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# SYNTHESIS OF METHYL 3-DEOXY-3-METHYLAMINOARABINOPYRANOSIDE, A COMPONENT OF SOME AMINOGLYCOSIDE ANTIBIOTICS

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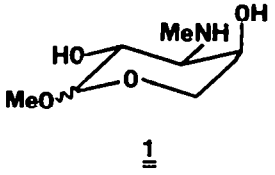
Abstract - Amino sugar 1 has been synthesized in racemic form as a mixture of anomers from sorbic aldehyde. An intramolecular N-sulfinyl dienophile Diels-Alder strategy was used to stereospecifically generate the chiral centers of pentose 1.

There has been a surge of interest in recent years in synthesis of sugars from non-carbohydrate precursors.[1] We have developed a general method for stereospecific construction of unsaturated vicinal amino alcohol derivatives via Diels-Alder adducts of N-sulfinyl dienophiles.[2] An intramolecular version of this methodology was recently applied to synthesis of the unnatural C-5 epimer of the common deoxyhexose desosamine.[3] In this paper we describe a new synthesis of the deoxyaminopentose 1, a component of the Schering aminoglycoside antibiotic 66-40D (2) as well as some gentamycin antibiotics.[4,5] Our basic approach to 1 uses an intramolecular Diels-Alder cycloaddition of a N-sulfinylcarbamate to generate the C-2,3,4 chiral centers of the amino sugar.

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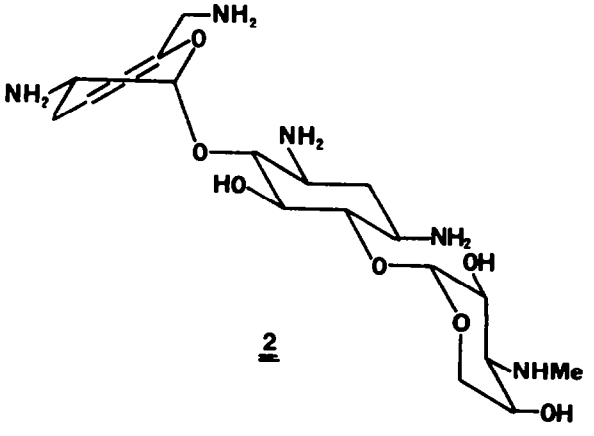
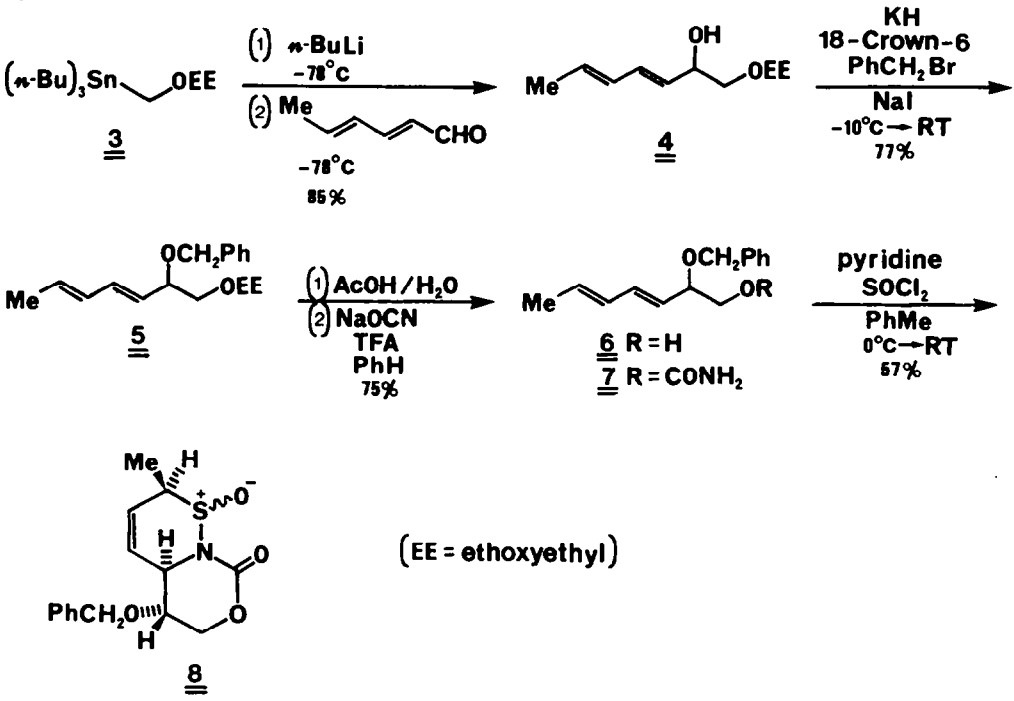



