** (isolated in 80% yield by chromatography) routinely used without purification in the next step (Scheme 6).



a → **35** $R^1 = R^2 = H$ → **38** R^1 = TBS, R^2 = Bz → **39** $R^1 = H$, R^2 = Bz

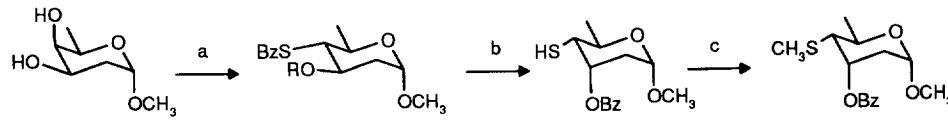
a → **36** R^1 = TBS, $R^2 = H$ → **40** R^1 = TBS, R^2 = Ac → **41** $R^1 = H$, R^2 = Ac

b → **37** R^1 = TBS, R^2 = Tf → **42** R^1 = TBS, R^2 = Me → **43** $R^1 = H$, R^2 = Me

a: 1.5 eq. Bu_2SnO, toluene, reflux, 4 h., then 2 eq. NBu_4Br, 1.3 eq $tBu(CH_3)_2SiCl$, 80°C, 10 mn., 85%. b: 1.5 eq. Tf_2O, pyridine, CH_2Cl_2, r.t., 1.5 h. c: 3 eq R^2SK, DMF, r.t., 4 h.. d: HCl, CH_3OH, r.t., 4 h.

Scheme 6

Displacement of the axial triflate **37** was best accomplished with potassium thiobenzoate, giving **38** in good yield (79%) and fully compatible with the end of the synthesis. Removal of the silyl protecting group in acidic methanol gave the alcohol **39**, ready for the next C-3 inversion. Potassium thioacetate gave much lower yields for the two steps (66% of **40** and 55% of **41**). Sodium methylthiolate was also effective (85% of **42** and 86% of **43**) but was not suitable for the subsequent C-3 inversion. As was already encountered in the first part of this work, the thiomethyl group participated during the nucleophilic substitution at C-3. Finally, the four-step procedure (**35**→**39**) could be avoided; treating diol **35** under Mitsunobu conditions (PPh_3, DEAD, toluene at 80°C) with thiol benzoic acid gave a rewarding 77% yield of **39**[35] (Scheme 7).



35 **39** R = H **45** **4**

44 R = Tf

a: 2 eq. PPh_3, 1.2 eq. DEAD, 1.2 eq. PhCOSH, 4Å molecular sieves, 80°C, 30 min., 77%. b: 1.5 eq. Tf_2O, pyridine, CH_2Cl_2, 0°C, 1 h., then H_2O, 50%. c: 1.1 eq. DBU, CH_3I, THF, r.t., 10 mn., 90%.

Scheme 7

The benzoate thiol **45** with the correct stereochemistry at C-3 was obtained in one step from alcohol **39** by treament with triflic anhydride in the presence of pyridine.[36] In this transformation the transient triflate **44** undergoes an intramolecular nucleophilic displacement by the carbonyl oxygen of the benzoyl group which migrates to the oxygen atom (Scheme 7). Depending on the experimental conditions, a small amount of the corresponding disulfide was also isolated (0-15%). Methylation with iodomethane and DBU gave the final product **4** (90% yield).

This synthesis is remarkably short, providing **4** with good overall yield (35.5%) in only three steps from diol **35**. Methylation of the thiol function of **45** to **4** gave an esperamicin B-ring precursor which has been used in the total synthesis of the esperamicin trisaccharide **1**.[37] It is also important to emphasize that suitable protection of the thiol function of **45** will give an entry in the synthesis of the calicheamicin oligosaccharide as well.

EXPERIMENTAL SECTION

Experiments were carried out under Ar in dry, deoxygenated solvents purified by standard methods. Flash chromatography was run on silica gel (Merck, 0.036-0.063 mm). TLC plates (Merck 60 with F_{254} fluorescent indicator) were revealed with 10% H_2SO_4 in ethanol or the phosphomolybdic reagent. Molecular rotations were measured on a Perkin-Elmer 141 polarimeter in a 1 dm long cell at 20 ± 2°C. ^1H NMR spectra were recorded at 300 MHz on a Bruker AM-300 WB spectrophotometer in a $CDCl_3$ solution. All chemical shifts were reported from TMS as internal standard. ^{13}C NMR were recorded on the same spectrometer working at 75 MHz. Mass spectra were recorded at the *Centre de Mesures Physiques de l'Université d'Orléans* by Dr. G. Keravis. Chemical ionization with ammonia was used in every case. Microanalyses were performed by the *Service Central de Microanalyse du CNRS* in Vernaison, France.

6-O-[Dimethyl(1,1,2-trimethylpropyl)]silyl-hex-2,4-diyn-1,6-diol **6**

Compound **5**[15] (17.3 g, 157 mmol) in 200 mL of anhydrous THF was slowly added to a suspension of NaH (6.3 g, 157 mmol, washed twice with hexane) in 100 mL of THF at 0°C. The mixture was then heated at 50°C until the end of the gas evolution (1 h). After cooling to room temperature, thexyldimethylsilylchloride (23 mL, 118 mmol, 0.75 eq) was added dropwise and the reaction mixture was stirred for 1 h 30. Methanol (20 mL) and water (100 mL) were added and the solvents evaporated. Extraction of the aqueous residue with ether and chromatography (hexane/ethyl acetate, 9:1 then 7:3) gave 23.9 g of **6** as a slightly yellow oil (60%)[38]. ^1H NMR: 0.20 (s, 6 H, Me_2Si), 0.89 (s, 6 H, Me_2 thexyl), 0.92 (d, 6 H, $J_{Me,H}$ 7 Hz, Me_2 thexyl), 1.67 (m, 1 H, thexyl), 2.14 (m, 1 H, OH), 4.37 (d, 2 H, $J_{1,OH}$ 2 Hz, H-1), 4.40 (s, 2 H, H-6). MS: *m/z* 253 (M + 1) 270 (M + 18).

