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Carbohydrate-Derived Partners Display Remarkably High Stereoselectivity in Aldol Coupling Reactions[1]

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Abstract

Aldol condensation between 3-keto and aldehyde sugars have been studied The enolate **3** reacts with aldehydes preferentially from the β-face to give axial C2 condensation products However, if the reaction conditions are not controlled properly some C2 epimerization may be observed With respect to the aldehyde partner, facial selectivity can be predicted on the basis of the preferred, permissible chelation pattern Thus α/β chelation (which occurs whenever possible) produces Cram products, while α-chelation produces anti-Cram products For the major (C2-axial) products, the stereochemistry around the newly forged C2-C7 bond can be determined by the magnitude of $J_{2,7=}$ 8-10 Hz for the C7-(S) condensation product, and ~5 Hz for the C7-(R) analogue

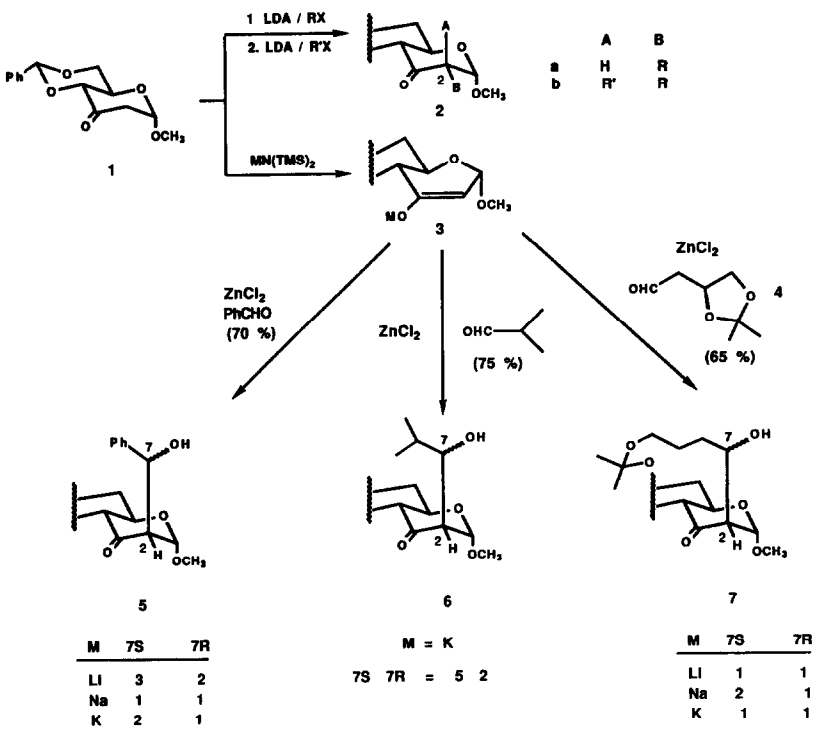
The C3-carbonyl group of the aldol products can be reduced with DIBAL and $LiALH_4$ to give products bearing equatorial and axial C3-OH groups, respectively On the other hand, $LiBHEt_3$ gives axial alcohols only The ease of formation of an isopropylidene ring between the equatorial C3-OH and C7-OH can be used to deduce the C7 orientation For example, with the C7-(R) isomer **25** (eq), an isopropylidene ring was readily formed whereas for the C7-(S) analogue **28,** ring formation was not observed

Among the many objectives of synthetic organic chemistry, the formation of carbon-carbon bonds efficiently with good, and preferably predictable, stereocontrol is one of the most important In the last decade, advances in the areas of carbohydrate manipulations[3] and aldol methodology[4] have contributed significantly to this objective The factors governing the stereochemical preferences exhibited in both areas, even where shrouded in controversy, can be exploited to great advantage Therefore, we have been interested in applying the aldol reaction to carbohydrate ketones[5] in hope of developing a convergent strategy for the efficient preparation of arrays with multiple contiguous chiral centers as an alternative to the linear strategy that we have described as pyranosidic homologation [6]

In view of the striking selectivities that have emerged in aldol methodology,[4] the proposed application would be viable only if the carbohydrate partner offered special attributes In this connection, ready NMR proof of structure is a valuable attribute of most carbohydrate derivatives, and it was conceivable that this would be true for the proposed aldol products In this manuscript, we report some of our recent observations

Methyl 4,6-O-benzylidene-2-deoxy-α-D-erthryo-hexopyranosid-3-ulose, **1** is a readily prepared keto sugar[7] and studies in our laboratories[8] and Chapleur's[9] have established that the methoxy group of **1** is remarkably resistant to base catalyzed β-elimination (*vide infra*) Thus, the

Scheme 1



methoxyl group survived direct monoalkylation to give products, such as **2a**, and even dialkylation to give **2b** [10] The fact that sequential alkylations led to structure **2b**, in which the second electrophile is axially oriented, implies that the preferred site for electrophilic attack is from the β-face, and that formation of the monoalkylation product **2a** was due to *in situ* epimerization at C2

The last observation is consistent with steric approach control in that the anomeric methoxyl impedes attack from the α-face of the corresponding enolate **3** Hence, an aldol condensation would be expected to give the C-2 axial adduct as the product of kinetic control If the aldehyde partner also showed good stereoselectivity, double asymmetric induction[11] should

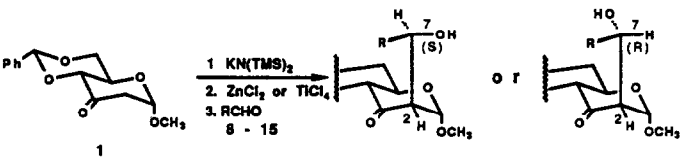
result, which in the ideal setting of a matched pair of reactants,[12] would lead to a single aldol diastereomer with predictable stereochemistry around the newly forged bond

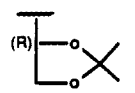
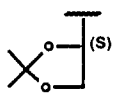
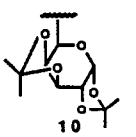
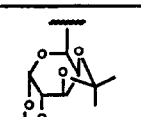
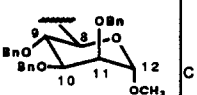
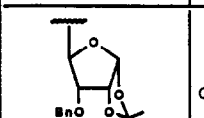
In the early stages of this study,[5] benzaldehyde, isobutyraldehyde, and the 2-deoxy tetrose, **4**,[13] were used to determine the facial selectivity preferences of the enolate **3** The aldol products **5-7** were obtained in good yields (Scheme 1) as the only C-2 isomers, results which fulfilled the expectation for preferential attack from the β-face It was also gratifying to note that under the reaction conditions, *in situ* C-2 epimerization was not occurring, as it did in the aforementioned alkylations [9,10]

The selectivity at C-7 was poor in the products **5-7**, and on the basis of ample precedents,[11,12] it was assumed that improvement would require moving the chiral center closer to the aldehydo group Therefore, the (R) and (S) O-isopropylidene glyceraldehydes **8** and **9**[14] were tested and found to give the diastereomers **16** and **17**, respectively [Table 1, entries (i) and

