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Synthesis of the polyketomycin disaccharide

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Abstract—The disaccharide portion of the anthracycline antibiotic polyketomycin consists of the trideoxy sugar D-amicetose attached to the methyl-branched sugar L-axenose. The polyketomycin disaccharide was synthesized from methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (methyl α-D-amicetoside) and phenyl 3,4-di-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-1-thio-α,β-L-*xylo*-hexopyranoside. The key coupling step was carried out by *N*-bromosuccinimide activation of the thioglycoside and gave the desired α (1→4) linked disaccharide exclusively in 71% yield, which was debenzylated by sodium and liquid ammonia.

1. Introduction

Polyketomycin (Fig. 1) is an anthracycline antibiotic isolated from *Streptomyces* sp. MK277-AF1.[1,2] Structurally related to dutomycin,[3] polyketomycin has been found to possess cytotoxic activity against nine tumor cell lines and against multi-drug resistant strains of Gram-positive bacteria such as *Staphylococcus aureus* MS9610, and methicillin-resistant *S. aureus* (MRSA). The proliferation of MRSA has become a major health concern and several approaches have been taken to develop more effective treatments, including the development of more effective antibiotics and drug analogues, some of which have modified sugar residues.[4,5] Studies have shown that modification of the carbohydrate residues in other anthracycline antitumor antibiotics provides a viable means for the development of more effective drug analogues, providing glycosides that possess better bioavailability and lower toxicity than the parent compounds.[6] Our laboratory has reported the synthesis of both amicetose and axenose.[7,8] The synthesis of the disaccharide of polyketomycin is a challenging problem owing to the presence of the 2-deoxy glycosidic linkage and because multiple steps are required to obtain suitably protected monosaccharide derivatives. To date, neither the synthesis of the polyketomycin disaccharide nor of other disaccharides which contain the constituent sugars has been reported.

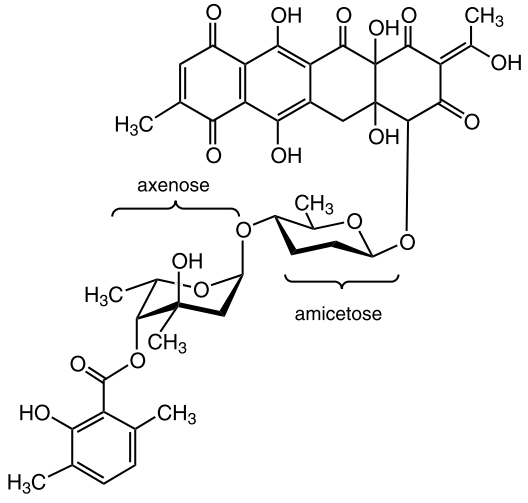

Figure 1. Polyketomycin.

Both polyketomycin and dutomycin are glycosylated with a disaccharide that contains the trideoxy sugar D-amicetose[9] and the methyl-branched sugar L-axenose,[10] which are attached by an α (1→4) linkage. Interestingly, the same two monosaccharides comprise the disaccharide of the antibiotic axenomycin,[10,11] but the order of attachment is reversed, with amicetose being the terminal sugar residue, and the linkage between the two sugars is a β-linkage. Owing to the extent of deoxygenation, especially at the C-2 positions, synthesis of disaccharides of these unusual carbohydrates was anticipated to be difficult. Also, the lack of a substituent at the 2-position precludes the use of