2

Synthesis of the Diels-Alder precursor, diene carbamate 7, is outlined in Scheme 1. Stannane 3 was transmetallated to give the corresponding lithio derivative,[6] which added cleanly to sorbic

aldehyde to yield alcohol 4 as an inseparable 1:1 mixture of diastereomers. The secondary alcohol group of 4 was protected as its benzyl ether 5, and the ethoxyethyl protecting group was removed

*Scheme 1*



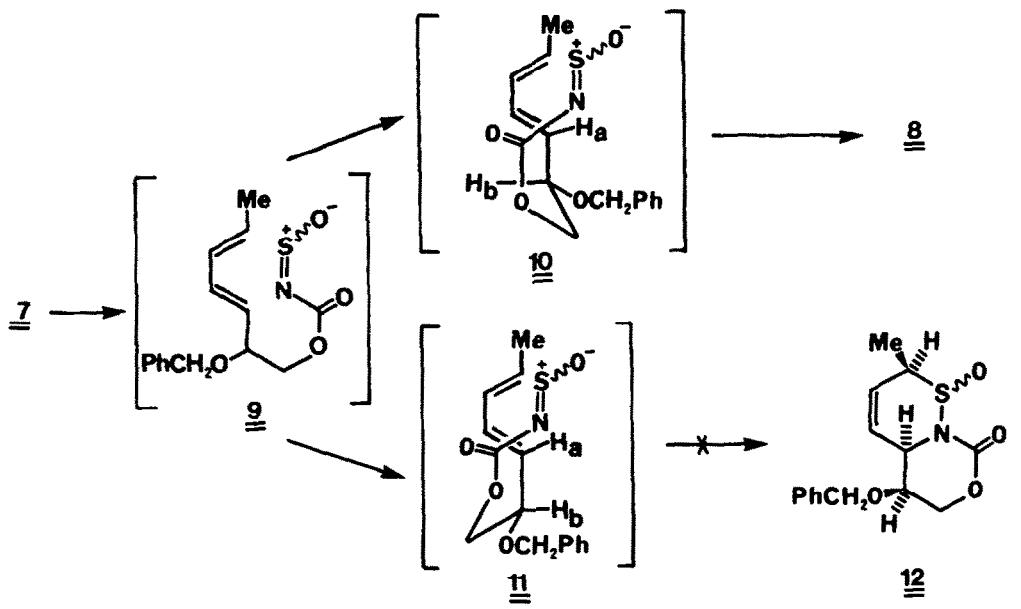

with acetic acid to afford primary alcohol 6. Using the procedure of Loev and Kormendy,[7] this compound was converted to the desired carbamate 7. When 7 was treated with thionyl chloride, dihydrothiazine S-oxide 8 was produced as an inseparable 15:1 mixture of sulfur epimers.[8]

Adduct 8 is presumably formed via N-sulfinylcarbamate 9 (Scheme 2) which was not detected. We belive that the relative stereochemistry in 8 is produced through a Diels-Alder transition state like 10. An alternative conformation such as 11 would yield adduct 12, which is epimeric at the remote benzyloxy center. We have previously observed a strong preference for a cycloaddition conformation like 9, rather than 11, in two intramolecular imino Diels-Alder reactions,[9] and a N-sulfinyl-dienophile case.[3]

Since it was not clear to us from inspection of molecular models just what interactions are primarily responsible for these consistent results, we have performed some molecular mechanics calculations on a closely related "all carbon" system (Scheme 3) reported by Taber and Gunn.[10] Cycloaddition of 13 was shown to produce a 9:1 mixture of adducts 15 and 17, respectively. This reaction was chosen since the MM1 program[11] available to us was not parameterized for heteroatom-containing functional groups.