Table 1

Some Aldol Condensation Reactions of **1**



Entry	Aldehyde Partner R=	Aldol Product	$J_{2,7}$
(i)	 8	16 C 7(S)	10 0 Hz
(ii)	 9	17 C 7(R)	5 5 Hz
(iii)	 10	18 C-7(R)	5 6 Hz
(iv)	 11	19a C 7(S)	9 0 Hz
		19b C 7(R)	4 6 Hz
(v)	 12	20 C-7(S)	11 0 Hz
(vi)	 13	21 C 7(S)	11 3 Hz
(vii)	 14	22 C-7(S)	10 8 Hz
(viii)	 15	23 C 7(S)	8 1 Hz

(ii)] However, if the reaction conditions were not properly controlled, some epimerization occurred at C-2 to give, for example, 2-epi-**16**, (*vide infra*) Extending the spectrum of substrates to the sugar aldehydes **10-15**[15] gave similarly excellent selectivities, the major products being **18-23**, respectively Table 1 [entries (iii)-(viii)]

With respect to proof of structure of the aldol products, the C-2 orientation was immediately apparent from the value $J_{1,2}$=~0 Hz, observed in all products, **16-23** As expected, the C-7 orientation was more problematic, so for the test cases **16** and **17**, we resorted to X-ray analysis

Proof by X-Ray Analysis

Compound **17** gave a satisfactory X-ray analysis (Fig 1), but compound **16** did not The latter was therefore reduced with DIBAL (*vide infra*) and the resulting crystalline diol, **24(eq)** was analyzed (Fig 2) The C-7 centers in **16** and **17** were thereby established to be (S) and (R), respectively

Figure 1

X-Ray Crystal Structure of Compound **17**

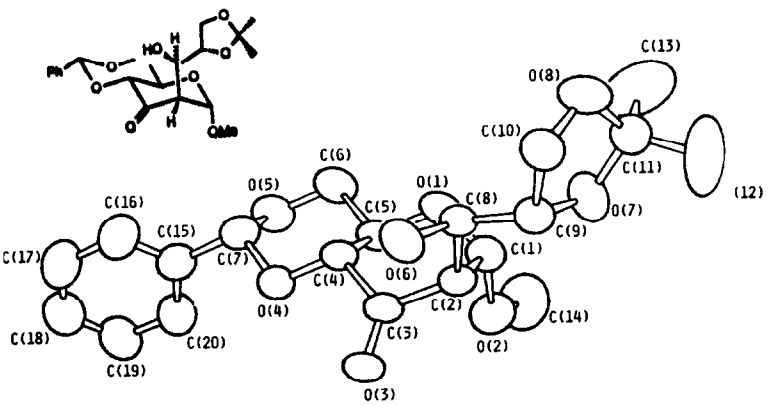
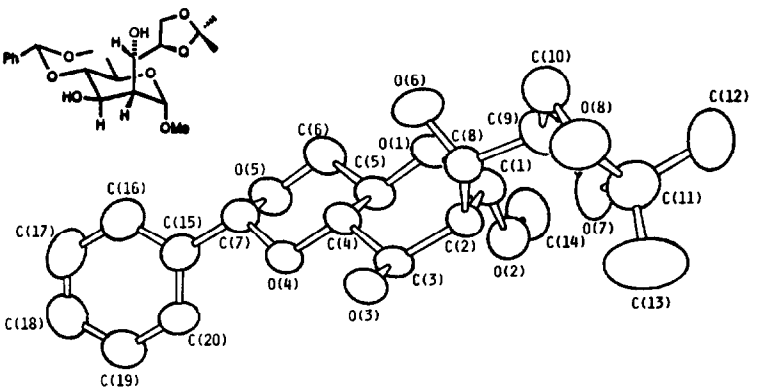


Figure 2

X-Ray Crystal Structure of Compound **24(eq)**



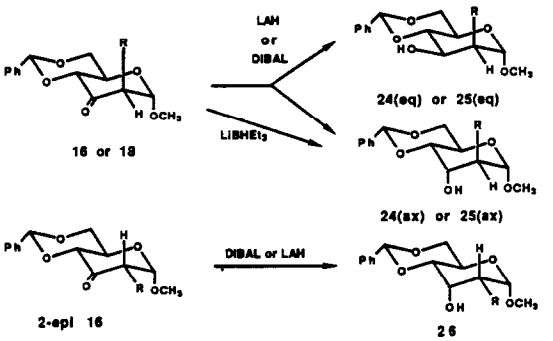
Proof by Chemical Transformations

In the foregoing section it was reported that reduction of **16** with DIBAL gave **24(eq)** having the C3-OH in equatorial orientation [Table 2, entry (i)] On the other hand, we found that

with $LiAlH_4$ the C3 epimer, **24(ax)**, was formed predominantly [Table 2, entry (ii)]. This trend turned out to be general. Thus, in the case of **18**, reduction with DIBAL in CH_2Cl_2 gave **25(eq)** and **25(ax)** in 5:2 ratio, and with THF as solvent the ratio improved to 12:1 [Table 2, entries (v) and (vi)]. However, with $LiAlH_4$, the selectivity was reversed, the ratio being 2:3 [Table 2, entry (vii)].

Table 2

Hybride Reduction of Aldol Products



Entry	Aldol	Reducing Agent	Solvent	Major Product	C3-OH eq. : ax.
(i)	16	DIBAL	CH_2Cl_2	24(eq)	9 : 1 [a]
(ii)	16	LAH	THF	24(ax)	1 : 11 [a]
(iii)	2-epi 16	DIBAL	CH_2Cl_2	26	0 : 100 [a]
(iv)	2-epi 16	LAH	THF	26	0 : 100 [a]
(v)	18	DIBAL	CH_2Cl_2	25(eq)	5 : 2 [b]
(vi)	18	DIBAL	THF	25(eq)	12 : 1 [b]
(vii)	18	LAH	THF	25(ax)	2 : 3 [b]
(viii)	18	$LiBHEt_3$	CH_2Cl_2	25(ax)	0 : 100 [c]
(ix)	18	$LiBHEt_3$	THF	25(ax)	0 : 100 [c]

a) This ratio is based on the isolated yield.

b) This ratio was measured by the ^{1}H-NMR spectrum of the crude products.

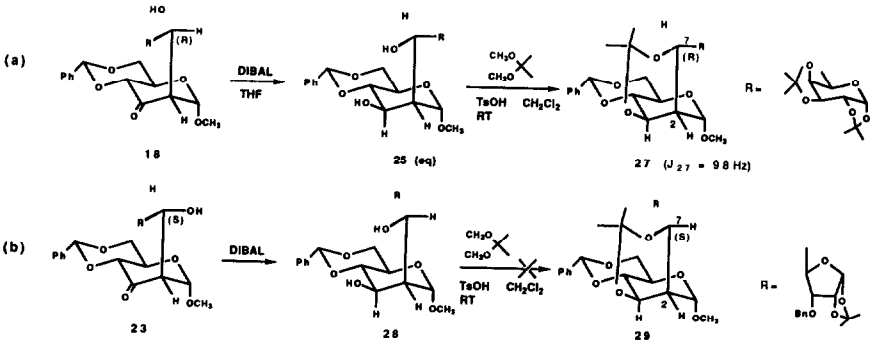
c) The 3-eq. isomer was not detected by ^{1}H NMR and TLC in the crude product.