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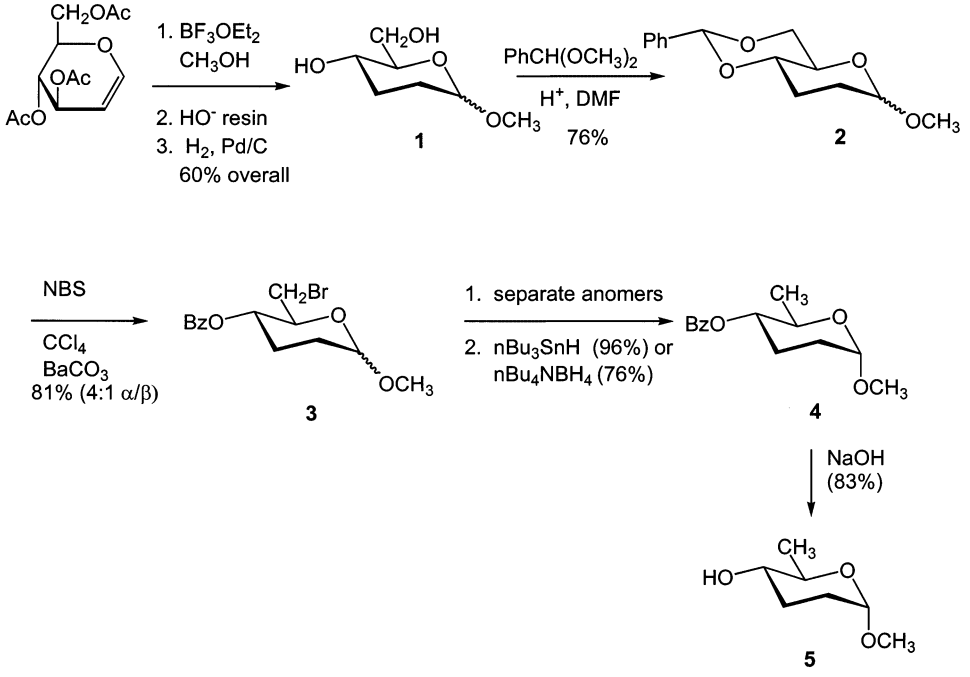
neighboring group participation for the control of stereochemistry in glycoside bond formation. Our initial attempts at disaccharide synthesis based on coupling glycosyl donors of axenose with methyl amicetoside were met with limited success, in particular low yields in the glycosylation and poor stereoselectivity. Herein, we report an efficient and stereoselective synthesis of the polyketomycin disaccharide **10**, based on the NBS-activation[12] of the thioglycoside of axenose.

2. Results and discussion

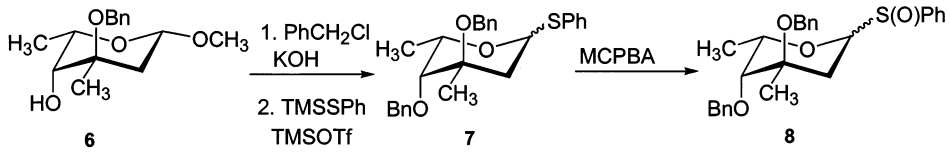
Both the glycosyl donor for axenose and the acceptor for amicetose were synthesized from carbohydrate starting materials. Several syntheses of amicetose from carbohydrate and non-carbohydrate precursors have been reported.[13] Horton and Albano synthesized methyl α-D-amicetoside from methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, which was obtained from methyl α-D-glucopyranoside.[14] NBS cleavage of the α-anomer of benzylidene acetal **2** is a key step in this route, as it provides for deoxygenation of the C-6 via hydrogenolysis of an iodo derivative. Our synthesis of methyl αβ-D-amicetoside is similar, except that **2** was prepared from tri-*O*-acetyl-D-glucal, and the deoxygenation of C-6 was carried out directly on the 6-bromo sugar, using either of two methods that were found to be suitable for this reduction (Scheme 1).

We utilized an efficient, three-step sequence of Ferrier rearrangement, deacetylation, and reduction to prepare methyl 4,6-*O*-benzylidene-2,3-dideoxy-α,β-D-*erythro*-hexopyranoside **2** as a mixture of anomers which were not separated at this stage.[15] Cleavage of the benzylidene acetal with *N*-bromosuccinimide[16] gave a separable mixture of anomers of bromo ester **3**. While it is assumed that both α- and β-anomers (or the anomeric mixture) of methyl amicetoside would be suitable as glycosyl acceptors, we selected the α-anomer for further studies since it was the major one formed. We found that reduction of **3** could be carried out by two methods, either with tributyltin hydride or with tetrabutylammonium borohydride.[17] The use of tetrabutylammonium borohydride avoids the hazards of handling organotin reagents, however, some deesterification occurs along with reduction. The alcohol **5** is easily separated from the ester **4** by straightforward column chromatography. Hydrolysis of **4** gave methyl α-D-amicetoside **5** in 20–25% overall yield, depending on which reduction method is used.