2E-6-O-[Dimethyl(1,1,2-trimethyl propyl)]silyl-hexen-4-yn-1,6-diol **7**

Compound **6** (22.1 g, 87.7 mmol) in 140 mL of anhydrous THF was treated dropwise with a Red-Al® solution in toluene (39 mL of a 3.4 M solution, 1.5 equiv) at 0°C for 1h30. After warming to room temperature, the reaction was treated cautiously with ethyl acetate (60 mL) and saturated NH_4Cl (20 mL) and stirred vigorously for 1 h before filtration on Celite. The aluminum salts were taken up in 60 mL of ethyl acetate and 20 mL of a saturated NH_4Cl solution and the treatment was repeated. The combined filtrates were

decanted, the organic phase washed with saturated NH_4Cl and dried. Chromatography (hexane/EtOAc, 4:1) gave **7** as a colorless oil[38] (17.8 g, 80%). ^1H NMR: 0.20 (s, 6 H, Me_2Si), 0.89 (s, 6 H, Me_2 thexyl), 0.92 (d, 6 H, Me_2 thexyl), 1.67 (m, 1 H, thexyl), 2.18 (m, 1 H, OH), 4.22 (dd, 2 H, $J_{1,2}$ 4.5, $J_{1,OH}$ 1.5 Hz, H-1), 4.44 (d, 2 H, $J_{6,3}$ 1.5 Hz, H-6), 5.79 (m, 1 H, $J_{3,2}$ 16.2, $J_{3,1} = J_{3,6}$ 1.5 Hz, H-3), 6.25 (dt, 1 H, $J_{2,3}$ 16.2, $J_{2,1}$ 4.5 Hz, H-2). MS: m/z 255 (M+1), 271 (M+18).

(2R,3R)-6-O-[Dimethyl(1,1,2-trimethylpropyl)]silyl-2,3-epoxy-hex-4-yn-1,6-diol **8**

To 150 mL of anhydrous CH_2Cl_2 at -20°C were added sequentially 6 g of powdered 4 Å molecular sieves, (D)-(-)-diethyl tartrate (3.1 g, 15.2 mmol, 0.24 equiv), $Ti(OtBu)_4$ (4.8 mL, 12.6 mmol, 0.2 equiv) and TBHP (38 mL of 5 M solution in CH_2Cl_2, 189 mmol, 3 equiv) and the mixture was stirred for 30 min at -20°C before addition of **7** (16 g, 63 mmol) in 250 mL of CH_2Cl_2. The reaction was over after 12 h. Workup[18] (workup C) and chromatography (hexane/EtOAc, 4:1) gave **8** as a slightly yellow oil[38](14.5 g, 85%). $[\alpha]_D^{20}$ -5 (*c* = 1.1, $CHCl_3$). ^1H-NMR: 0.20 (s, 6 H, Me_2Si), 0.85 (s, 6 H, Me_2 thexyl), 0.87 (d, 6 H, Me_2 thexyl), 1.62 (m, 1 H, H thexyl), 1.62 (m, 1 H, OH), 3.30 (m, 1 H, H-2), 3.47 (m, 1 H, $J_{3,2} = J_{3,6} = J_{3,6'}$ 2 Hz, H-3), 3.71 (ddd, $J_{1,1'}$ 12.8, $J_{1,OH}$ 7.1, $J_{1,2}$ 3 Hz, H-1), 3.95 (bd, 1 H, $J_{1',1}$ 12.8 Hz, H-1'), 4.32 (d, 2 H, $J_{6,3}$ 1.8 Hz, H-6). MS: *m/z* 271 (M + 1) 288 (M + 18). Mosher ester analysis gave a 95% enantiomeric excess for this product. (^1H-NMR in C_6D_6)

(2R,3S)-6-O-[Dimethyl 1,1,2-(trimethylpropyl)silyl]-3-methylthio-hex-4-yn-2,3,6-triol **9**

A solution of sodium methanolate (50 mL, 0.75 M) was treated at 0°C by a rapid stream of methane thiol for 5 min. Compound **8** (12.1 g, 44.8 mmol) in 40 mL of MeOH was then added and the reaction was allowed to continue for 10 min at 0°C before the addition of 12 N HCl (5.6 mL). The solvents were evaporated and the solid residue was taken up in CH_2Cl_2. Filtration removed the bulk of the precipitated inorganic salts and chromatography (hexane/EtOAc, 6:4) gave pure **9** as a colorless oil (11.75 g, 82%). $[\alpha]_D^{20}$ +20 (*c* = 1.1, $CHCl_3$).^1H NMR: 0.18 (s, 6 H, Me_2Si), 0.86 (s, 6 H, Me_2 thexyl), 0.89 (d, 6 H, Me_2 thexyl), 1.63 (m, 1 H, H thexyl), 2.03 (m, 1 H, OH), 2.23 (s, 3 H, SMe), 2.58 (m, 1H, OH), 3.69 (m, 1 H, $J_{3,2}$ 6, $J_{3,6} = J_{3,6'}$ 2 Hz, H-3), 3.81 (m, 2 H, H-1 and H-1'), 4.37 (d, 2 H, $J_{6,3}$ 2 Hz, H-6), 4.39 (m, 1 H, H-2). MS: *m/z* 319 (M + 1) 336 (M + 18). Anal. Calc. for $C_{14}H_{30}O_3SSi$: C, 56.56; H, 9.49. Found: C, 56.26; H, 9.39.