Entries (viii) and (ix) show that use of $LiBHEt_3$ gave **25(ax)** exclusively, in keeping with trends normally observed with this reagent.

The results in entries (iii) and (iv) are in sharp contrast to those in entries (i) and (ii). Thus, reduction of **2-epi-16** (obtained by treating **16** with sodium methoxide) with either DIBAL or $LiAlH_4$ gave **26(ax)** only.

Given the stereochemical course normally observed in reductions of C3-trigonal centers,[16] the results shown in entries (i), (v), and (vi) must be judged to be abnormal These stereochemical outcomes may be rationalized by assuming that DIBAL coordinates with the glycosidic methoxy group and delivers the hydride ion at C3 However, with **2-epi-16**, the C2-equatorial substituent causes unfavorable steric interactions, and β-face approach leading to **26** is therefore preferred

Scheme 2



The results in Table 2 suggested a simple procedure for determining C7-configuration *via* isopropylidination of the C3 and C7 hydroxyl groups This is illustrated in Scheme 2, where these hydroxyl groups are presented in the ideal orientations for acetonation In the case of **25(eq)**, the bulky substituent, R, is ideally oriented away from the pyranosidic ring, however, in the case of **28**, the bulky substituent experiences severe interactions with the pyranosidic ring Therefore, the latter should undergo isopropylidination less readily and this was indeed observed Thus, diol **25(eq)** reacted readily with dimethoxypropane in the presence of para-toluene sulfonic acid to afford the acetonide **27**, which showed the value $J_{2,7}$=9 8 Hz This parameter indicated the C2 and C7 hydrogens were in antiperiplanar orientation, and on this basis, the C7 figuration of **18** was assigned as (R)

In contrast, diol **28** did not undergo acetonide formation This adverse result was expected, since models showed clearly that the acetonide **29** would be strongly destabilized by interactions between the furanose and pyranose rings Thus, these data can be used to establish the C7 orientation

Proof by ^{1}H NMR Analysis

In keeping with statements in the introduction, it was our hope that the C7 configuration could be assigned by simple NMR methods Thus, it was interesting to note that in the products that had been assigned by X-ray and on the basis of acetonide formation, the value, $J_{2,7}$ was 8-10 Hz for the C7-(S)-isomers **16** and **23**, but much smaller (~5 Hz) for the C7-(R)-analogs **17** and **18** These parameters implied that the major rotamer populations for the (R) and (S) aldol products were those depicted in Table 1 and, by corollary, that the magnitude of $J_{2,7}$ in the aldol

products could be used for C7 assignments On the basis of these criteria, the C7 configurations of the remaining aldol products **19-22** in Table 1 were assigned

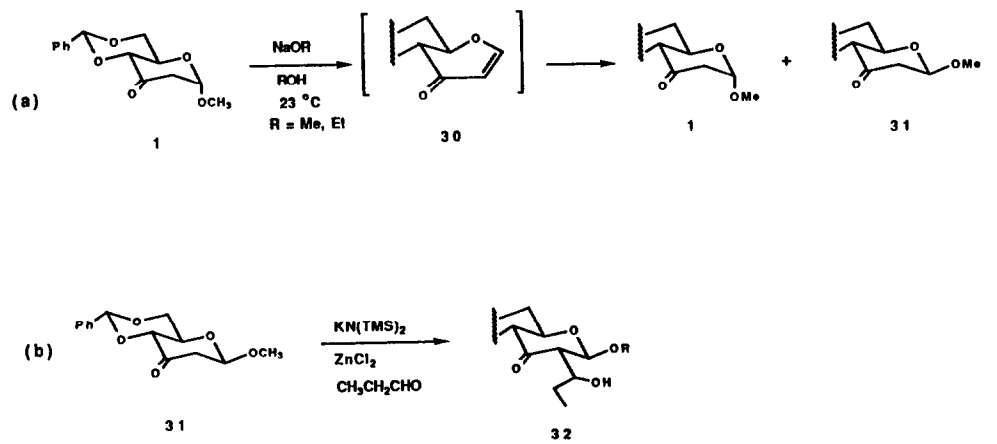
Independent evidence supporting these structural assignments for **20** and **21** came from the benzylidene methine proton chemical shifts These signals were detected at 5 3 ppm in both cases, instead of 5 6 ppm, as in ketone **1** and the aldol products Chemical models suggested that this upfield shift of 0 3 ppm was due to anisotropic shielding by the aromatic ring at C9 of **20** and **21** (see numbering in Table 1) Consistent with this conclusion was the observation that in the corresponding azido derivative **22**, the benzylidene methine proton resonated at the normal frequency, 5 6 ppm

The results observed for the aldol reactions shown in Table 1 indicate high facial selectivities for both partners With respect to the enolate **3**, it appears that steric hindrance by the glycosidic -OCH_3 is responsible for the β-face addition at C2 Two questions therefore arise (i) How resistant is the -OCH_3 to β elimination, and (ii) what would be the stereoselectivity of the β anomer?

With regard to (i), we have confirmed the findings of Horton and Weckerle[7b] that treatment of **1** with sodium methoxide in methanol (Scheme 3a) at room temperature gives a ~1 1 mixture of **1** and **31**, the intermediate being undoubtedly the vinylogous lactone **30**

In the aldols, as in the alkylations,[9,10] the anomeric center of **1** retains its configurational integrity and there is no evidence of **30**, a known type of compound,[17] after work-up However, if the aldol reactions were carried out at 0°C instead of -78°C, appreciable amounts of **30** were obtained It therefore appears that the anomerization is temperature dependent Even so, enolate **3** seems remarkably stable to β elimination, and this may be attributed to strengthening of the C1-O bond due to the *exo*-anomeric effect [18] Notably, the n-σ* delocalization (*y*) depicted in Fig 3 opposes the β-elimination pathway (*x*)

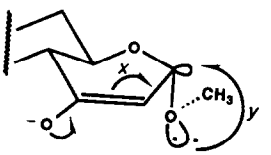
Scheme 3



Question (ii) was tested by carrying out the aldol condensation of ketone **31** with propanal (Scheme 3b). Under the standard conditions, the major product was the C2-equatorial adduct **32** ($J_{1,2}$ = 8.2 Hz) obtained as a single diastereomer of undetermined C7-configuration.