The glycosyl donors of axenose used in this study were phenyl thioglycosides, which were prepared by the route we have previously reported.[8] Methyl 3-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-β-L-*xylo*-hexopyranoside **6** was synthesized from 2-deoxyribose, benzylated at the C-4 hydroxyl, and treated with phenylthiotrimethylsilane and TMS-triflate to give an anomeric mixture of phenyl thioglycosides **7** (Scheme 2).[12] We chose thioglycosides as the glycosyl donor for axenose because they can be activated under mild reaction conditions either with halonium electrophiles or by several other methods.[18] The versatility of thioglycosides would provide multiple options in what was considered to be a difficult glycosylation step. The results of our study of coupling reactions are shown in Scheme 3. Methyl α-D-amicetoside was reacted with thioglycoside **7** under a variety of conditions and with the sulfoxide derivative **8**. In one of the first attempts at disaccharide synthesis, a 3:2 ratio



Scheme 1. Synthesis of methyl α-D-amicetoside.



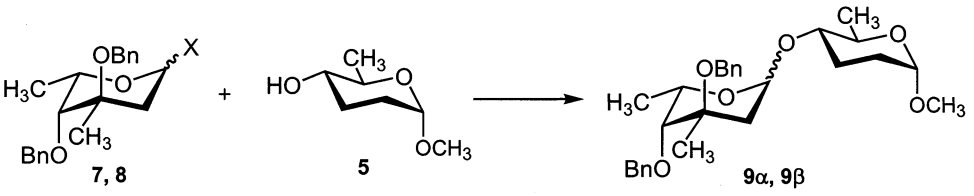
Scheme 2. Synthesis of glycosyl donors of axenose.

of α and β glycosides of **9** was obtained using *N*-iodosuccinimide/triflic acid to activate the thioglycoside.[20] These conditions had been used previously with different substrates in our synthesis of the cororubicin trisaccharide, in which the major product was the β-anomer.[21] It was the only method in this study that was found to produce any of the β-anomer, and while the natural configuration of the disaccharide is α, we remain interested in the synthesis of 2-deoxy-β-glycosides owing to their occurrence in the disaccharides found in other antibiotics, for example, axenomycin.[11] It was interesting to observe that activation with *N*-iodosuccinimide in the polar solvent *N*-methylpyrrolidinone or with NBS in a mixture of acetonitrile–dichloromethane gave exclusively the desired α-anomer. High selectivity for α-glycosylation with NBS-activation of thioglycosides in acetonitrile has been reported by Nicolaou et al.[12] In the coupling of thioglycoside **7** and **5**, temperature control was found to be critical, with reductions in yield being observed for reactions run at higher temperatures.

Glycosylation by the sulfoxide method was also attempted.[19] Thioglycoside **7** was oxidized to its sulfoxide **8** and the mixture of isomers was treated with methyl amicetoside with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. While the selectivity of the reaction was exclusive for the desired α-anomer, higher yields were obtained with NBS activation. Attempted debenzylation of **9α** by catalytic hydrogenolysis over palladium-on-carbon was not successful; however, treatment with sodium in liquid ammonia gave the polyketomycin disaccharide as its methyl glycoside **10** in 71% yield (Scheme 4).