(2R,3S)-6-O-[Dimethyl-(1,1,2-trimethypropyl)silyl]-3-methylthio-1-O-(4-methylbenzenesulfonyl)-hex-4-yn-1,2,6-triol **10**

Compound **9** (11.5 g, 36.16 mmol) in 55 mL of dry CH_2Cl_2 was stirred with pyridine (9 mL, 109 mmol., 3 equiv), DMAP (2.2 g, 18 mmol., 0.5 equiv) and tosyl chloride (6.8 g, 1.0 equiv) for 12 h at 0°C. Hydrolysis workup and chromatography (hexane/AcOEt, 4:1) gave **10** as a slightly colored unstable oil[38] (14.5 g, 85%) used immediately in the next step. $[\alpha]_D^{20}$ +12° (*c* = 2, $CHCl_3$). ^1H NMR: 0.13 (s, 6 H, Me_2Si), 0.84 (s, 6 H, Me_2 thexyl), 0.88 (d, 6 H, Me_2 thexyl), 1.62 (m, 1 H, H thexyl), 2.20 (s, 3 H SMe), 2.45 (s, 3 H, Me tosyl), 3.67 (dt, $J_{3,2}$ 5.2, $J_{3,6} = J_{3,6'}$ 2 Hz, H-3), 3.96 (m, 1 H, H-2), 4.17 (dd, 1 H, $J_{1,1'}$ 10.5, $J_{1,2}$ 5.5 Hz, H-1), 4.22 (dd, 1 H, $J_{1',1}$ 10.5, $J_{1',2}$ 5.5 Hz, H-1'), 4.30 (d, 2 H, $J_{6,3} = J_{6',3}$ 2 Hz, H-6,6'), 7.35 (d, *J* 9 Hz, 2 H, H tosyl), 7.81 (d, 2 H, *J* 9 Hz, H tosyl). MS: *m/z* 473 (M + 1) 430 (M + 18).

(4S,5R)-4-Methylthio-6-O-(4-methylbenzenesulfonyl)-hex-2-yn-1,5,6-triol **11**

A solution of **10** (14.5 g, 30.7 mmol) in 120 mL of methanol was treated with HCl (5 mL of a 12 N aqueous solution) and left 10 min before neutralization with triethylamine (78.5 mL). The solvents were evaporated, the residue was taken up in CH_2Cl_2 followed by filtration and chromatography (hexane/EtOAc, 1:1) which gave **11** as a slightly yellow oil (8.6 g, 85%). $[\alpha]_D^{20}$ +18° (*c* = 1.6, $CHCl_3$). ^1H NMR: 2.21 (s, 3 H, SCH_3), 2.46 (s, 3 H, CH_3 tosyl), 3.66 (dt, 1 H, $J_{4,5}$ 5, $J_{4,1} = J_{4,1'}$ 2 Hz, H-4), 3.99 (m, 1 H, $J_{5,6} = J_{5,6'}$ 5.5, $J_{5,4}$ 5 Hz, H-5), 4.18 (dd, 1 H, $J_{6,6'}$ 10.5, $J_{6,5}$ 5.5 Hz, H-6), 4.23 (dd, 1 H, $J_{6',6}$ 10.5, $J_{6',5}$ 5.5 Hz, H-6'), 4.27 (d, 2 H, $J_{1,4}$ 2 Hz, H-1), 7.37 (d, 2 H, *J* 9 Hz, H tosyl), 7.81 (d, 2 H, *J* 9 Hz, 2 H tosyl). MS: *m/z* 348 (M + 18). Anal. Calc. for $C_{14}H_{18}O_5S_2$: C, 50.89; H, 5.49. Found: C, 51.07; H, 5.51.

(2E,4S,5R)-4-Methylthio-hexen-1,5-diol **12**

Compound **11** (8.6 g, 26 mmol) in 100 mL of anhydrous THF was treated with lithium aluminum hydride (2.9 g, 78 mmol., 3 equiv) at room temperature for 12 h. The reaction was quenched at 0°C with 2.9 mL of water, 2.9 mL of a 15% NaOH solution and 8.7 mL of water followed by further dilution with EtOAc (100 mL). After vigorous stirring for 2 h, the precipitated aluminum salts were filtered, thoroughly washed with EtOAc and the filtrate was evaporated. Chromatography (CH_2Cl_2/MeOH, 10:1) gave **12** as a white solid. Recrystallization in toluene afforded enantiomerically pure white needles (2.5 g, 60%). mp = 67°C (toluene); $[\alpha]_D^{20}$ -5° (*c* = 1, methanol). ^1H NMR: 1.25 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.72 (m, 1 H, OH-1), 2.05 (s, 3 H, SCH_3), 2.29 (m, 1 H, OH-5), 3.15 (dd, 1 H, $J_{4,3}$ 9.3, $J_{4,5}$ 4.9 Hz, H-4), 3.41 (m, 1 H, H-5), 4.19 (t, 2 H, $J_{1,2} = J_{1,OH}$ 5 Hz, H-1), 5.65 (ddt, 1 H, $J_{3,2}$ 15.5, $J_{3,4}$ 9.3, $J_{3,1}$ 1.3 Hz, H-3), 5.80 (dt, $J_{2,3}$ 15.5, $J_{2,1}$ 5 Hz, H-2). MS: *m/z* 163 (M + 1) 180 (M + 18). Anal. Calc. for $C_7H_{14}O_2S$: C, 51.82; H, 8.69. Found: C, 51.92; H, 8.39.

The same compound was obtained in 60% yield by refluxing **10** in THF with 4 equiv of LAH for 2 h.

(2E,4S,5R)-4-Methylthio-1-O-pivaloyl-hexen-1,5-diol **18**

Compound **12** (2.5 g, 15.4 mmol) in pyridine (27 mL) was treated with pivaloyl chloride (1.9 mL, 1.0 equiv) at -10°C for 4 h. Evaporation and chromatography (hexane/AcOEt, 3/1) gave **18** as a colorless oil (3.22 g, 85%). $[\alpha]_D^{20}$ -3° (*c* = 0.8, $CHCl_3$). ^1H NMR: 1.21 (s, 9 H, *t*Bu), 1.24 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 2.04 (s, 3 H, SCH_3), 2.12 (m, 1 H, OH), 3.15 (m, 1 H, H-4), 3.91 (m, 1 H, $J_{5,6}$ 6.5, $J_{5,4} = J_{5,OH}$ 4.5 Hz, H-5), 4.59 (d, 2 H, $J_{1,2}$ 4.7 Hz, H-1), 5.70 (m, 2 H, H-2,3). MS: *m/z* 229 (M + 1 - H_2O) 264 (M + 18). Anal. Cald. for $C_{12}H_{22}O_3S$: C, 58.50; H, 9.00. Found: C, 58.32; H, 9.24.