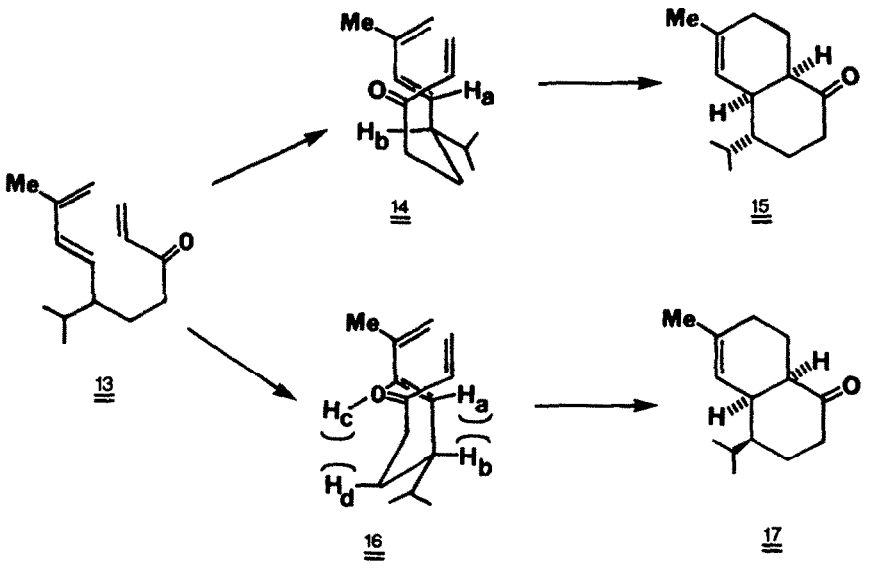
Taber and Gunn suggested that conformer 16, leading to the minor product, is destabilized relative to 14 by a non-bonded interaction between hydrogen $H_c$ and $H_d$. Our modeling results indicate that this particular interaction is negligable, and that a $H_a/H_b$ eclipsing interaction is actually the major one in 16 (~2 Kcal/mole). Furthermore, conformer 14 was found to be approximately 2.5 Kcal/mole more stable than 16. It is emphasized that these calculations should only be interpreted qualitatively, but they are certainly in line with experimental results. A similar rationale would apply to our imino and other N-sulfinyl dienophile examples.[3,9]

*Scheme 2*

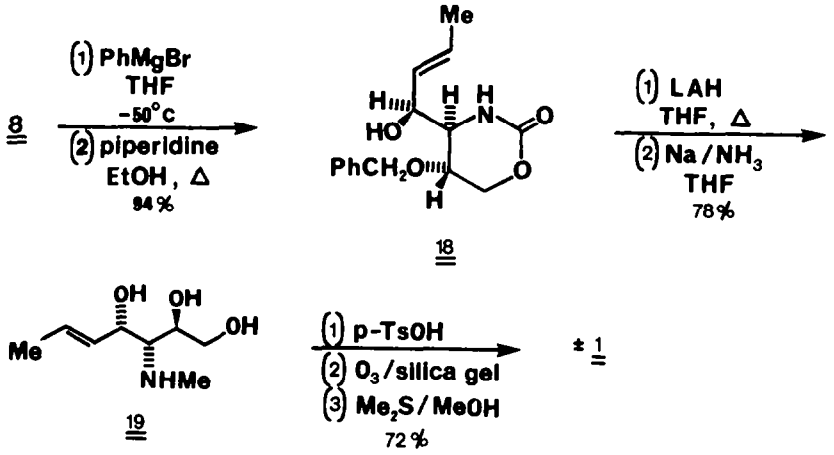


In order to complete the synthesis of 1, adduct 8 was rearranged as previously described[2,3] to give allylic alcohol 18 as a single stereoisomer. The carbamate moiety of 18, which held together diene and dienophile for the intramolecular cycloaddition, now served a second purpose. Thus, reduction of 18 with lithium aluminum hydride gave a N-methylamine. Deprotection of the

*Scheme 3*



benzylated oxygen of this product afforded N-methylaminotriol 19. Amine 19 was converted to its salt with p-toluenesulfonic acid, and this material was subjected to dry silica gel ozonolysis,[14] followed by methanolic dimethyl sulfide reduction, to afford pentose 1 as a 1:1 mixture of




anomers. It is not clear if the methyl glycoside is being directly formed via an intermediate from the ozonolysis step, or by acid catalyzed exchange on the hemiacetal of 1. A comparison of the spectra[15] of our racemic 1 with spectra ($^1$H NMR, $^{13}$C NMR) of the individual pure anomers kindly supplied by Dr. A.K. Mallams[5] confirmed the assigned structure.