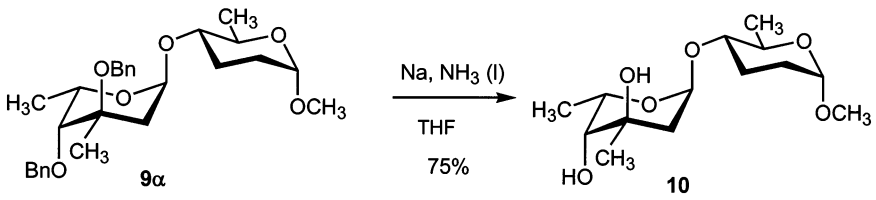
3. Conclusion

In conclusion, we have developed an efficient and stereoselective synthesis of the polyketomycin disaccharide, by coupling methyl α-D-amicetoside with a thioglycoside derivative of axenose. Best results in the key coupling step were obtained by activation of the thioglycoside with NBS in acetonitrile–dichloromethane. A feature of this approach that is worth noting is that the glycosyl donor could be substituted with groups other than benzyl at the C-4 hydroxyl. In polyketomycin, this position is acylated with a salicylate group. Also, compound **6**, the precursor to thioglycoside **7**, is unprotected at C-4 and could therefore be used as the acceptor in the synthesis of the axenomycin disaccharide. Further studies are in progress in these areas.



glycosyl donor	solvent	activation	% yield	9α/9β
7 X = SPh	CH_2Cl_2	NIS/TfOH	20	3:2
7 X = SPh	NMP	NIS	19	1:0
7 X = SPh	CH_2Cl_2/CH_3CN	NBS	71	1:0
8 X = S(O)Ph	CH_2Cl_2	Tf_2O	34	1:0

Scheme 3. Coupling of D-amicetose and L-axenose derivatives.



Scheme 4. Debenzylation of polyketomycin disaccharide.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded at 300 MHz with TMS as an internal reference in $CDCl_3$, and ^{13}C NMR spectra were recorded at 75 MHz and referenced with $CDCl_3$, unless otherwise noted. Melting points were determined in an open capillary tube with a Thomas Hoover apparatus and are uncorrected. TLC analyses were conducted on aluminum-backed silica gel Kieselgel 60 F254 plates and visualized by UV 254 nm or with ammonium molybdate-ceric sulfate reagent. Flash chromatography was carried out with 'Baker' silica gel. Optical rotations were recorded on a Perkin Elmer 241 polarimeter at 23°C. Elemental analyses were carried out at Merck Research Laboratories. High resolution mass spectra were measured at Merck Research Laboratories using ES-FT/ICR/MS with propylene glycol as the internal standard or at the University of Pennsylvania by electrospray ionization.

4.2. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α/β-D-*erythro*-hexopyranoside 2

To a stirred solution of methyl 2,3-dideoxy-α/β-D-*erythro*-hexopyranoside **1** (14 g, 86 mmol, 4:1 α/β) in *N*,*N*-dimethylformamide (80 mL) was added benzaldehyde dimethyl acetal (16.8 mL, 112 mmol) and pyridinium *p*-toluenesulfonate (1.4 g) and the resulting solution was heated at 80–85°C under reduced pressure (26 mm) for 2 h. After cooling, the reaction mixture was poured into sat. aq. $NaHCO_3$ (200 mL) and extracted with ethyl acetate (3×200 mL). The combined organic phases were washed with sat. aq. NaCl, dried over $MgSO_4$, and concentrated to a syrup that was purified by flash chromatography using hexanes/ethyl acetate (9:1–8:2) to yield 16.4 g (76%) of α/β **2**. The ^{1}H NMR spectrum of the α-anomer matched that reported.[14]