The aldehydes in Table 1 also exhibit diastereofacial selectivities and the results can be correlated with the orientation of their α- and/or β-alkoxy substituents. Thus, three types of metal chelation with these alkoxy aldehydes can be envisaged: α, β, and α/β.[14,19] Aldehydes **8-11** (Table 1) gave Cram products predominantly, and these results are consistent with α/β chelation (c.f. **33**) which promotes addition from the *re*-face of the aldehydo group. On the other hand aldehydes **12-15** experience α chelation leading to *si*-face addition, which affords anti-Cram products.

Figure 3



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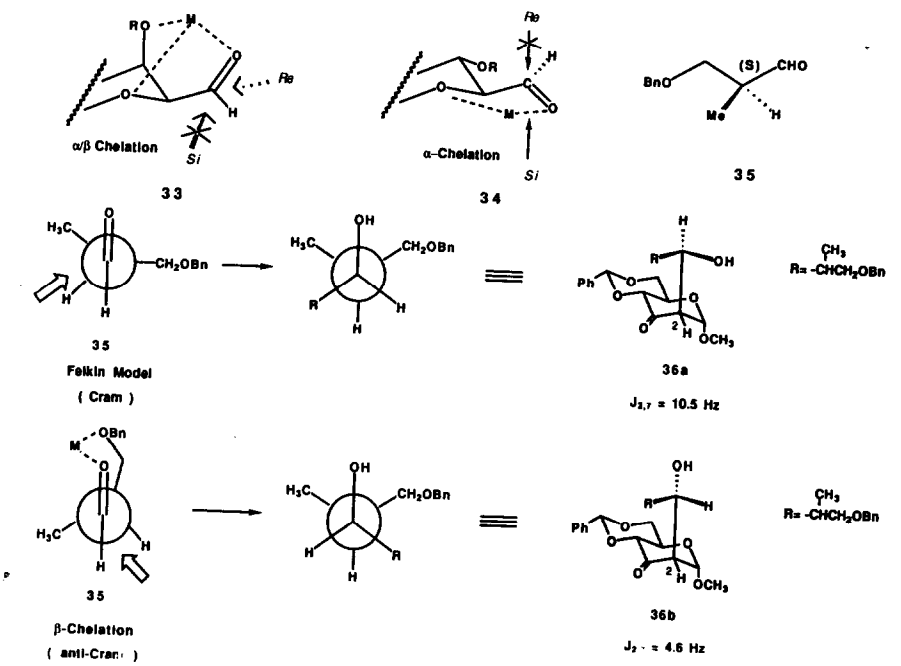
Scheme 4



α-Chelation, shown in **34**, favors attack from the *si*-face, and the work of Frye and Eliel[19] suggests that α chelation is more important than β chelation To test this concept, we have reacted the uloside **1** with the (S)-3-benzyloxy-2-methyl propanal **35**,[20] which is capable only of β–chelation Of the two possible products, **36a** and **36b** (Scheme 4), the former arises from Cram-Felkin selectivity, while the latter is consistent with β-chelation These were present in 2 3 ratio, judging from the values for $J_{2,7}$, 10 5 and 4 6 Hz, respectively Thus, very little selectivity was observed

In conclusion, the above results show that sugars can be connected in a stereoselective manner by aldol condensations The enolate **3** reacts preferentially from the β-face to give axial substitution at C2, although if the reaction conditions are not controlled properly, some epimerization may be observed With respect to the aldehyde partner, facial selectivity can be predicted on the basis of the preferred, permissible chelation pattern Thus, α/β chelation (which occurs whenever possible) produces Cram products, while α-chelation produces anti-Cram products The C3-carbonyl group of the aldol products can be reduced with DIBAL and $LiAlH_4$ to give products bearing equatorial and axial C3-OH groups, respectively On the other hand, $LiBHEt_3$ gives axial alcohols only The ability to rapidly assemble arrays such as **25** with 11 continuous chiral centers is a promising development that is currently being pursued in our laboratory

Experimental Section

Melting points were determined in capillary tubes using a Buchi Model 510 apparatus and are uncorrected Elemental analyses were performed by M-H-W laboratories (Phoenix, Arizona) The specific rotation were measured with at 589 nm (Na D-line) Flash Column chromatography was effected on silica gel (Merck 230-400 mesh A S T M) and ^1H NMR spectra were recorded for solution in $CDCl_3$ ($CHCl_3$ at 7 24 ppm was used as standard) at 300 MHz IR spectrum was recorded with Perkin Elmer 297 infrared spectrometer CI-mass spectrum were performed by Dr George R Dubay at Duke University using ammonia as an ion source

General Procedure for Aldol Reactions of Methyl 4,6-O-Benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose, 1 To a cooled (-40°C) solution of the uloside (**1**) (1 32 g, 5 mmol), in dry THF (50 mL), sodium bis(trimethylsilyl) amide (1 M solution in THF) or potassium bis(trimethylsilyl)amide (0 65 M solution in toluene) (6 5 mmol) was added rapidly The pale yellow solution was stirred at that temperature for 30 min, and then cooled to -78°C To this cooled solution 1M $ZnCl_2$ solution in Et_2O (6 5 mmol) was added and the resulting solution was stirred for 15 minutes The aldehyde (6 5 mmol) was then added in one portion and the reaction mixture was stirred at -78°C for 0 5 hr, and then allowed to warm slowly to -40°C After the reaction was complete (1 5 ~2 hr), saturated aqueous ammonium chloride solution (15 mL) was added at -40°C The reaction mixture was diluted with ethyl acetate (20 mL), the two phases separated, and the aqueous layer extracted with EtOAc (3 x 15 mL) The combined organic layers were dried over anhydrous $MgSO_4$ and solvent removed *in vacuo* to yield the crude product

Aldol Reaction with Benzaldehyde The crude product obtained from benzaldehyde (0 65 mL, 6 5 mmol), as described in the General Procedures, was purified by flash chromatography (petroleum ether ethyl acetate 1 1), to give recovered **1** (0 15 g, 11%) and a crystalline solid (1 30 g, 79% yield) Small amounts of each epimer were obtained by fractional crystallization (CH_2Cl_2-petroleum ether)

7(S)-**5** : mp 190-192°C, $[\alpha]_D$ +20° (*c* 0.26, CH_2Cl_2), ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (b s, 1H, OH), 3.09 (d, $J_{2,7}$=7.3 Hz, 1H, 2-H), 3.30 (s, 3H, OCH_3), 3.94 (t, $J_{5,6}$=$J_{6,6}$=10.1 Hz, 1H, 6-Ha), 4.17 (dt, $J_{4,5}$=4.7, $J_{5,6}$=10.1 Hz, 1H, 5-H), 4.37 (dd, $J_{5,6}$=4.7, $J_{6,6}$=10.1 Hz, 1H, 6-He), 4.39 (d, 1H, $J_{4,5}$=10.1 Hz, 4-H), 5.05 (d, $J_{2,7}$=7.3 Hz, 1H, 7-H), 5.16 (s, 1H, 1-H), 5.54 (s, 1H, benzylidene H), 7.26-7.40 and 7.40-7.49 (m, 10H, aromatic H's). MS, m/e 388 (M+ NH_4^+).