(2E,4S,5R)-5-O-tertbutyldimethylsilyl-4-methylthio-1-O-pivaloyl-hexen-1,5-diol **19**

A DMF (30 mL) solution of **18** (3.22 g, 13.1 mmol), imidazole (1.95 g, 2.2 equiv) and *tert*butyldimethylsilyl chloride (2.1 g, 1.2 equiv) was stirred at 40°C for 1.5h. Workup and chromatography (hexane/AcOEt, 10:1) gave **19** as a colorless oil (4.5 g, 95%). $[\alpha]_D^{20}$ -4° (*c* = 1, $CHCl_3$). ^1H NMR: 0.06 and 0.08 (2 s, 6 H, $SiMe_2$), 0.88 (s, 9 H, *t*BuSi), 1.18 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.21 (s, 9 H, *t*Bu piv), 1.98 (s, 3 H, SCH_3), 2.95 (dd, 1 H, $J_{4,3}$ 9.7, $J_{4,5}$ 4.8 Hz, H-4), 3.95 (m, 1 H, $J_{5,6}$ 6.5, $J_{5,4}$ 4.8 Hz, H-5), 4.58 (dd, 2 H, $J_{1,2}$ 5.8, $J_{1,3}$ 1 Hz, H-1), 5.54 (dt, 1 H, $J_{2,3}$ 15.5, $J_{2,1}$ 5.8 Hz, H-2), 5.70 (m, 1 H, $J_{3,2}$ 15.5, $J_{3,4}$ 9.7, $J_{3,1}$ 1 Hz, H-3), MS: *m/z* 378 (M + 18). Anal. Calc. for $C_{18}H_{36}O_3SSi$: C, 59.95; H, 10.06. Found: C, 59.73; H, 10.11.

(2E,4S,5R)-5-O-Tertbutyldimethylsilyl-4-methylthio-hexen-1,5-diol **14**

Compound **19** (4.5 g, 12.4 mmol) in methanol (3 mL) was treated with potassium carbonate (1.7 g, 1 equiv) for 3 h at 40°C. Chromatography (hexane/EtOAc, 7:3) gave **14** as a colorless oil (3.26 g, 95%). $[\alpha]_D^{20}$ -8° (*c* = 1.3, $CHCl_3$). ^1H NMR: 0.06 and 0.08 (2 s, 6 H, Me_2Si), 0.89 (s, 9 H, *t*Bu), 1.19 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.31 (m, 1 H, OH), 2.20 (s, 3 H, SCH_3), 2.97 (m, 1 H, H-4), 3.98 (m, 1 H, $J_{5,6}$ 6.5, $J_{5,4}$ 4.5 Hz, H-5), 4.18 (t, 2 H, $J_{1,2} = J_{1,OH}$ 4.5 Hz, H-1), 5.65 (m, 2 H, H-2,3). MS: *m/z* 294 (M + 18). Anal. Calc. for $C_{13}H_{28}O_2SSi$: C, 56.47; H, 10.20. Found: C, 56.56; H, 10.11.

(2E,4S,5R)-5-O-Tertbutyldimethy)silyl-4-methylthio-hex-5-olenal **20**

A solution of **14** (3 g, 10.9 mmol) in CH_2Cl_2 (22 mL) was oxidized with manganese dioxide (37.9 g, 40 equiv) for 1 h. Concentration, filtration on sodium sulfate and chromatography (hexane/EtOAc, 10:1 = 1% NEt_3) gave **20** as a colorless oil (2.54 g, 85%). $[\alpha]_D^{20}$ 12° (*c* = 1, $CHCl_3$). ^1H NMR: 0.08 and 0.10 (2 s, 6 H, Me_2Si), 0.89 (s, 9 H, *t*Bu), 1.22 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.99 (s, 3 H, SCH_3), 3.13 (dd, 1 H, $J_{4,3}$ 10, $J_{4,5}$ 4.5 Hz, H-4), 4.08 (m, 1 H, $J_{,6}$ 6.5, $J_{5,4}$ 4.5 Hz, H-5), 5.99 (dd, $J_{2,3}$ 15.7, $J_{2,1}$ 8 Hz, H-2), 6.77 (dd, 1 H, $J_{3,2}$ 15.7, $J_{3,4}$ 10 Hz, H-3), 9.34 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), MS: *m/z* 275 (M + 1). Anal. Calc. for $C_{13}H_{26}O_2SSi$: C, 56.88; H, 9.55. Found: C, 56.67; H, 9.44.

*Methyl 4-S-Methyl-2,3,6-trideoxy-4-thio-α,β-D-*erythro*-hex-2-enopyranoside* **21**

Compound **20** (2.54 g, 9.27 mmol) was refluxed with pyridinium *para*toluenesulfonate (1.3 g, 0.5 equiv) for 5 h in methanol (30 mL). Chromatography (hexane/AcOEt, 8:1) gave the unseparable mixture of anomers as a colorless volatile liquid (1.2 g, 75%). The anomeric ratio determined by NMR was 4:1. ^1H NMR: 1.41 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6α), 1.44 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6β), 2.02 (s, 3 H, SMeα), 2.05 (s, 3 H, SMeβ), 2.94 (m, 1 H, $J_{4,5}$ 10, $J_{4,3} = J_{4,2}$ 2 Hz, H-4α), 3.02 (m, 1 H, H-4β), 3.42 (s, 3 H, OMeα), 3.47 (s, 3 H, OCH_3β), 3.88 (m, 1 H, $J_{5,4}$ 10, $J_{5,6}$ 6.5 Hz, H-5α, H-5β), 4.82 (m, 1 H, *J* H-1α), 4.99 (m, 1 H, H-1β), 5.82 (dt, 1 H, $J_{3,2}$ 10.5, $J_{3,4} = J_{3,1}$ 2 Hz, H-3β) 5.85 (dt, 1 H, $J_{3,2}$ 10, $J_{3,4} = J_{3,1}$ 2.5 Hz, H-3α), 5.92 (dd, 1 H, $J_{2,3}$ 10.5, $J_{2,1}$ 1.5 Hz, H-2β) 5.94 (dd, $J_{2,3}$ 10, $J_{2,1}$ 2 Hz, H-2α). MS: *m/z* 175 (M + 1) 192 (M + 18).

