EXTENSION OF SUGAR CHAINS BY ENOLATE ADDITION TO METHYL 2,3-DI-*O*-ACETYL-4-DEOXY-β-L-*threo*-HEX-4-ENODIALDO-1,5-PYRANOSIDE*†

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ABSTRACT

Methyl 2,3-di-*O*-acetyl-4-deoxy-β-L-*threo*-hex-4-enodialdo-1,5-pyranoside (**2**) reacts readily with enolate anions by attack at the aldehyde carbonyl group. Nitromethane gives initially the adduct **1**, which readily undergoes elimination to afford the conjugated, unsaturated derivative **5**, reduction of the latter with borohydride effects selective reduction of the exocyclic double bond to give the nitro sugar derivative **6**. The aldehyde **2** undergoes condensation with acetone to give a conjugated, 9-carbon sugar derivative **7**, having a carbonyl group at C-8 that can be reduced selectively by borohydride to a secondary alcohol derivative, isolated as its acetate **8** The readily available, unsaturated aldehyde **2**, which can be condensed with 1,2-bis(anilino)-ethane to give a stable, crystalline imidazolidine derivative **3**, thus provides a useful starting point for synthesis of higher-carbon sugars by chain extension at the ω-carbon atom. Addition of dimethylamine at C-4 of **2** was not observed under a variety of experimental conditions

INTRODUCTION

Several papers from this laboratory have described reactions useful for the extension of carbohydrate chains by addition of unsaturated Grignard reagents to aldehydo sugar derivatives[2], and the reaction has been applied for synthesis of branched-chain derivatives by use of keto sugar derivatives[3] Acetylenic alcohol derivatives of sugars obtained by this route have been converted into α,β-unsaturated aldehydes[4]. Compounds of the latter class are themselves of interest for synthesis of higher sugars through addition of carbon nucleophiles to the aldehyde group, the possible addition of various nucleophiles by the Michael route at the β carbon atom offers interesting potential for synthesis of 2-deoxyaldoses having selected functionality at C-3 A convenient route to an α,β-unsaturated aldehyde derivative of a sugar is

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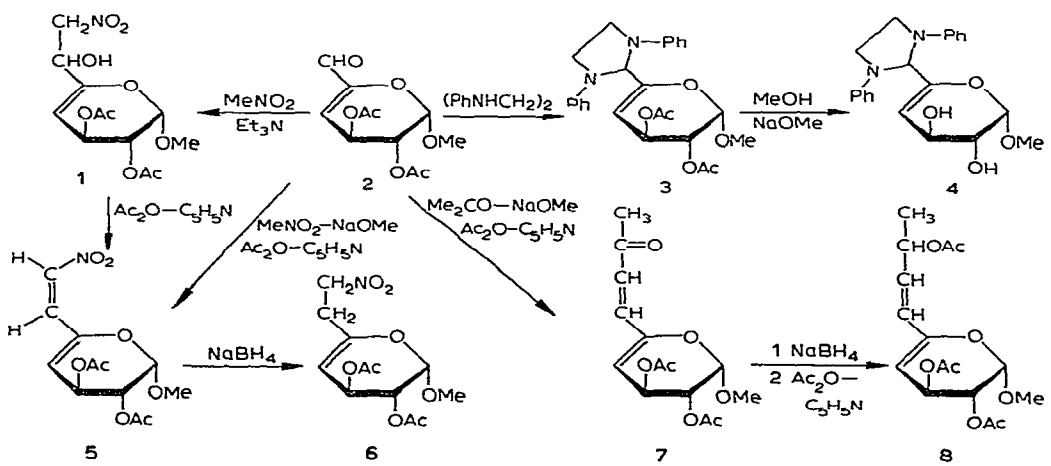
afforded by photolysis of methyl 6-azido-6-deoxy-α-D-glucopyranoside, hydrolysis of the resultant imine, and subsequent treatment with base, to give methyl 2,3-di-*O*-acetyl-4-deoxy-β-L-*threo*-hex-4-enodialdo-1,5-pyranoside[5] (**2**) This α,β-unsaturated aldehyde, also obtainable by oxidation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[6], has an oxygen atom at the position α to the aldehyde group, and might therefore be expected to show low reactivity in the Michael sense toward nucleophiles and to undergo favored attack at the aldehyde group