4.3. Methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α/β-D-*erythro*-hexopyranoside 3

A suspension of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α/β-D-*erythro*-hexopyranoside **2** (15.5 g, 62 mmol), *N*-bromosuccinimide (13.2 g, 74.3 mmol), and barium carbonate (18.3 g, 93 mmol) in anhydrous carbon tetrachloride (300 mL) was stirred under reflux for 1 h. After cooling to room temperature, the mixture was filtered and the solids were washed with dichloromethane (200 mL). The combined organic solutions were washed successively with sat. aq. $NaHCO_3$ (200 mL) and sat. aq. NaCl (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a syrup that was purified by flash chromatography (480 g silica gel) with 9:1 hexanes/ethyl acetate to give 13.0 g of α-anomer and 3.5 g of β-anomer (81% combined yield). α-Anomer: $[\alpha]_D$ +124 (*c* 1.25, chloroform) lit.[14] $[\alpha]_D^{21}$ +133 (*c* 1.1, chloroform); R_f 0.63 (3:1 hexanes/ethyl acetate); The ^{1}H NMR spectrum of the α-anomer of **3** matched that reported;[14] ^{13}C NMR δ 165.3, 133.2, 129.7, 128.4, 97.6, 70.9, 70.0, 54.8, 32.9, 28.7, 23.9; β-anomer: recrystallized from hexanes/ethyl acetate to give white needles, mp 104–105°; $[\alpha]_D$ +14.6 (*c* 1.00, chloroform); R_f 0.60 (3:1 hexanes/ethyl acetate); ^{1}H NMR δ 8.06–8.01 (m, 2H, Ar), 7.63-7.42 (m, 3H, Ar), 4.94 (m, 1H, H-4), 4.54 (m, 1H, H-1), 3.84 (ddd, 1H, $J_{4,5}$ 8.7, $J_{5,6}$ 7.5, 3.3 Hz, H-5), 3.62 (dd, 1H, $J_{6,6'}$ 9.9 Hz, H-6), 3.56 (dd, 1H, H-6′), 3.49 (s, 3H, OCH_3), 2.33 (m, 1H), 1.96 (m, 1H), 1.71 (m, 2H); ^{13}C NMR δ 165.3, 137.9, 133.2, 129.5, 128.3, 102.3, 76.6, 70.4, 56.3, 32.1, 29.2, 26.4. Anal. calcd for $C_{14}H_{17}O_4Br$: C, 51.04; H, 5.21. Found: C, 51.14; H, 5.05.

4.4. Methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside 4

Method A: To a solution of methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside **3** (1.0 g, 3.0 mmol) in anhydrous benzene (10 mL) under nitrogen was added tributyltin hydride (900 μL, 3.3 mmol) and 2,2′-azobisisobutyronitrile (5 mg) with the mixture left to stir under reflux for 20 h. After cooling to rt, the mixture was concentrated and purified by flash chromatography, eluting first with hexanes to separate the alkyltin by-products, then with 9:1 hexanes/ethyl acetate to afford 0.73 g (96%) of **4** as a colorless oil: $[\alpha]_D$ +161 (*c* 1.28, chloroform) lit.[22] $[\alpha]_D^{26}$ +170 (*c* 1.0, chloroform); R_f 0.61 (4:1 hexanes/ethyl acetate); ^{1}H NMR δ 8.06–8.01 (m, 2H, Ar), 7.62–7.40 (m, 3H, Ar), 4.76 (m, 1H, H-4), 4.70 (m, 1H, H-1), 3.96 (dq, 1H, $J_{4,5}$ 9.4, $J_{5,6}$ 6.3 Hz, H-5), 3.41 (s, 3H, OCH_3), 2.10–1.86 (m, 2H), 1.62 (m, 1H), 1.36 (m, 1H), 1.23 (d, 3H, H-6); ^{13}C NMR δ 165.6, 132.8, 129.5, 128.2, 97.4, 73.9, 66.4, 54.4, 29.0, 24.1, 17.9.

Method B: To a solution of bromo ester **3** (6.6 g, 20.0 mmol) in anhydrous benzene (66 mL) under nitrogen was added tetrabutylammonium borohydride (10.3 g, 40 mmol) with the mixture left to stir under reflux for 3 h. After cooling to 0°C, the excess borohydride was decomposed by the addition of ice until bubbling ceased. The mixture was then extracted with ethyl acetate and the combined extracts washed with sat. aq. NH_4Cl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated to a residue that was purified by flash chromatography with 9:1 hexanes/ethyl acetate to give 3.8 g (76%) of **4** and 350 mg (12%) of methyl α-D-amicetoside **5**.