*Phenyl 4-S-Methyl-2,3,6-trideoxy-4-thio-α-D-*erythro*-hex-2-en-selenopyranoside* **22**

Compound **21** (1.2 g, 6.9 mmol as the anomeric mixture) in CH_2Cl_2 (15 mL) was treated at -90°C with selenophenol (0.82 mL, 1.1 equiv) and $BF_3.OEt_2$ (0.87 mL, 1.0 equiv) for 5 h. The reaction mixture was quenched at -90°C with saturated sodium hydrogen carbonate and extracted with CH_2Cl_2. Chromatography (hexane/AcOEt, 10:1 + 1% NEt_3) gave an unseparable mixture of **22**, **23** and **24** (1.6 g, 80%) used directly in the next step. ^1H NMR (**22** only): 1.45 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 2.05 (s, 3 H, SCH_3), 3.12 (m, 1 H, $J_{4,5}$ 10, $J_{4,3} = J_{4,2}$ 2 Hz, H-4), 4.22 (m, 1 H, $J_{5,4}$ 10, $J_{5,6}$ 6.5 Hz, H-5), 5.81 (m, 1 H, $J_{3,2}$ 10, $J_{3,4} = J_{3,1}$ 2 Hz, H-3), 6.06 (m, 1 H, H-1), 6.14 (m, 1 H, $J_{2,3}$ 10, $J_{2,1} = J_{2,4}$ 2 Hz, H-2), 7.29 (m, 3 H, Ph), 7.62 (m, 2 H, Ph). MS: *m/z* 299 and 301 (M + 1) 316 and 318 (M + 18).

*1,5-Anhydro-2,6-dideoxy-4-S-methyl-4-thio-D-*ribo*-hex-1-enitol* **2**

Compound **22** (contaminated with **23** and **24**, 300 mg, 1 mmol) in 16 mL of dry CH_2Cl_2 was treated sequentially at 0°C with diethylamine (0.23 mL, 2.2 equiv) and MCPBA (380 mg, 2.2 equiv). The reaction was left 12 h at room temperature and quenched with a saturated sodium sulfite solution. Workup and

chromatography gave **2** as a colorless oil (120 mg, 75%). $[\alpha]_D^{20}$ +215° (*c* = 1, $CHCl_3$); Lit.[14] = +170° (*c* = 1.8, $CHCl_3$). ^1H NMR: 1.45 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 2.18 (s, 3 H, SMe), 2.58 (m, 1 H, OH), 2.70 (dd, 1 H, $J_{4,5}$ 11, $J_{4,3}$ 3.5 Hz, H-4), 4.01 (m, 1 H, $J_{5,4}$ 11, $J_{5,6}$ 6.5 Hz, H-5), 4.12 (dd, 1 H, $J_{3,2}$ 5.5, $J_{3,4}$ 3.5 Hz H-3), 5.01 (m, 1 H, $J_{2,1}$ 6, $J_{2,3}$ 5.5 Hz, H-2), 6.47 (d, $J_{1,2}$ 6 Hz, 1 H, H-1). MS: *m/z* 143 (M + 1 - H_2O) 160 (M + 18 - H_2O).

*1,5-Anhydro-3-O-benzoyl-2,6-dideoxy-4-S-methyl-4-thio-D-*ribo*-hex-1-enitol* **3**

Benzoylation of **2** (20 mg, 0.125 mmol) with BzCl (1.5 equiv.) in pyridine gave **3** (31 mg, 95%). $[\alpha]_D^{20}$ +330 (c = 1.2, $CHCl_3$). ^1H NMR: 1.57 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 2.19 (s, 3 H, SMe), 2.81 (dd, 1 H, $J_{4,5}$ 11.5, $J_{4,3}$ 3.5 Hz, H-4), 4.24 (m, 1 H, $J_{5,4}$ 11.5, $J_{5,6}$ 6.5 Hz, H-5), 5.13 (m, 1 H, $J_{2,1}$ 6, $J_{2,3}$ 5.5 Hz, H-2), 5.52 (dd, $J_{3,2}$ 5.5, $J_{3,4}$ 3.5 Hz, H-3), 6.56 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 7.43 (m, 2 H, Ar), 7.55 (m, 1 H, Ar), 8.03 (m, 2 H, Ar). MS: *m/z* 265 (M + 1). IR (neat) 1720 cm-1. ^{13}C NMR: 17.22 (C6) 20.38 (C4) 52.73 (SMe) 66.65 (C5) 73.49 (C3) 100.03 (C2) 128.96 (Ar) 129.36 (Ar) 130.72 (Ar) 133.94 (Ar) 149.03 (C1) 171.35 (C=O).