This report describes the base-catalyzed addition of nitromethane and acetone to the aldehyde group of **2**, and the selective reduction of the resulting adducts Attempts to introduce a dimethylamino group at C-4 of **2** were unsuccessful

DISCUSSION

The unsaturated aldehyde **2** used in this work was obtained by the photochemical route[5] A crystalline derivative of the aldehyde was conveniently obtained by treating it with 1,2-bis(anilino)ethane[7] to give the imidazolidine derivative **3**, deacetylation of the latter by the Zemplén method gave the crystalline 2,3-diol analog **4** N m r spectral data for these and other products are recorded in Table I, the shift of the H-6 signal from its low-field position in the spectrum of the aldehyde **2** to about τ 4 45 in those of the imidazolidine derivatives **3** and **4** is noteworthy The base peak in the mass spectra of **3** and **4** (see Table II) was the diphenylimidazolium cation (*m/e* 223) arising by rupture of C-4–C-5



Treatment of the aldehyde **2** with nitromethane in methanol containing ~20 mM sodium methoxide, according to the general procedure described by Baer[8], gave a mixture that, upon treatment with acetic anhydride in pyridine, gave one major product, obtained pure in 63% yield as a pale-yellow syrup after column chromatography This product was formulated as the conjugated, unsaturated, nitro diene

derivative **5**, based on the evidence of microanalysis, i r. and n m r spectroscopy, and mass spectrometry Its n m r spectrum (see Table I) showed that two acetate groups were present, and an AB pair of doublets at low field was indicative of vinylic protons at C-6 and C-7, probably in *cis*-disposition ($J_{6,7}$ 13 Hz) The mass spectrum (see Table II) showed a small parent ion (*m/e* 301) and the fragmentations anticipated from loss of OMe, CH_2CO, and CH_3CO_2H, together with fragments arising through loss of the $-CH=CHNO_2$ group Presumably, the initial adduct of **2** with nitromethane underwent spontaneous dehydration to some extent, and complete elimination occurred upon exposure to the conditions of acetylation, to give **5** Dehydroacetoxylation of a nitromethane adduct by the action of acetic anhydride and pyridine has been reported[9]

When the aldehyde **2** was treated with nitromethane in the presence of triethylamine, only one product was obtained, isolated as a syrup in 81% yield after purification on a column of silica gel It was formulated as the initial adduct **1**, and probably consisted of a mixture of epimers at C-6 Its n m r spectrum showed that two acetoxyl groups were present, and the molecular ion (*m/e* 319) in its mass spectrum was 18 daltons higher than that of the elimination product **5** Compound **1** was readily dehydroacetoxylated by the action of acetic anhydride in pyridine, and the product obtained was identical with the nitro diene **5**

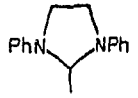
When the aldehyde **2** was brought into reaction with acetone in the presence of methanolic sodium methoxide, and the product then treated with acetic anhydride and pyridine, the conjugated dienone **7** having a 9-carbon sugar structure was obtained Compound **7**, obtained as a syrup in 77% yield, showed a molecular-ion peak (*m/e* 298), and its n m r spectrum (see Table I) showed the signals anticipated for the OMe, COMe, and two acetoxyl groups, together with a low-field AB pattern for the olefinic protons H-6 and H-7 ($J_{6,7}$ 15 Hz) Attempts to prepare **7** from **2** by using triethylamine as catalyst, instead of sodium methoxide, were unsuccessful, even when the reaction time in the boiling solvent was extended to several hours

Several attempts to add dimethylamine to the unsaturated aldehyde **2**, for possible formation of a 4-deoxy-4-(dimethylamino) sugar, were unsuccessful The failure of **2** to undergo Michael-type reactions at C-4 is understandable on the basis of electronic hindrance by the ring-oxygen atom attached to C-5 Attack by a nucleophile at C-4 would involve development of negative charge at C-5, a process rendered unfavorable by the presence of an oxygen atom attached to C-5