## EXPERIMENTAL

Synthesis of Diene Alcohol 4: A solution of (ethoxyethyloxymethyl)tributylstannane (3) (4.49 g, 12.1 mmol) in anhydrous THF (100 mL) was cooled to -78°C and 0.88 M n-butyl lithium in hexane (14.0 mL, 12.3 mmol) was added over 5 min. The resulting solution was stirred at -78°C for 15 min and E,E-hexadienal (1.35 mL, 12.2 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 1 h and was diluted with saturated $NH_4Cl$ solution (25 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined organic extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo and purification of the residue by flash chromatography (25% ethyl acetate/hexane) afford 2.07 g (85%) of diene alcohol 4 as a pale yellow oil: IR (film) 3450, 3025, 3000, 2940, 2875, 1610, 1445, 1380, 1340, 1130, 1090, 1055, 990, 950, 930 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) δ 6.29 (m, 1H), 6.04 (m, 1 H), 5.52 (m, 1H), 4.73 (q, J = 5.3 Hz, 1 H), 4.32 (m, 1 H), 5.72 (m, 1H), 3.70-3.31 (m, 4H), 1.76 (d, J = 6.5 Hz 3H), 1.33 (d, J = 5.4 Hz), 1.19 (t, J = 7.1 Hz); CIMS (M + 1)/z 201.

Synthesis of Benzyl Ether 5: Potassium hydride (2.62 g, 35% dispersion in mineral oil, 23 mmol) was washed with hexane (15 mL) and dry THF (45 mL) was added. The stirred suspension was cooled to -15°C and alcohol 4 (3.80 g, 19 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at -15°C for 20 min and a catalytic amount of 18-crown-6 was added. The resulting mixture was stirred for 45 min during which time the mixture was allowed to warm to 0°C. Benzyl bromide (2.30 mL, 21.2 mmol) and a catalytic amount of dry NaI were added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 12 h and saturated $NH_4Cl$ solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined extract was washed with brine, dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (12% ethyl acetate/hexane) to afford 4.26 g (77%) of benzyl ether 5: IR (film) 3100, 3175, 3130, 2980, 2945, 2875, 1660, 1500, 1450, 1380, 1340, 1130, 1090, 1060, 990, 945, 925; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.20 (m, 2H), 5.74 (m, 1H), 5.54 (m, 1H), 4.68 (m, 3H), 3.99 (m, 1H), 3.71-3.43 (m 4H), 1.78 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 5.3 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); CIMS (M + 1)/z 291.

Preparation of Carbamate 7: Benzyl ether 5 (3.06 g, 10.5 mmol) was dissolved in THF (15 mL), and water (10 mL) and acetic acid (10 mL) were added. The mixture was stirred for 20 h and was concentrated in vacuo. The residue was dissolved in ether (20 mL), and was washed with saturated $NaHCO_3$ solution (3 x 20 mL) and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to afford crude alcohol 6 (2.22 g) as a yellow oil which was used in the next step without further purification.

Alcohol 6 was dissolved in benzene (40 mL) and sodium cyanate (3.32 g, 51 mmol) was added. Trifluoroacetic acid (2.30 mL, 29.9 mmol) was added in 0.5 mL portions over 2.5 h, and the resulting mixture was stirred at room temperature for 12 h. Anhydrous $K_2CO_3$ was added and the mixture was filtered. The solid residue was washed thoroughly with ethyl acetate and the combined filtrate was evaporated in vacuo. Flash chromatography (30% ethyl acetate/hexane) of the residue yielded 2.06 g (75%) of carbamate 7: IR ($CHCl_3$) 3550, 3450, 3000, 2950, 2875, 1730, 1590, 1450, 1400, 1340, 1110, 1060 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.16 (m, 2H), 5.76 (m, 1H), 5.47 (m, 1H), 4.84 (s, 1H), 4.63 (d, J = 11.9 Hz, 1 H), 4.39 (d, J = 12.3 Hz, 1 H), 4.09 (m, 3H), 1.77 (d, J = 7.2 Hz, 3H); CIMS (M + 1)/z 262.