(2E,4S)-4,6-O-Benzylidene-hexen-1,4,6-triol **29**

Epoxy alcohol **8A**[39] (1.26 g, 5.22 mmol) in 26 mL of anhydrous DME was treated with Red-Al® at 0°C (2.6 mL of a 2 M solution in toluene, 0.96 equiv.). After 45 min, 1h15 and 1h30 were added respectively 0.67 mL (0.25 equiv.), 0.35 mL (0.13 equiv.) and 0.75 mL (0.28 equiv.) of the same Red-Al® solution. The reaction was diluted with EtOAc (100 mL) and 5% HCl (9 mL), allowed to warm to room temperature and stirred for 1h. Filtration of the solids (EtOAc washing) drying of the filtrates and evaporation gave a crude mixture of **26** and **27**, contaminated by a small amount of **25**. Chromatography (CH_2Cl_2/MeOH, 12:1) gave pure **27** as a colorless oil (715 mg, 50%). ^1H NMR: 0.08 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi), 0.90 (s, 9 H, *t*BuSi), 1.80 (m, 2 H, H-2), 2.34 (m, 2 H, OH), 3.65 (m, 2 H, H-1), 4.18 (dd, 2 H, $J_{6,5}$ 4, $J_{6,4}$ 1 Hz, H-6), 4.43 (m, 1 H, H-3), 5.79 (2m, 2 H, $J_{4,5}$ 15.8 Hz, H-4,5).

Compound **27** (715 mg, 2.6 mmol) was dissolved in anhydrous DMF (7 mL) and treated with dimethoxy toluene (0.43 mL, 2.85 mmol, 1.1 equiv.) and CSA (120 mg, 0.2 equiv.) for 4 h. The reaction was neutralized with triethylamine (5 mL), evaporated and filtrated through silica gel (hexane/EtOAc, 4:1). After evaporation, the residue was taken up in THF (15 mL) and treated with NBu_4F (820 mg, 1.2 equiv.) for 3 h. Chromatography after removal of the solvent gave **29** as a colorless oil (516 mg, 90%). ^1H NMR: 1.44 (t, 1 H, $J_{OH,1} = J_{OH,1'}$ 6 Hz, OH), 1.61 (m, $J_{5e,5a}$ 13.5, $J_{5e,6a} = J_{5e,4}$ 2.5, $J_{5e,6e}$ 1.5 Hz, H-5e), 1.95 (m, $J_{5a,5e}$ 1.35, $J_{5a,6a}$ 12.5, $J_{5a,4}$ 11.5, $J_{5a,6e}$ 5 Hz, H-5a), 4.00 (m, 1 H, $J_{6a,5a}$ 12.5, $J_{6a,6e}$ 11.5, $J_{6a,5e}$ 2.5 Hz, H-6a), 4.17 (m, 2 H, H-1,1'), 4.29 (ddd, 1 H, $J_{6e,6a}$ 11.5, $J_{6e,5a}$ 5, $J_{6e,5e}$ 1.5 Hz, H-6e), 4.41 (m, 1 H, H-4), 5.57 (s, 1 H, benzylidene), 5.83 (m, 1 H, $J_{3,2}$ 15.8, $J_{3,4}$ 5.5 $J_{3,1} = J_{3,1'}$ 1.5 Hz, H-3), 5.96 (m, 1 H, $J_{2,3}$ 15.8, $J_{2,1} = J_{2,1'}$ 5, $J_{2,4}$ 1 Hz, H-2), 7.35 (m, 3 H, Ar), 7.53 (m, 2 H, Ar); MS: *m/z* 221 (M + 1) 238 (M + 18). $[\alpha]_D^{20}$ + 8 (*c* = 0.6, $CHCl_3$). Anal. Calc. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.66; H, 7.54.

(2R,3R,4S)-4,6-O-Benzylidene-2,3-epoxy-hexan-1,4,6-triol **30**

Sharpless epoxidation was carried out as already described for **8** on 704 mg (3.2 mmol) of **29**. Chromatography (toluene/acetone, 6:4) gave **30** as a white solid. ^1H NMR analysis of the product showed a 91% diastereoisomeric excess (715 mg, 95%). Recrystallization in toluene gave optically pure **30**. mp = 94°C

(toluene); $[\alpha]_D^{20}$ +28 (c = 1.5, $CHCl_3$). ^1H NMR: 1.53 (m, 1 H, $J_{5e,5a}$ 13.5, $J_{5e,6a} = J_{5e,4}$ 2.7, $J_{5e,6e}$ 1.4 Hz, H-5e), 1.67 (dd, $J_{OH,1}$ 8, $J_{OH,1'}$ 5.5 Hz, OH), 2.05 (m, 1 H, $J_{5a,5e}$ 13.5, $J_{5a,6a} = J_{5a,4}$ 12, $J_{5a,6e}$ 5.2 Hz, H-5a), 3.22 (m, 2 H, H-2,3), 3.69 (ddd, $J_{1,1'}$ 13, $J_{1,OH}$ 8, $J_{1,2}$ 3.5 Hz, H-1), 3.89 (ddd, 1 H, $J_{4,5a}$ 12, $J_{4,3}$ 5, $J_{4,5e}$ 2.7 Hz, H-4), 3.97 (ddd, 1 H, $J_{1',1}$ 13, $J_{1',OH}$ 5.5, $J_{1',2}$ 2 Hz, H-1'), 3.98 (m, $J_{6a,6e}$ 11.5, $J_{6a,5a}$ 12, $J_{6a,5e}$ 2.7 Hz, H-6a), 4.32 (ddd, $J_{6e,6a}$ 11.5, $J_{6e,5a}$ 5.2, $J_{6e,5e}$ 1.4 Hz, 1 H, H-6e), 5.57 (s, 1 H, H benzylidene), 7.35 (m, 3 H, Ar), 7.54 (m, 2 H, Ar); MS: *m/z* 237 (M + 1) 254 (M + 18). Anal. Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.07; H, 6.82.

General procedure for nucleophilic opening of **30**

Compound **30** (200 mg, 0.85 mmol) in 10 mL of dry CH_2Cl_2 was treated at 0°C with $Ti(OiBu)_4$ (0.49 mL, 1.5 equiv.) and thiol acetic acid (0.30 mL, 5 equiv.) for 5 h. After dilution with a 1:1 concentrated ammonia:saturated NH_4Cl solution (2 mL) and Et_2O (4 mL), the reaction mixture was warmed to room temperature and stirred for 1 h before the addition of $MgSO_4$ and Celite. Filtration and evaporation of the filtrate gave the crude mixture of opened products immediately acetylated (pyridine, Ac_2O). Purification on silica gel (hexane/EtOAc, 5:1) gave a mixture of **31** and **32** (252 mg, 75%). Opening selectivity was measured by ^1H NMR in $CDCl_3$ by the ratio of H-2 of **31** (m, 5.55 ppm) to H-3 of **32** (m, 5.25 ppm). Other conditions were tried on a smaller scale (50 mg of **30**).