Anal. Calcd for $C_{21}H_{22}O_6$: C,68.08 ; H,5.99. Found: C, 67.96; H, 5.83.

7(R)-**5** : mp 172-174°C, $[\alpha]_D$ -38.7° (*c* 0.32, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (b d, J= 3.7 Hz, 1H, OH), 3.06 (d, $J_{2,7}$=10.0 Hz, 1H, 2-H), 3.23 (s, 3H, OCH_3), 3.99 (t, $J_{5,6}$=$J_{6,6}$=10.0 Hz, 6-Ha), 4.16 (dt, $J_{5,6}$=4.6, $J_{5,6}$=10.0 Hz, 1H, 5-H), 4.38 (dd, $J_{5,6}$=4.6, $J_{6,6}$=10.0 Hz, 1H, 6-He), 4.57 (s, 1H, 1-H), 4.66 (d, 1H, $J_{4,5}$=10.0 Hz, 4-H), 5.03 (dd, $J_{7,OH}$=3.7, $J_{2,7}$=10.0 Hz, 1H, 7-H), 5.63 (s, 1H, benzylidene H), 7.31-7.41 and 7.48-7.55 (m, 10H, aromatic H's).

Anal. Calcd for $C_{21}H_{22}O_6$: C,68.08 ; H,5.99. Found: C, 67.91; H, 5.85.

Aldol Reaction With Isobutyraldehyde. The reaction was carried out as described above except that 2 equivalents of isobutyraldehyde was used. A mixture of two diastereoisomers, 7-(S)-**6** and 7-(R)-**6** (5:2) was obtained in 75% yield. The mixture was fractionated by flash chromatography (Et_2O:petroleum ether=2:1) to give pure compounds.

7-(S)-**6**: mp 134-135°C, $[\alpha]_D$ +23.4° (*c* 1.08, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, $J_{8,9}$=6.6 Hz, 3H, 9-CH_3), 0.99 (d, $J_{8,9}$=6.9 Hz, 3H, 9-CH_3), 1.59-1.77 (m, 1H, 8-H), 2.90 (d, $J_{2,7}$=6.4Hz, 1H, 2-H), 3.35 (s, 3H, OCH_3), 3.69-3.75 (m, 1H, 7-H), 3.91 (t, $J_{5,6}$=$J_{6,6}$=10.2 Hz, 6-Ha), 4.12 (dt, $J_{5,6}$=4.6, $J_{4,5}$=$J_{5,6}$=10.1 Hz, 1H, 5-H), 4.35 (dd, $J_{5,6}$=4.7, $J_{6,6}$=10.2 Hz, 1H, 6-He), 4.62 (d, 1H, $J_{4,5}$=10.0 Hz, 4-H), 4.88 (s, 1H, 1-H), 5.58 (s, 1H, benzylidene H), 7.30-7.38 and 7.45-7.52 (m, 5H, aromatic H's). MS, m/e 354 (M+ NH_4^+).

Anal. Calcd for $C_{18}H_{24}O_6$: C,64.27; H,7.19. Found: C,63.94 ; H, 7.29 .

7-(R)-**6**: mp 140-142 °C, $[\alpha]_D$ +28.4° (*c* 0.74, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, $J_{8,9}$=6.8 Hz, 3H, 9-CH_3), 0.99 (d, $J_{8,9}$=6.8 Hz, 3H, 9-CH_3), 1.52-1.70 (m, 1H, 8-H), 2.83 (d, $J_{2,7}$=8.8 Hz, 1H, 2-H), 3.37 (s, 3H, OCH_3), 3.83 (b dd, $J_{7,8}$=2.7, $J_{2,7}$=8.8 Hz, 1H, 7-H), 3.91 (t, $J_{5,6}$=$J_{6,6}$=10.1 Hz, 1H, 6-Ha), 4.15 (dt, $J_{5,6}$=4.6, $J_{4,5}$=$J_{5,6}$=10.1 Hz, 1H, 5-H), 4.26 (d, 1H, $J_{4,5}$=10.1 Hz, 4-H), 4.37 (dd, $J_{5,6}$=4.6, $J_{6,6}$=10.1 Hz, 1H, 6-He), 5.21 (s, 1H, 1-H), 5.57 (s, 1H, benzylidene H), 7.30-7.44 and 7.44-7.52 (m, 5H, aromatic H's).

Anal. Calcd for $C_{18}H_{24}O_6$: C,64.27; H,7.19. Found : C, 64.43; H, 7.36.

Aldol Reaction With 3-(S)-3,4-Dihydroxy-3,4-O-Isopropylidene butyraldehyde (4). The general procedure for the aldol was followed using 0.132 g of the uloside **1** (0.5 mmol) and 0.9 ml of 0.65 M solution in toluene (0.6 mmol), the aldehyde **4**[13] (0.087 g, 0.6 mmol), 0.6 mL of the 1M zinc chloride solution in Et_2O. The crude product was purified by flash chromatography (ethyl acetate:petroleum ether = 2:3) to give 70 mg (35%) of each diastereoisomer. In addition, some starting material (25 mg) was recovered.

7-(R)-**7**: $[\alpha]_D$ +13.6° (*c* 1.72, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 and 1.41 (s, 3H ea, isopropylidene CH_3), 1.56-1.68 (m, 2H, 8-H), 2.69 (d, $J_{2,7}$=8.8 Hz, 1H, 2-H), 3.37 (s, 3H, OCH_3), 3.55 (dd, $J_{9,10}$=7.0, $J_{10,10}$=8.3 Hz, 1H, 10-H), 3.90 (d, J=10 Hz, 1H, OH), 3.92 (t, $J_{5,6}$=$J_{6,6}$=10.2 Hz, 1H, 6-Ha), 4.08 (dd, $J_{9,10}$=6.1, $J_{10,10}$=8.3 Hz, 1H, 10-H), 4.26 and 4.10-4.30 (d over m, $J_{4,5}$=9.8 Hz, 4H, 4-H and 5-H, 7-H, 9-H), 4.38 (dd, $J_{5,6}$=4.6, $J_{6,6}$=10.2 Hz, 1H, 6-He), 5.28 (s, 1H, 1-H), 5.55 (s, 1H, benzylidene H), 7.30-0-7.37, 7.44-7.50 (m, 5H, aromatic H's). MS, m/e 426 (M+ NH_4^+).

Anal. Calcd for $C_{21}H_{28}O_8$: C,61.73 ; H,6.91. Found: C, 61.62; H, 6.82.