Treatment of the nitro diene **5** with ethanolic sodium borohydride gave rise to two major products, which were separated by column chromatography The faster-migrating product was obtained as a syrup in 35% yield and was formulated as the selectively reduced product **6** in which the exocyclic double bond had been reduced The slower-migrating product, obtained as a syrup in 21% yield, appeared from its n m r spectrum to have a dimeric structure (see Experimental section) When the reduction was conducted in aqueous acetonitrile, the selectively reduced product **6** was obtained in 70% yield, and the proportion of dimer resulting was decreased to 10% The mass spectrum of **6** showed the molecular ion (*m/e* 303) and a series of

TABLE I

N M R. SPECTRAL DATA[a] FOR THE C-5-SUBSTITUTED METHYL 2,3-DI-*O*-ACETYL-4 DEOXY-1-*threo*-PENT-4-ENOPYRANOSIDES 1–8

Compound	*Substituent at C-5*	*Chemical shifts,*[b] *τ units (first-order couplings in Hz)*								
		H-1	*H-2*	*H-3*	*H-4*	*H-6*	*H-7*	*OMe*	*OAc*	*Other*
1	$-CHOHCH_2NO_2$	———		4 46–5 55m			———	6 45s, 6 46s	7 86s, 7.90s	
2[c]	-CHO	4 72———	4.90m $J_{2,3}$ 9	4 30dd $J_{3,4}$ 3	4.09d	0 73s		6 48s	7 88s, 7 89s	
3		4 69bd $J_{1,2}$ 3	4 50bdd $J_{2,3}$ 6 5[d]	4 97dd $J_{3,4}$ 2	5 16d	4 40s		6 76s	7 94s, 7 99s	2 54–2 78m (Ph), 3.02–3 24m (Ph), 6 20bs (CH_2CH_2)
4[e]		4 86d $J_{1,2}$ 3	6 57dd $J_{2,3}$ 7	5.91dd $J_{3,4}$ 2 5	5.34d	4 50s		6 93s		2 60–2 72m (Ph), 3 10–3.30m (Ph), 6 30bs (CH_2CH_2)
5	$-CH=CHNO_2$	———		4 25–4 35m and 4 65–4 78m		2 48d and $J_{6,7}$ 13	2 63d	6 46s	7.90s, 7.92s	
6	$-CH_2CH_2NO_2$	5 04d $J_{1,2}$ 2 5	4 93dd $J_{2,3}$ 7	4 68bdd $J_{3,4}$ 3 5	5 13bd $J_{4,6}$ 1	7 10bt $J_{6,7}$ 7	5 44t	6 45s	7.82s, 7.85s	
7	$-CH=CHCOCH_3$	4 70———	4 81m $J_{2,3}$ ~8	4 38bdd $J_{3,4}$ 3,5	4 58d	3 06d and $J_{6,7}$ 16	3 39d	6 48s	7 86s, 7.89s	7 67s (H-9)
8	$-CH=CHCHCH_3$ | OAc	———	4 48–4 66m and 4 84–5.07m[f]			4 07m $J_{6,7}$ 15	3 93m $J_{7,8}$ ~5	6 44s	7.82s, 7 86s	8.59d (H-9) $J_{8,9}$ 6 5

[a]At 100 MHz in chloroform-*d* [b]b, broadened, d, doublet, dd, doublet of doublets, m, multiplet, s, singlet, t, triplet. [c]Data from ref 5. [d]May be subject to substantial second-order effects [e]*O*-Deacetylated derivative after treatment with D_2O [f]Also includes H-8 signal