4.5. Methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (methyl α-D-amicetoside) 5

A solution of methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside **4** (250 mg, 0.98 mmol) in ethanol (3 mL) and 2 M NaOH (4.5 mL) was stirred at 90°C for 15 min. Progress was monitored by TLC (3:1 hexanes/ethyl acetate), until it was shown no starting material remained. Water (6 mL) was then added and the mixture extracted with dichloromethane (4×10 ml). The combined organic phases were washed with satd. aq. NaCl dried over Na_2SO_4 and concentrated under reduced pressure to give an oil; yield, 119 mg (83%): $[\alpha]_D$ +145 (*c* 1.14, H_2O) lit.[14] $[\alpha]_D^{18}$ +142 (*c* 1.2, H_2O); R_f 0.48 (1:1 hexanes/ethyl acetate); ^{1}H NMR δ 4.63 (d,

1H, $J_{1,2}$ 1.7 Hz, H-1), 3.55 (dq, 1H, $J_{4,5}$ 9.1, $J_{5,6}$ 6.3 Hz, H-5), 3.28 (m, 1H, H-4), 3.34 (s, 3H, OCH_3), 1.81–1.66 (m, 4H), 1.27 (d, 3H, H-6); ^{13}C NMR δ 97.2, 71.9, 69.1, 54.2, 29.4, 27.4 (2C), 17.8.

4.6. Phenyl 3,4-di-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-1-(*RS*)-sulfinyl-α,β-L-*xylo*-hexopyranoside 8

m-Chloroperoxybenzoic acid (64 mg, 57–86%, 1.0–1.3 equiv.) was added to a stirred solution of phenyl 3,4-di-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-1-thio-α/β-L-*xylo*-hexopyranoside (124 mg, 0.29 mmol, 3:1 b/a) in anhydrous dichloromethane (6 mL) at −78°C. The reaction was allowed to warm to 0°C over 2 h, then poured into sat. aq. $NaHCO_3$ and extracted with dichloromethane. The organic phase was washed with sat. aq. NaCl, dried over Na_2SO_4, concentrated, and purified by flash chromatography (4:1 hexanes/ethyl acetate) to give the syrupy sulfoxide (98 mg, 76%) as a mixture of α,β/*R*,*S* isomers that was not separated: ^{1}H NMR δ 7.68–7.12 (m, 15H, Ar), 4.66 (ABq, *J* 11.9 Hz, 2H, OCH_2Ph), 4.34 (br d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 4.28 (ABq, *J* 11.6 Hz, 2H, OCH_2Ph), 4.05 (dq, 1H, $J_{4,5}$ 0.9, $J_{5,6}$ 6.5 Hz, H-5), 3.08 (br s, 1H, H-4), 2.09–2.04 (m, 2H, H-2), 1.37 (s, 3H, 3-CH_3), 1.19 (d, 3H, H-6); ^{13}C NMR δ 141.5 (ipso SOPh), 138.2, 138.7 (Ar ipso), 128.61-124.8 (Ar), 91.8 (C-1), 80.2 (OBn), 76.1 (C-3), 75.8 (C-4), 72.8 (C-5), 63.1 (OBn), 28.2 (C-2), 21.6 (3-CH_3), 16.8 (C-6).

4.7. Methyl 3,4-di-*O*-benzyl-2,6-dideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranosyl-(1→4)-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside 9α