*Methyl 2,6-Dideoxy-α,β-D-*lyxo*-pyranoside* **35** and its β anomer

D-Fucal[32] (1.23 g, 9.5 mmol) was treated in methanol with camphor sulfonic acid (45 mg, 0.19 mmol) for 1 h. at room temperature. After neutralization with solid potassium carbonate (26 mg, 0.19 mmol) the solvent was evaporated. Chromatography (CH_2Cl_2/methanol 10:1) gave the title compound (1.3 g, 85%) as a 8.5:1 mixture of the α and β anomers.

*Methyl 3-*O*-tertButyldimethylsilyl-2,6-dideoxy-α-D-*lyxo*-pyranoside* **36**

Methyl 2,6-Dideoxy-α,β-D-*lyxo*-hexopyranoside (**35** and its β anomer, 1.2 g, 7.4 mmol) and dibutyl tin oxide (2.77 g, 1.5 equiv.) were heated in toluene (80 mL) for 4 h in a Dean-Stark apparatus. NBu_4Br (4.8 g, 2 equiv.) was then added and the mixture was allowed to cool down to 80°C before adding *tert*butyldimethylsilyl chloride (1.46 g, 1.3 equiv.). The reaction was over in 10 min. Evaporation and chromatography (hexane/EtOAc, 4:1) gave the α-anomer **36** (1.74 g, 85%) and the β-anomer (0.20 g, 10%) as colorless oils. **36**: $[\alpha]_D^{20}$ +95° (c = 1.9, $CHCl_3$). ^1H NMR: 0.08 and 0.09 (2 s, 6 H, $(Me)_2Si$), 0.89 (s, 9 H, *t*BuSi), 1.31 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.71 (m, 1 H, $J_{2e,2a}$ 13.2, $J_{2e,3}$ 5.5, $J_{2e,4} = J_{2e,1}$ 1 Hz, H-2e), 1.89 (ddd, $J_{2a,2e}$ 13.2, $J_{2a,3}$ 11.5, $J_{2a,1}$ 3.8 Hz, H-2a), 2.36 (s, 1 H, OH), 3.31 (s, 3 H, OMe), 3.51 (m, 1 H, H-4), 3.83 (m, 1 H, $J_{5,6}$ 6.5, $J_{5,4}$ 1 Hz H-5), 4.07 (ddd, $J_{3,2a}$ 11.5, $J_{3,2e}$ 5.5, $J_{3,4}$ 3.5 Hz, H-3), 4.76 (dd, 1 H, $J_{1,2a}$ 3.8, $J_{1,2e}$ 1 Hz, H-1). MS: *m/z* 277 (M + 1). Anal. Calc. for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.21. Found: C, 56.51; H, 10.12.

*Methyl 4-*S*-Benzoyl-3-*O*-tertbutyldimethylsilyl-2,6-dideoxy-4-thio-α-D-*arabino*-hexopyranoside* **38**

A solution of **36** (60 mg, 0.21 mmol) in CH_2Cl_2 (2 ml) was treated at 0°C with pyridine (52 mL, 3 equiv.) and triflic anhydride (55 mL, 1.5 equiv.). After 1 h 30 at room temperature, the solvent was evaporated and the crude triflate **37** taken up in DMF (1 mL). Potassium thiobenzoate (115 mg, 3 equiv.) was added and

the mixture stirred at room temperature for 4 h. Hydrolysis, CH_2Cl_2 extraction and chromatography (hexane/AcOEt, 15:1 then 10:1) gave **38** as an unstable colorless oil[38] (68 mg, 80%). $[\alpha]_D^{20}$ +70° (*c* = 1.6, $CHCl_3$). ^1H NMR: 0.01 and 0.05 (2 s, 6 H, Me_2Si), 0.78 (s, 9 H, *t*BuSi), 1.32 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.82 (ddd, 1 H, $J_{2a,2e}$ 13.3, $J_{2a,3}$ 11, $J_{2a,1}$ 3.5, H-2a), 2.14 (ddd, 1 H, $J_{2e,2a}$ 13.3, J_{2e} 5, $J_{2e,1}$ 1.5 Hz, H-2e), 3.34 (s, 3 H, OMe), 3.59 (t, 1 H, $J_{4,5} = J_{4,3}$ 10.8 Hz, H-4), 3.89 (m, 1 H, $J_{5,4}$ 10.8, $J_{5,6}$ 6.5 Hz, H-5), 4.03 (m, 1 H, $J_{3,4} = J_{3,2a}$ 11, $J_{3,2e}$ 5 Hz, H-3), 4.81 (dd, 1 H, $J_{1,2a}$ 3,5, $J_{1,2e}$ 1.5 Hz, H-1), 7.46 (m, 2 H, Bz), 7.56 (m, 1 H, Bz), 2.94 (m, 2 H, Bz). MS: *m/z* 365 (M + 1 - MeOH); IR (neat) 1620 cm^{-1}.