TABLE II

MASS-SPECTRAL DATA FOR THE C-5-SUBSTITUTED METHYL 2,3 DI-*O*-ACETYL-4 DEOXY-L *threo* PENT-4 ENOPYRANOSIDES

Fragment	m/e *Values (relative intensities) for compound number*						
	1	**3**	**4**[a]	**5**	**6**	**7**	**8**
$M^{\ddagger}$	319 (0 1)	452 (5)	368 (5)	301 (0 1)	303 (0 1)	298 (0 2)	342 (0 3)
$M^{+}-MeOH$						266 (1)	310 (1)
$M^{\ddagger}-AcOH$	259 (0 1)	392 (0 2)		241 (7)	243 (4)	238 (15)	282 (10)
$M^{\ddagger}-AcOH-CH_2CO$	217 (0 5)			199 (22)	201 (5)	196 (32)	240 (10)
$M^{+}-AcOH-\cdot OMe$		361 (0 1)					251 (12)
$M^{\ddagger}-AcOH-\cdot OAc$		333 (2)			184 (3)		
$M^{\ddagger}-AcOH-CH_2CO-$ OMe					170 (6)	165 (48)	209 (10)
$M^{\ddagger}-\cdot MeOH-$ OAc					212 (2)	107 (15)	
C-5 substituent		223 (100)	223 (100)				
$M^{\ddagger}-AcOH-$C-5 substituent	169 (30)						
$M^{\ddagger}-AcOH-CH_2CO-$C-5 substituent	127 (80)			127 (5)			
Other major ions	74 (100)		291 (1)	168 (20)	85 (15)	180 (15)	225 (10)
			282 (1)	74 (100)	74 (100)	153 (27)	121 (100)
						149 (33)	
						137 (45)	
						113 (50)	
						76 (100)	

[a] *O*-Deacetylated derivative

fragments (see Table II) containing the intact C-5 substituent, all having *m/e* values 2 daltons higher than corresponding ions in the spectrum of the unsaturated precursor **5** The n m r spectrum of **6** (see Table I) clearly established that reduction had taken place at the exocyclic double bond, and not the endocyclic one, the low-field, AB doublet for H-6 and H-7 in the precursor **5** was absent for **6** and was replaced by 2-proton triplets at τ 5 44 and 7 10 that could be assigned to the exocyclic methylene groups, other features in the spectrum of **6** showed little change from those in the precursor **5**

The formation of a dimer accompanying compound **6** in the reduction of the nitro diene **5** probably arises from a Michael type of addition of an anion of **5** to C-6 of a second molecule of **5** The formation of dimeric products in the treatment of conjugated nitroalkenes with sodium borohydride has been reported in the literature[10]

The dienone **7** underwent selective reduction at the ketonic carbonyl group when treated with ethanolic sodium borohydride, and acetylation of the product gave the syrupy 4,6,7,9-tetradeoxynono-4,6-dienose derivative **8** in 75% yield The structure of **8** was evident from its n m r spectrum, which closely resembled that of the precursor **7**, except that the signal for the C-9 methyl group appeared as a doublet, and an additional acetate group was present (see Table I) A molecular-ion peak (*m/e* 342) was observed in the mass spectrum of **8**, together with fragmentation ions (see Table II) in accord with the structure proposed No direct information on the stereochemistry at C-8 of compound **8** was obtained, and the product was probably a mixture of 8-epimers

The foregoing reactions illustrate the considerable potential of unsaturated aldehydes of sugars, such as compound **2**, for the preparative elaboration of higher-carbon sugar derivatives having side-chains possessing synthetically useful functional groups Such products should serve as useful starting points for synthesis of structural variants of antibiotics and their components and, by way of various cyclization reactions, of heterocycles having sugar moieties attached

EXPERIMENTAL

General methods — Solutions were evaporated under diminished pressure below 50° Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected N m r spectra were recorded at 100 MHz with a Varian HA-100 spectrometer by W N Rond, for solutions in chloroform-*d* containing tetramethylsilane as the internal standard Mass spectra were recorded with an AEI MS-902 double-focusing, high-resolution spectrometer at an ionizing potential of 70 eV, an accelerating potential of 8 kV, and a source temperature of 250° T l c was performed with 250-μm layers of Silica Gel G (E. Merck) as the adsorbent and 5 1 benzene–methanol as the developer, and zones were detected by use of 10% sulfuric acid in ethanol Column chromatography was performed on Silica Gel 7734 (E Merck) with an adsorbent·sample ratio of 50–100 1. Microanalyses were performed by W N Rond