A mixture of methyl α-D-amicetoside **5** (24.5 mg, 0.17 mol) and thioglycoside **7** (68 mg, 0.15 mmol) was azeotropically dried with benzene (3×2 mL) and dissolved in 1:1 CH_3CN–CH_2Cl_2 (2 mL). Molecular sieves (4 Å, 40 mg) were added and the mixture stirred under argon at room temperature for 25 min and then cooled to −78°C. *N*-Bromosuccinimide (32 mg, 0.18 mmol, 1.2 equiv., recrys from H_2O and dried) was added in one portion and progress of the reaction was monitored by TLC (3:1 hexanes/ethyl acetate). After 2 h, the major component of the reaction was the disaccharide (R_f 0.38). The reaction was diluted with dichloromethane (10 mL), filtered, and the filtrate extracted with 5% aq. $NaHSO_3$, sat. aq. NaCl, dried over Na_2SO_4, and concentrated to a syrup that was purified by chromatography on a Waters Vacuum Manifold on a silica gel cartridge (2 g) with 5–25% ethyl acetate/hexanes as the eluant. Obtained was 52 mg (71%) of disaccharide **9α** as a colorless oil: $[\alpha]_D$ −63 (*c* 0.33, chloroform); R_f 0.42 (3:1 hexanes/ethyl acetate) ^{1}H NMR (400 MHz) δ 7.60–7.22 (m, 10H, Ar), 4.94 (br d, 1H, $J_{1',2'}$ 3.3 Hz, H-1′), 4.67 (ABq, 2H, *J* 11.2 Hz, OCH_2Ph), 4.60 (br d, 1H, $J_{1,2}$ 2.9 Hz, H-1), 4.56 (br q, 1H, $J_{5,6}$ 6.6 Hz, H-5′), 4.50 (ABq, 2H, *J* 10 Hz, OCH_2Ph), 3.56 (dq, 1H, $J_{5,6}$ 6.1 Hz, H-5), 3.32 (s, 3H, OCH_3), 3.15 (dt, 1H, $J_{3,4}$ 4.8, $J_{4,5}$ 9.2 Hz, H-4), 3.10 (br s, 1H, H-4′), 2.06 (br d, 1H, $J_{2,2'}$ 14.9 Hz, H-2′ax), 1.90–1.71 (m, 4H, H-2, H-3), 1.82 (dd, 1H, H-2′eq), 1.33 (s, 3H, 3′-CH_3), 1.16 (d, 3H, H-6′), 1.14 (d, 3H, H-6); ^{13}C NMR (100 MHz) δ 128.2, 128.1, 128.1, 127.8, 127.7, 127.2, 99.0, 97.3, 81.6, 80.4, 77.4, 75.9, 67.6, 63.6, 63.3, 52.2, 32.1, 29.4, 26.12, 22.4, 18.2, 17.1. HRMS calcd for $C_{28}H_{38}O_6Na$ (M+Na): 493.2560. Found: 493.2565.

4.8. Methyl 2,6-dideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranosyl-(1→4)-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside 10

Sodium metal (12 mg, 0.54 mmol) was added to a stirred solution of ammonia (5 mL) at −78°C under argon. Blue color appeared within 5 min and a solution of **9α** (51 mg, 0.108 mmol) in anhydrous THF (1.5 mL) was added in one portion. Additional sodium was added in small pieces until the color persisted. The reaction was then stirred for 30 min. Solid ammonium chloride was added until the color dissipated at which point the reaction was allowed to warm to room temperature.

The residue was dissolved in ethyl acetate (75 mL), extracted with water, dried over Na_2SO_4 and concentrated to give a solid product (29 mg) which was triturated with diethyl ether (0.5 mL) and dried under high vacuum; yield, 24 mg (75%). Recrystallization from ethyl acetate–hexane gave needles: mp 130–132°C; $[\alpha]_D$ +44.7 (*c* 0.94, chloroform); R_f 0.61 (3:2 hexanes/ethyl acetate) ^{1}H NMR δ 5.00 (dd, 1H, $J_{1',2a'}$ 4.1, $J_{1',2e'}$ 1.2 Hz, H-1′), 4.61 (br d, 1H, *J* 2.9 Hz, H-1), 4.43 (br q, 1H, $J_{5',6'}$ 6.7 Hz, H-5′), 3.93 (br s, 1H, OH), 3.65 (m, 1H, $J_{5,6}$ 6.3 Hz, H-5), 3.35 (s, 3H, OCH_3), 3.22 (m, 1H, $J_{4,5}$ 9.7, $J_{3a,4}$ 10.4 Hz, H-4), 3.15 (dd, 1H, $J_{2e,4}$ 1.2, $J_{4,5}$ 0, $J_{4,OH}$ 5.7 Hz, H-4′), 2.02–1.64 (m, 7H, $J_{2a',2e'}$ 14.4 Hz, H-2′, H-2, H-3, OH), 1.25 (s, 3H, 3′-CH_3), 1.24 (d, 3H, H-6′), 1.21 (d, 3 H, H-6); ^{13}C NMR δ 99.8, 96.9, 80.1, 74.5, 70.0, 67.3, 63.0, 54.6, 36.2, 29.7, 26.4, 26.3, 18.5, 17.0. HRMS calcd for $C_{14}H_{26}O_6Na$ (M+Na): 313.1627. Found: 313.1630.

Acknowledgements

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