7-(S)-**7** :$[\alpha]_D$ -2.8° (*c* 1.60, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 and 1.41 (s, 3H ea, isopropylidene CH_3), 1.67-1.80 (m, 2H, 8-H), 2.72 (d, $J_{2,7}$=5.6 Hz, 1H, 2-H), 3.36 (s, 3H, OCH_3),

3 58 (t, $J_{9,10}=J_{10,10}=7$ 8 Hz, 1H, 10-H), 3 92 (t, $J_{5,6}=J_{6,6}=10$ 1 Hz, 1H, 6-Ha), 4 02-4 20 (m, 2H, 5-H and 10-H), 4 35 and 4 25-4 40 (dd over m, $J_{5,6}=4$ 7, $J_{6,6}=10$ 1 Hz, 3H, 6-He and 7-H, 9-H), 4 61 (d, $J_{4,5}=9$ 8 Hz, 1H, 4-H), 4 92 (s, 1H, 1-H), 5 58 (s, 1H, benzylidene H), 7 30-7 37, 7 45-7 51 (m, 5H, aromatic H's)

Anal Calcd for $C_{21}H_{28}O_8$ C,61 73 , H,6 91 Found C, 61 51, H, 7 17

Aldol Reaction With (R)-2,3-O-Isopropylidene-glyceraldehyde (8) The reaction was performed as above using 0 70 g (2 65 mmol) of ketone **1**, 4 9 mL of 0 65 M potassium bis(trimethylsilyl)amide solution in toluene (3 18 mmol), 3 2 mL of the zinc chloride solution in Et_2O and **8**[14] (0 45 g, 3 46 mmol) The crude product was purified by flash chromatography (ethyl acetate petroleum ether=1 1) to give 50 mg of uloside **1** (7%) and 0 76 g (73%) of aldol **16** mp 146-147°C, $[\alpha]_D$ +27 8° (*c* 1 20, $CHCl_3$) ^1H NMR (300 MHz, $CHCl_3$) δ 1 33, 1 45 (s, 3H ea, isopropylidene CH_3), 2 45 (b d,J=2 6 Hz, 1H, OH), 2 65 (d, $J_{2,7}=10$ 3 Hz, 1H, 2-H), 3 40 (s,3H, OCH_3), 3 88-4 05 (m, 4H, 6-Ha, 8-H and 9-H's), 4 13-4 27 (m, 2H, 5-H and 7-H), 4 33 (d, $J_{4,5}=9$ 6 Hz, 1H, 4-H), 4 40 (dd, $J_{5,6}=4$ 7, $J_{6,6}=10$ 2 Hz, 1H, 6-He), 5 28 (s, 1H, 1-H), 5 58 (s, 1H, benzylidene H), 7 33-7 40 and 7 46-7 53 (m, 5H, aromatic H's) MS, m/e 412 (M+ NH_4^+)

Anal Calcd for $C_{20}H_{26}O_8$ C, 60 88, H, 6 64 Found C, 60 90, H, 6 64

In addition, some of the 2-C epimer (**16e**) (7%) was also isolated mp 139-140°C, $[\alpha]_D$ +73 4° (*c* 0 72, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$) δ 1 32, 1 38 (s, 3H ea, isopropylidene CH_3), 3 04 (ddd, $J_{2,4}=1$ 1, $J_{1,2}=4$ 1, $J_{2,7}=9$ 6 Hz, 1H, 2-H), 3 36 (s, 3H, OCH_3), 3 43 (d, J=3 7 Hz, 1H, OH), 3 92 and 3 90-4 01(t over m, $J_{5,6} = J_{6,6} =10$ 2 Hz, 3H, 6-Ha and 7-H, 9-H), 4 06-4 18 (m, 3H, 5-H, 8-H and 9-H), 4 29 (dd, $J_{2,4}=1$ 1, $J_{4,5}=9$ 6 Hz, 1H, 4-H), 4 37 (dd, $J_{5,6}=4$ 6, $J_{6,6}=10$ 2 Hz, 1H, 6-He), 5 31 (d, $J_{1,2}=4$ 1 Hz, 1H, 1-H), 5 56 (s, 1H, benzylidene H), 7 32-7 38 and 7 45-7 52 (m, 5H, aromatic H's) MS, m/e 412 (M+ NH_4^+)

Anal Calcd for $C_{20}H_{26}O_8$ C, 60 88, H, 6 64 Found C, 61 02, H, 6 43

Aldol Reaction With (S)-2,3-O-Isopropylidene-glyceraldehyde (9) The reaction was performed using 0 40 g (1 5 mmol) of the uloside **1**, 2 8 mL of 0 65 M potassium bis(trimethylsilyl)amide solution in toluene (1 8 mmol), 1 8 mL of 1 0 M the zinc chloride solution in Et_2O and **9**[14](0 239 g, 1 8 mmol) Flash chromatography (ethyl acetate petroleum ether=1 1) gave **17** and its C-2 epimer **17e** as inseparable products (25 1) (0 245 g, 40% yield) as colorless solid Some unreacted uloside **1** was also recovered (0 103 g, 26% yield) The ^1H NMR spectrum of aldol **17** was able to be assigned ^1H NMR (300 MHz, $CDCl_3$) δ 1 35, 1 44 (s, 3H ea, isopropylidene CH_3), 2 33 (bd, $J_{5,6}=3$ 4 Hz, 1H, OH), 2 90 (d, $J_{2,7}=5$ 5 Hz, 1H, 2-H), 3 38 (s,3H, OCH_3), 3 93 (t, $J_{5,6}=J_{6,6}=10$ 2 Hz, 1H, 6-Ha), 3 39-4,00(m, 1H, 9-H), 4 00-4 10 (m, 3H, 3-H,7-H, 8-H), 4 15 (dt, $J_{5,6}=4$ 6, $J_{4,5}=J_{5,6}=10$ 0 Hz, 1H, 5-H), 4 38 (dd, $J_{5,6}=4$ 6, $J_{6,6}=10$ 2 Hz, 1H, 6-He), 4 58 (d, $J_{4,5}=10$ 0 Hz, 1H, 4-H), 5 08 (s, 1H, 1-H), 5 59 (s, 1H, benzylidene H), 7 32-7 40 and 7 45-7 55 (m, 5H, aromatic H's) MS, m/e 412 (M+NH_4^+)