*Methyl 2,3-di-O-acetyl-4-deoxy-5-C-(1,3-diphenylimidazolin-2-yl)-β-*L-threo-*pent-4-enopyranoside* (**3**) — A solution of methyl 2,3-di-*O*-acetyl-4-deoxy-β-L-*threo*-hex-4-enodialdo-1,5-pyranoside[5] (**2**, 200 mg) and 1,2-bis(anilino)ethane (230 mg) in toluene (5 ml) was stirred for 2 h at 110° Toluene was removed by evaporation, and ethanol was added, whereupon the product crystallized, yield 240 mg (68%), m p 158–159° An analytical sample was obtained by recrystallization from benzene–petroleum ether (b p 30–60°), m p 159–160°, $[\alpha]_D^{25}$ +175° (*c* 1, chloroform); R_F 0 8, λ_{max}^{KBr} 5 70 (C=O), 5 90 (C=C), 6 24, 6 60, and 14 4 μm (phenyl)

Anal Calc for $C_{25}H_{28}N_2O_6$· C, 66 33, H, 6 23, N, 6 21. Found. C, 66.43, H, 6 37, N, 6 00

*Methyl 4-deoxy-5-C-(1,3-diphenylimidazolin-2-yl)-β-*L-threo-*pent-4-enopyranoside* (**4**) — To a solution of the diacetate **3** (100 mg) in methanol (3 ml) was added 0 1 ml of M methanolic sodium methoxide, and, after 1 h at ~25°, the solution was evaporated Extraction of the residue with acetone, followed by removal of the acetone, gave crystalline **4**, which was recrystallized from acetone–petroleum ether (b p 30–60°), yield 68 mg (84%), m p 132–133°, $[\alpha]_D^{25}$ +82° (*c* 1, chloroform), R_F 0 5, λ_{max}^{KBr} 2 90 (OH), 5 90 (C=C), 6 25, 6 65, and 14 5 μm (phenyl)

Anal Calc for $C_{21}H_{24}N_2O_4$ C, 68 45, H, 6 57, N, 7 60 Found C, 68 16, H, 6 87; N, 7 38

*Methyl 2,3-di-O-acetyl-4,7-dideoxy-7-nitro-*D-glycero (*and* L-glycero)-β-L-threo-*hept-4-enopyranoside* (**1**) — To a solution of the aldehyde **2** (200 mg) in nitromethane (3 ml) was added triethylamine (0 1 ml), and the mixture was stirred for 1 h at ~25° T l c of the mixture showed conversion of the reactants into a product giving a single, major spot The mixture was evaporated, the resulting syrup was extracted with benzene, and the extract was purified on a column of silica gel Elution with 8 1 benzene–ether gave the chromatographically homogeneous nitro derivative **1** as a pale-yellow syrup, yield 200 mg (81%), $[\alpha]_D^{25}$ +213° (*c* 1, chloroform), R_F 0 4, λ_{max}^{film} 2 85 (OH), 5 70 (C=O), and 6 35 μm (C–NO_2)

*Methyl 2,3-di-O-acetyl-4,6,7-trideoxy-7-nitro-*cis-β-L-threo-*hepto-4,6-dienopyranoside* (**5**) — *A From the aldehyde* **2** To a solution of the aldehyde **2** (250 mg) in methanol (2 ml) were added nitromethane (2 ml) and M methanolic sodium methoxide (0 1 ml), and the mixture was stirred for 2 h at ~25° The mixture was then evaporated, and the residue extracted with acetone Evaporation of the extract gave a syrup consisting of several components (t l c) Pyridine (3 ml) and acetic anhydride (0 2 ml) were added to the syrup, and the mixture was kept for 18 h at ~25° Concentration of the mixture afforded a dark syrup that was extracted with benzene The extract was purified on a column of silica gel, and the chromatogaphically homogeneous title-compound was eluted with 14 1 benzene–ether to give a syrup, yield 175 mg (63%), $[\alpha]_D^{25}$ +253° (*c* 0 9, chloroform), R_F 0 75, λ_{max}^{film} 5 70 (C=O), 6 0 (C=C), and 6 50 μm (C–NO_2)

Anal. Calc for $C_{12}H_{15}NO_8$ C, 47 84; H, 5 01, N, 4 64 Found C, 47 81, H, 4 98, N, 4 43

B From the 6-hydroxy-7-nitro derivative **1** To a solution of **1** (180 mg) in pyri-

dine (3 ml) was added acetic anhydride (0 1 ml), and the mixture was kept for 18 h at ~25°. The syrupy product obtained after evaporation and purification by column chromatography was found by t l c and n m r spectroscopy to be identical with 5 prepared by the foregoing route *A*