*Methyl 4-*S*-Benzoyl-2,6-dideoxy-4-thio-*α*-D-*arabino*-hexopyranoside* **39**

From **38**: Compound **38** (800 mg, 2.02 mmol) was desilylated in methanol (20 mL) containing HCl (1 mL of a 12 N aqueous solution) at room temperature for 4 h. Chromatography of the dried CH_2Cl_2 extract gave **39** as a colorless oil (480 mg, 84%). $[\alpha]_D^{20}$ +99° (*c* = 0.9, $CHCl_3$). ^1H NMR: 1.33 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.81 (ddd, 1 H, $J_{2a,2e}$ 13.3, $J_{2a,3}$ 11.5, $J_{2a,1}$ 3.5 Hz, H-2a), 2.26 (d, 1 H, $J_{OH,3}$ 5 Hz, OH) 2.29 (ddd, 1H, $J_{2e,2a}$ 13.3, $J_{2e,3}$ 5, $J_{2e,1}$ 1.5 Hz, H-2e), 3.35 (s, 3 H, OCH_3), 3.56 (t, 1 H, $J_{4,5} = J_{4,3}$ 11 Hz, H-4), H 3.89 (m, 1 H, $J_{5,4}$ 11, $J_{5,6}$ 6.5 Hz, H-5), 4.02 (m, 1 h, $J_{3,4} = J_{3,2a}$ 11, $J_{3,2e} = J_{3,OH}$ 5 Hz, H-3), 4.87 (dd, 1 H, $J_{1,2a}$ 3.5, $J_{1,2e}$ 1.5 Hz, H-1), 7.48 (m, 2 H, Bz), 7.61 (m, 1 H, Bz), 8.01 (m, 2 H, Bz). MS: *m/z* 300 (M + 18). IR (neat) 3440, 1620. Anal. Calc. for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.42. Found: C, 59.29; H, 6.80.

From **35**: Compound **35** (590 mg, 3.64 mmol), triphenylphosphine (1.14 g, 2 equiv.) and 4 Å molecular sieves were stirred for 30 min at room temperature. DEAD (0.69 mL, 1.2 equiv.) was added and the white suspension was heated at 80°C for 5 min before thiol benzoic acid (0.52 mL, 1.2 equiv.) was added. The reaction was completed in 30 min. Toluene was evaporated and the residue taken up in ether and filtered on Celite. Evaporation of the filtrate and chromatography gave **39** (0.79 g, 77%).

*Methyl 3-*O*-Benzoyl-2,6-dideoxy-4-thio-*α*-D-*ribo*-hexopyranoside* **45**

Compound **39** (285 mg, 1.01 mmol) in 25 mL of dry CH_2Cl_2 was treated with pyridine (0.25 mL, 3 equiv.) and triflic anhydride (0.27 mL, 1.5 equiv.) at 0°C for 1 h. To this mixture was added 1 mL of water and stirring was continued for 1 h. CH_2Cl_2 extraction and chromatography (hexane/EtOAc, 10:1) gave **45** as a colorless oil (143 mg, 50%). $[\alpha]_D^{20}$ +193° (*c* = 1.4, $CHCl_3$). ^1H NMR: 1.42 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 1.63 (d, 1 H, $J_{SH,4}$ 10.2 Hz, SH), 2.05 (dt, 1 H, $J_{2a,2e}$ 15, $J_{2a,3} = J_{2a,1}$ 4 Hz, H-2a), 2.32 (ddd, 1 H, $J_{2e,2a}$ 15, $J_{2e,3}$ 3, $J_{2e,1}$ 1 H, H-2e), 2.84 (m, 1 H, $J_{4,SH} = J_{4,5}$ 10.2, $J_{4,3}$ 3 Hz, H-4), 3.34 (s, 3 H OCH_3), 4.18 (m, 1 H, $J_{5,4}$ 10.2, $J_{5,6}$ 6.5 Hz, H-5), 4.77 (bd, 1 H, $J_{1,2a}$ 4 Hz, H-1), 5.33 (m, 1 H, $J_{3,4} = J_{3,2a}$ 4, $J_{3,2e}$ 3 Hz, H-3), 7.46 (m, 2 H, Bz), 7.56 (m, 1 H, Bz), 8.08 (m, 2 H, Bz). MS: *m/z* 251 (M + 1 - MeOH) 268 (M + 18 - MeOH) 300 M + 18); IR 2550, 1720. Anal. Calc. for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.42. Found: C, 59.26; H, 6.69.

*Methyl 3-*O*-Benzoyl-2,6-dideoxy-4-*S*-methyl-4-thio-*α*-*D*-ribo-hexopyranoside* **4**

Compound **45** (130 mg, 0.46 mmol) was methylated in THF (30 ml) with DBU (75 µL, 1.1 equiv.) and iodomethane (145 µL, 5 equiv.). Evaporation and chromatography (hexane/EtOAc, 6:1) gave **4** as a colorless oil (120 mg, 90%). $[\alpha]_D^{20}$ +218° (*c* = 1, $CHCl_3$). ^1H NMR: 1.43 (d, 3 H, $J_{6,5}$ 6.5 Hz, H-6), 2.02 (m, 1 H, $J_{2a,2e}$ 5.2, $J_{2a,3} = J_{2a,1}$ 4 Hz, H-2a), 2.16 (s, 3 H, SMe), 2.27 (ddd, 1 H, $J_{2e,2a}$ 15.2, $J_{2e,3}$ 3, $J_{2e,1}$ 1 Hz, H-2e), 2.60 (dd, 1 H, $J_{4,5}$ 10.5, $J_{4,3}$ 3 Hz, H-4), 3.35 (s, 3 H, OMe), 4.29 (m, 1 H, $J_{5,4}$ 10.5, $J_{5,6}$ 6.5 Hz, H-

5), 4.37 (bd, 1 H, $J_{1,2a}$ 4 Hz, H-1), 5.48 (m, 1 H, H-3), 7.43 (m, 2 H, Bz), 7.54 (m, 1 H, Bz), 8.07 (m, 2 H, Bz). ^{13}C NMR: 16.59 (C6) 20.72 (C4) 35.16 (C2) 53.68 (SMe) 56.04 (OMe) 65.40 (C5) 69.54 (C3) 98.26 (C1) 129.25 (Ar) 130.81 (Ar) 131.75 (Ar) 133.76 (Ar). MS: *m/z* 265 (M + 1 - MeOH) 314 (M + 18); IR 1720. Anal. Calc. for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.82; H, 6.89.

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