Synthesis of Diels-Alder Adduct 8: Carbamate 7 (773 mg, 2.96 mmol) was dissolved in a mixture of dry toluene (120 mL) and dry pyridine (0.90 mL, 19 mmol) and the solution was cooled to 0°C. Thionyl chloride (0.65 mL, 8.9 mmol) in toluene (20 mL) was added to the solution via syringe pump over 2 h, during which time a white precipitate formed. After the addition was complete, the reaction mixture was warmed to room temperature and was stirred for 14 h. The reaction mixture was filtered through Celite and the filtrate was reduced to approximately 30 mL in vacuo. The resulting mixture was refiltered and the filtrate was evaporated to dryness at reduced pressure. Flash chromatography of the residue on silica gel (20% acetone/dichloromethane) afforded 380 mg of starting carbamate 7 and 261 mg (57%) of adduct 8 which was an inseparable mixture of sulfur epimers: IR ($CHCl_3$) 3100, 3010, 2940, 2910, 2875, 1710, 1460, 1410, 1340, 1260, 1170, 1090 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.98 (m, 2H), 4.69 (s, 2H), 4.36 (m, 3H), 3.74 (m, 1H), 3.36 (m, 1H), 1.34 (d, J = 7.2 Hz, 3H); $^{13}C$ NMR (200 MHz, $CDCl_3$, 2 sulfur epimers) δ 152.88, 152.29, 137.16, 136.89, 128.46, 128.23, 128.07, 128.00, 127.70, 127.64, 125.21, 124.03, 123.65, 71.56, 71.39, 69.54, 68.87, 66.98, 65.67, 55.04, 54.44, 52.32, 51.29, 15.60, 13.21; CIMS (M + 1)/z 309.

Preparation of Alcohol 18: Adduct 8 (513 mg, 1.67 mmol) was dissolved in dry THF (20 mL) and the stirred solution was cooled to -50°C. To this solution 3.0 M phenylmagnesium bromide in ether (0.62 mL, 1.86 mmol) was added dropwise. The reaction mixture was stirred at -50°C for 10 min and was diluted with saturated $NH_4Cl$ solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and was evaporated in vacuo to afford an allylic sulfoxide (644 mg) which was used without further purification in the next step.

The crude sulfoxide was dissolved in absolute ethanol (30 mL) and piperidine (0.50 mL, 8.5 mmol) was added. The resulting solution was refluxed for 10 h and the solvent evaporated in vacuo. The residue was purified by flash chromatography on silica gel (25% acetone/dichloromethane) to afford 440 mg (95%) of alcohol 18: IR ($CHCl_3$) 3450, 3025, 3000, 2950, 2920, 2860, 1740, 1445, 1380, 1360, 1225, 1080, 1040, 990, 960 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.49 (s, 1H), 5.48 (m, 2H), 4.74 (d, J = 11.9 Hz, 1H), 4.60, (t, J = 6.7 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 3.85 (m, 1H); 3.63 (m, 3H), 3.32 (m, 1H), 1.67 (d, J = 5.4 Hz, 3H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 158.95, 137.26, 132.10, 128.71, 128.30, 128.18, 127.45, 79.72, 77.92, 72.17, 60.89, 59.89, 17.59; CIMS (M+1)/z 276.

Preparation of Amino Triol 19: Alcohol 18 (346 mg, 1.26 mmol) was dissolved in dry THF (10 mL) and the solution was cooled to 0°C. To this solution was added a solution of 1.0 M $LiAlH_4$ in THF (3.5 mL, 3.5 mmol) and the mixture was refluxed for 12 h. Saturated $Na_2SO_4$ solution was added dropwise to the mixture until no $H_2$ evolution was observed. The resulting mixture was filtered and the filter cake was thoroughly washed with chloroform. The combined filtrate was evaporated in vacuo to afford 331 mg of amino diol which was used in the next step without further purification.

The above amino-diol was dissolved in dry THF (3 mL) and dry ammonia (15 mL) was condensed into the reaction vessel. Sodium metal was added to the reaction mixture until a dark blue color persisted. The blue mixture was stirred for 30 min. The ammonia was evaporated, saturated $NH_4Cl$ solution (0.5 mL) was added, and the mixture was filtered. Evaporation of the filtrate at reduced pressure and purification of the residue by preparative thin layer chromatography on silica gel ($CHCl_3$/MeOH/conc $NH_4OH$, 2/1/1) afford 170 mg (78%) of amino-triol 19: IR (film), 3325, 2900, 2870, 2800, 1640, 1560, 1460, 1400, 1080, 1030, 965 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.50 (m, 1H), 4.23 (t, J = 5.5 Hz, 1H), 3.85 (s, 4H), 3.72 (s, 2H), 2.51 (s, 3H), 2.44 (m, 1H), 1.71 (d, J = 6.4 Hz, 3H); CIMS 176.