*Methyl 2,3-di-O-acetyl-4,6,7,9-tetradeoxy-β-*L-threo-*nono-4,6-dienopyranosid-8-ulose* (**7**) — To a solution of the aldehyde **2** (280 mg) in acetone (5 ml) was added M methanolic sodium methoxide (0 1 ml), and the mixture was boiled for 2 h under reflux The solid that had precipitated was filtered off and the filtrate was evaporated Acetylation of the resultant syrup as described for conversion of **1** into **5**, with subsequent purification on silica gel with 14 1 benzene–ether as eluant, gave chromatographically homogeneous **7**, yield 250 mg (77%), $[\alpha]_D^{25}$ +263° (*c* 1 3, chloroform), R_F 0 5, λ_{max}^{film} 5 70 (C=O) and 5 95 μm (C=C)

*Methyl 2,3-di-O-acetyl-4,6,7-trideoxy-7-nitro-β-*L-threo-*hept-4-enopyranoside* (**6**) — To a solution of the nitro derivative **5** (220 mg) in ethanol (5 ml) was added sodium borohydride (50 mg) The mixture was stirred for 10 min at ~25°, and then 10% acetic acid was added to decompose the excess of the reductant Evaporation of the mixture, extraction of the residue with acetone, and evaporation of the extract gave a syrup that, by t l c, showed a main component (R_F 0 7) and a substantial proportion of a side-product (R_F 0 5) Dissolution of the syrup in benzene, and purification on a column of silica gel with 14 1 benzene–ether as eluant, gave the syrupy, chromatographically homogeneous, title compound, yield 77 mg (35%), $[\alpha]_D^{25}$ +230° (*c* 1 2, chloroform)

Further elution of the column, with 3 1 benzene–ether, gave a second, syrupy product, possibly a dimeric adduct, yield 46 mg (21%), $[\alpha]_D^{25}$ +225° (*c* 0 8, chloroform); n m r (60 MHz) τ 6 44, 6 50 (3-proton singlets, nonequivalent OMe), 7 90, 7 92, 7 93 (3 singlets, 12 protons, 4 OAc groups)

In a second experiment, the diene precursor **5** (60 mg) in 1 1 (*v*/*v*) acetonitrile–water (4 ml) was treated with sodium borohydride (20 mg), and, after 5 min at ~25°, the mixture was processed as just described, the yield of **6** was 42 mg (70%), and of the slower-migrating side-product, 6 mg (10%)

*Methyl 2,3,8-tri-O-acetyl-4,6,7,9-tetradeoxy-*D-glycero(*and* L-glycero)-*β-*L-threo-*nono-4,6-dienopyranoside* (**8**) — To a solution of the ketone **7** (400 mg) in ethanol (10 ml) was added sodium borohydride (45 mg), and the mixture was stirred for 15 min at ~25°. The solution was made neutral with 10% acetic acid, and then evaporated The residue was extracted with acetone, and the extract was evaporated Acetylation and chromatographic purification of the product with 14 1 benzene–ether, as described for the conversion of **1** into **5**, gave chromatographically homogeneous **8** as a pale-yellow syrup, yield 300 mg (75%); R_F 0.6, $[\alpha]_D^{25}$ +194° (*c* 0 9, chloroform), λ_{max}^{film} 5 75 (C=O) and 6 0 μm (C=C)

Treatment of the unsaturated aldehyde **2** *with dimethylamine* — A mixture of **2** (120 mg), dimethylamine (0 3 ml), and M sodium methoxide (0 1 ml) in methanol was kept for 18 h at ~25°. Evaporation of the solution gave a syrup that was identical, by i r spectrum and t l c properties, with the *O*-deacetylated derivative of **2** In a

second experiment, the aldehyde **2** (0 45 g) in benzene (3 ml) containing dimethylamine (2 ml) was kept for 18 h at ~25° T l c of the reaction mixture showed the presence of several spots, but *O*-deacetylation with sodium methoxide gave a syrup that contained, by t l c evidence, one major product that appeared identical with the product of the first experiment A similar result was obtained when a mixture of **2** (0 5 g) and dimethylamine (2 ml) was kept in a sealed tube for 3 days at ~25° and for an additional 5 h at 60°

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