Anal Calcd for $C_{20}H_{26}O_8$ C, 60 88, H, 6 64 Found C, 60 65, H, 6 54

Aldol Reaction of Uloside 1 and 1,2:3,4-Di-O-Isopropylidene-α-D-galacto-hexodialdo-1,4-hexapyranose (10) A modified procedure was performed for this aldol reaction To a cooled (-40 - -50°C) solution of uloside **1** (0 976 g, 3 69 mmol), in dry THF (50 mL), was added rapidly 8 8 mL of 0 5 M potassium bis(trimethylsilyl) amide solution in toluene (4 43 mmol) The pale yellow solution was stirred at that temperature for 30 min, then cooled further to -78°C To this cooled solution was added 4 8 mL (4 8 mmol)of 1M zinc chloride solution in diethyl ether The resulting solution was stirred for 15 min Aldehyde **10**[21] (1 05 g, 4 06 mmol) was added in one portion and the reaction mixture was stirred at -78°C for 2 h, then allowed to warm slowly to -45°C After the reaction was complete (1 h), it was quenched with

saturated aqueous ammonium chloride solution (15 mL) at -45°C and diluted with ethyl acetate The aqueous layer was extracted with ethyl acetate, the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure The crude product obtained was purified by flash chromatography (ethyl acetate petroleum ether = 2 3) to give 1 32 g (55% yield) of aldol **18** $[\alpha]_D$ -31 6° (c 1 39, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 33, 1 37, 1 47, 1 60 (all s, 3H ea, isopropylidene CH_3), 2 67 (d, J=5 4 Hz, 1H, OH), 3 04 (d, $J_{2,7}$=5 4 Hz, 1H, 2-H), 3 37 (s, 3H, OCH_3), 3 83 (dd, $J_{8,9}$=2 1, $J_{7,8}$=8 1 Hz, 8-H), 3 93 (t, $J_{5,6}$=$J_{6,6}$=10 1 Hz, 1H, 6-Ha), 4 12-4 22 (m, 2H, 5-H and 7-H), 4 34 (dd, $J_{10,11}$=2 7, $J_{11,12}$=5 0 Hz, 1H, 11-H), 4 37 (dd, $J_{5,6}$=4 8, $J_{6,6}$=10 1 Hz, 1H, 6-He), 4 38 (dd, $J_{8,9}$=2 1, $J_{9,10}$=7 8 Hz, 1H, 9-H), 4 65 (dd, $J_{10,11}$=2 7, $J_{9,10}$=7 8 Hz, 1H, 10-H), 4 66 (d, $J_{4,5}$=10 0 Hz, 1H, 4-H), 5 11 (s, 1H, 1-H), 5 52 (d, $J_{11,12}$=5 0 Hz, 1H, 12-H), 5 60 (s, 1H, benzylidene), 7 32-7 38 and 7 48-7 55 (m, 5H, aromatic H's) MS, m/e 540 (M+ NH_4^+)

Anal Calcd for $C_{26}H_{34}O_{11}$ C, 59 76, H, 6 56 Found C, 59 68, H, 6 65

Aldol Reaction of Uloside 1 and 1,2:3,4-Di-O-isopropylidene-α-L-galacto-hexodialdo-1,4-hexopyranose (11) The same procedure used for aldehyde **10** was followed using 490 mg of uloside **1** (1 90 mmol) and 540 mg of aldehyde **11** (2 09 mmol) The crude product containing a mixture of **19a** and **19b** (10 1) as determined by ^1H NMR was purified by flash chromatography (ethyl ether petroleum ether=2 1) to give **19a** (585 mg, 59% yield) which was recrystallized from CH_2Cl_2-Et_2O mp 188-190°C $[\alpha]_D$ +52 7° (c 3 5, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 28, 1 34, 144, 1 47 (all s, 3H ea, isopropylidene CH_3), 2 94 (d, $J_{2,7}$=9 0 Hz, 1H, 2-H), 3 37 (s, 3H, OCH_3), 3 62 (dd, $J_{8,9}$=1 8, $J_{8,7}$=6 2 Hz, 1H, 8-H), 3 91 (t, $J_{6,6}$=$J_{5,6}$=10 1 Hz, 1H, 6-Ha), 4 10-4 25 (m, 2H, 5-H and 7-H), 4 30 (dd, $J_{10,11}$=2 5, $J_{11,12}$=5 0 Hz, 1H,11-H), 4 36 (dd, $J_{5,6}$=5 0, $J_{6,6}$=10 0 Hz, 1H, 6-He), 4 37 (d, $J_{4,5}$=9 8 Hz, 1H, 4-H), 4 51 (dd, $J_{8,9}$=1 8, $J_{9,10}$=8 0 Hz, 1H, 9-H), 4 60 (dd, $J_{10,11}$=2 5, $J_{9,10}$=8 0 Hz, 1H,10-H), 5 28 (s, 1H, 1-H), 5 52 (d, $J_{11,12}$=5 0 Hz, 1H, 12-H), 5 53 (s, 1H, benzylidene H), 7 30-7 37 and 7 42-7 50 (m, 5H, aromatic H's), Ms, m/e 412 (M+ NH_4^+)

Anal Calcd for $C_{26}H_{34}O_{11}$ C, 59 75, H, 6 56 Found C, 59 40, H, 6 85

The relatively pure minor aldol product, **19b**, was obtained and the ^1H NMR spectrum of **19b** could be assigned umambiguously ^1H NMR (300 MHz, $CDCl_3$) δ 1 25, 1 29, 1 32, 1 44 (all s, 12H, isopropylidene CH_3), 3 00 (d, $J_{2,7}$=4 6 Hz,1H, 2-H), 3 08 (bs, 1H, OH), 3 36 (s, 3H, OCH_3), 3 56 (dd, $J_{8,9}$=1 6, $J_{7,8}$=7 0 Hz, 1H, 8-H), 3 93 (t, $J_{5,6}$=$J_{6,6}$=10 2 Hz, 1H, 6-Ha), 4 15 (dt, $J_{5,6}$=4 7, $J_{4,5}$=$J_{5,6}$=10 0 Hz, 1H, 5-H), 4 20 (dd, $J_{2,7}$=4 6, $J_{7,8}$=7 0 Hz, 1H, 7-H), 4 32 (dd, $J_{10,11}$=2 4, $J_{11,12}$=4 8 Hz, 1H, 11-H), 4 36 (dd, $J_{5,6}$=4 7, $J_{6,6}$=10 2 Hz, 1H, 6-He), 4 43 (dd, $J_{8,9}$=1 6, $J_{9,10}$=8 0 Hz, 1H, 9-H), 4 60 (dd, $J_{10,11}$=2 4, $J_{9,10}$=8 0 Hz, 1H, 10-H), 4 66 (d, $J_{4,5}$=10 0 Hz, 1H, 4-H), 5 01 (s, 1H, 1-H), 5 55 (d, $J_{11,12}$=4 8 Hz, 1H, 12-H), 5 57 (s, 1H, benzylidene H), 7 30-7 38 and 7 43-7 51 (m, 5H, aromatic H's)