(±) Methyl 3-Deoxy-3-Methylamino arabinopyranoside (1): Triol 19 (96 mg, 0.55 mmol) was dissolved in dry $CH_2Cl_2$ (10 mL), anhydrous p-toluenesulfonic acid (104 mg, 0.60 mmol) was added and the solution was stirred at room temperature for 30 min. E.M. Merck Silica Gel 60 (1.85 g, dried under vacuum at 200°C for 12 h) was added and the mixture was stirred for 45 min. The solvent was evaporated in vacuo and the silical gel mixture was dried under vacuum for 1 h at room temperature. The mixture was cooled to -78°C and a stream of dry $O_3$ (0.4 L/min) was carefully passed through the silica gel during which time the solid became blue. The mixture was purged with dry $O_2$ at -78°C until the blue color disappeared and dry $N_2$ was then passed through the silica gel at -78°C for 20 min. The solid was extracted with dry methanol (4 x 5 mL) and dimethyl sulfide (0.45 mL, 6.1 mmol) was added to the methanol solution. The resulting mixture was stirred for 2 h and the solvent was evaporated at reduced pressure. The residue was passed through Dowex AG 1-X8 ion exchange resin (5 mL, acetate form) using distilled water as the eluent. The solvent was evaporated in vacuo and the residue was chromatographed on Florisil (50% methanol/chloroform) to afford 87 mg (72%) of (±)-methyl 3-deoxy-3-methylaminoarabinopyranoside acetate as a mixture of α and β anomers: IR (film) 3020, 2970, 2920, 2850, 1570, 1400, 1140, 1050, 940 $cm^{-1}$ $^1$HNMR (200 MHz, $D_2O$, free base, mixture of glycoside anomers) δ 5.01 (d, J = 3.8 Hz, 1H), 4.43 (d, J = 7.5 Hz, 1H), 3.70-3.82 (m, 4H), 3.65 (dd, J = 3.7, 10.8 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 3.30 (dd, J = 7.5, 10.6 Hz, 1H), 3.06 (m, 3H), 2.62 (s, 4H), 2.61 (s, 3H); $^{13}$C NMR (200 MHz, $D_2O$) δ 181.28, 96.76, 91.20, 69.23, 66.75, 66.08, 64.69, 64.49, 64.12, 61.24, 60.87, 48.82, 30.71, 30.57, 23.28 CIMS (M+1)/z 178.

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## REFERENCES

1. For an excellent review see: G. J. McGarvey, M. Kimura, T. Oh, and J.M. Williams, J. Carbohydr. Chem., 1984, 3, 125.

2. R.S. Garigipati, and S.M. Weinreb, J. Am. Chem. Soc., 1983, 105, 4499. R.S. Garigipati, A.J. Freyer, R.R. Whittle and S.M. Weinreb, Ibid. 1984, 106, 0000.

3. S.W. Remiszewski, R.R. Whittle, and S.M. Weinreb, J. Org. Chem., 1984, 49, 3243.

4. D.H. Davies, D. Greeves, A.K. Mallams, J.B. Morton, and R.W. Tkach, J. Chem. Soc., Perkin I, 1975, 814.

5. For synthesis of the individual anomers of 1 from carbohydrates see: D.J. Cooper, D.H. Davies, A.K. Mallams, and A.S. Yehaskel, J. Chem. Soc., Perkin I, 1975, 785.

6. W.C. Still, J. Am. Chem. Soc., 1978, 100, 1481; G.J. McGarvey, and M. Kimura, J. Org. Chem. 1982, 47, 5420.

7. B. Loev, and M.R. Kormendy, J. Org. Chem., 1963, 28, 3421.

8. The configuration of these epimers could not be readily determined by spectral methods.

9. M.L. Bremmer, N.A. Khatri, and S.M. Weinreb, J. Org. Chem. 1983, 48, 3661. T.R. Bailey, R.S. Garigipati, J.A. Morton, and S.M. Weinreb, J. Am. Chem. Soc., 1984, 106, 3240.

10. D.F. Taber, and B.P. Gunn, J. Am. Chem. Soc., 1979, 101, 3992.

11. The modelling of compounds was performed using the ADAPT (Automated Data Analysis and Pattern recognition Tool Kit) chemical software system[12] in tandem with MMP1 and MM1 program.[13]

12. A.J. Stuper, W.E. Brugger, P.C. Jurs, "Computed Assisted Studies of Chemical Structure and Biological Function," Wiley-Interscience: New York, 1979.

13. N.L. Allinger, Quantum Chemistry Program Exchange 318, 1976.

14. I.E. Den Besten, T.H. Kinstle, J. Am. Chem. Soc., 1980, 102, 5968.

15. The arabino configuration was confirmed by $^1$H NMR decoupling experiments.