Aldol Reaction With Methyl 2,3,4-Tri-O-benzyl-α-D-gluco-hexodialdo-1,5-pyranose (12) The same procedure used for aldehyde **10** was followed using 86 mg of uloside **1** (0 325 mmol) and 100 mg (0 216 mmol) of aldehyde **12** except that $ZnCl_2$ was replaced with $TiCl_4$ (35 mL, 0 325 mmol) The crude product obtained was purified by flash chromatography (diethyl ether petroleum ether = 2 1) to give 157 mg (66%) of aldol **20** $[\alpha]_D$ +8 1° (*c* 0 97, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 2 18 (b d, J=11 0 Hz, 1H, OH), 2 89 (d, $J_{2,7}$=9 9 Hz, 1H, 2-H), 3 37, 3 44(s, 3H ea, OCH_3), 3 35-3 47 (m, 2H, 8-H, 11-H), 3 61 (t, $J_{8,9}$=$J_{9,10}$=8 9 Hz, 1H, 9-H), 3 67 (t, $J_{5,6}$=$J_{6,6}$=10 1 Hz, 1H, 6-Ha), 3 93 (d, $J_{4,5}$=9 8 Hz, 1H, 4-H), 3 98 (t, $J_{9,10}$=$J_{10,11}$=8 9 Hz, 1H, 10-H), 4 02-4 18 (m, 2H, 5-H and 7-H), 4 29 (dd, $J_{5,6}$=4 5, $J_{6,6}$=10 1 Hz, 1H, 6-He), 4 57 (d, $J_{11,12}$=2 2 Hz, 1H, 12-H), 5 04-4 58 (AB system, 6H, benzyl CH_2), 5 14 (s, 1H, 1-H), 5 27 (s, 1H, benzylidene), 7 26-7 47 (m, 20H, aromatic H's) MS, m/e 744 (M+ NH_4^+)

Anal Calcd for $C_{42}H_{46}O_{11}$ C, 69 41, H,6 38 Found C, 69 16, H, 6 43

Aldol Reaction With Methyl 2,3,4-Tri-O-benzyl-α-D-manno-hexodialdo-1,5-pyranoside (13) The same procedure used for aldehyde **10** was followed using 483 mg of uloside **1** (1 83 mmol) and 650 mg (1 41 mmol) of aldehyde **13** [22] The crude product obtained was purified by flash chromatography (ethyl acetate petroleum ether=1 4 then 1 3) to give 765 mg (57% yield) of aldol **21** $[\alpha]_D$ +18 4° (*c* 0 95, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 2 94 (d, $J_{2,7}$=10 3 Hz, 1H, 2-H), 3 29 (d, $J_{8,9}$=9 6 Hz, 1H, 8-H), 3 33, 3 37 (s, 3H ea, OCH_3), 3 63 (t, $J_{5,6}$=$J_{6,6}$=10 2 Hz, 1H, 6-Ha), 3 76 (dd, $J_{11,12}$=1 7, $J_{10,11}$=3 0 Hz, 1H, 11-H), 3 83 (dd, $J_{10,11}$=3 0, $J_{9,10}$=9 5 Hz, 1H, 10-H), 3 90 (d, $J_{4,5}$=9 8 Hz, 1H, 4-H), 4 01-4 10 (m, 2H, 5-H, 9-H), 4 19 (b d, $J_{2,7}$=10 3, Hz, 1H, 7-H), 4 26 (dd, $J_{5,6}$=4 7, $J_{6,6}$=10 2 Hz, 1H, 6-He), 4 70 (d, $J_{11,12}$=1 7 Hz, 1H, 12-H), 4 55-5 05 (benzyl CH_2, 6H), 5 05 (s, 1H, 1-H), 5 30 (s, 1H, benzylidene H), 7 25-7 40 (m, 20H, aromatic H's) MS, m/e 744 (M+ NH_4^+)

Anal Calcd for $C_{42}H_{46}O_{11}$ C, 69 41, H,6 38 Found C, 69 41, H,6 60

Aldol Reaction With Methyl 4-Azido-4-deoxy-2,3-di-O-benzyl-α-D-gluco-hexodialdo-1,5-pyranoside (14) The same procedure used for aldehyde **10** was followed using 415 mg of uloside **1** (1 57 mmol) and 540 mg (1 36 mmol) of aldehyde **14** [23] The crude product obtained was purified by flash chromatography (ethyl acetate petroleum ether=1 2) to give 633 mg (61% yield) of aldol **22:** $[\alpha]_D$ + 51 2° (*c* 0 75, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 2 19 (d, J=11 5 Hz, 1H, OH), 2 93 (d, $J_{2,7}$=10 9 Hz, 1H, 2-H), 3 37, 3 45 and 3 37-3 45 (s over m, 3H ea and 1H, OCH_3 and 11-H,), 3 65 (t, $J_{8,9}$=$J_{9,10}$=9 7 Hz, 1H, 9-H), 3 88 (t, $J_{9,10}$=$J_{10,11}$=9 7 Hz, 1H, 10-H), 3 98 (t, $J_{5,6}$=$J_{6,6}$=9 9 Hz, 1H, 6-Ha), 4 10-4 22 (m, 4H, 4-H, 5-H, 7-H, and 8-H), 4 37 (dd, $J_{5,6}$=3 8, $J_{6,6}$=9 9 Hz, 1H, 6-He), 4 55 (d, $J_{11,12}$=3 2 Hz, 1H, 12-H), 4 58-4 98 (benzyl CH_2, 4H), 5 31 (s, 1H, 1-H), 5 60 (s, 1H, benzylidene H), 7 27-7 30, 7 45-7 54 (m, 15H, aromatic H's) IR (in $CHCl_3$) 2110 cm^{-1} ($-N_3$) MS, m/e 679 (M+ NH_4^+)

Anal Calcd for $C_{35}H_{39}N_3O_{10}$ C, 63 53 , H, 5 94, N, 6 35 Found C, 63 24, H,5 90, N, 6 10

Aldol Reaction With 3-O-Benzyl-1,2-O-isopropylidene-α-D-ribo-pentodialdo-1,4-furanose (15) The same procedure used for aldehyde **10** was followed using 542 mg of uloside **1** (2 05 mmol) and 0 44 mg (1 58 mmol) of aldehyde **15** The crude product obtained was purified by flash chromatography (ethyl acetate petroleum ether=1 2) to give 481mg (56% yield) of aldol **23** $[\alpha]_D$ +54 1° (*c* 1 48, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 32 and 1 56(s, 3H ea, isopropylidene CH_3), 2 30 (b d, J=2 0 Hz, 1H, OH), 2 76 (d, $J_{2,7}$=8 5 Hz, 1H, 2-H), 3 34 (s, 3H, OCH_3), 3 87 (t, $J_{5,6}$=$J_{6,6}$=10 1 Hz, 1H, 6-Ha), 3 96 (dd, $J_{9,10}$=3 6, $J_{8,9}$=8 9 Hz, 1H, 9-H), 4 02-4 26 (m, 3H, 5-H, 7-H and 8-H), 4 33 (dd, $J_{5,6}$=4 7, $J_{6,6}$=10 1 Hz, 1H, 6-He), 4 40 (d, $J_{4,5}$=9 8 Hz, 1H, 4-H), 4 50 (t, $J_{9,10}$=$J_{10,11}$=3 6 Hz, 1H, 10-H), 4 68 (d, J=11 7 Hz, 1H, OCH_2), 4 77 (d, J=11 7 Hz, 1H, OCH_2), 5 22 (s, 1H, 1-H), 5 53 (s, 1H, benzylidene H), 5 61 (d, $J_{10,11}$=3 6 Hz, 1H, 11-H),7 30-7 39, 7 42-7 50 (m, 5H, aromatic H's) MS, m/e 560 (M+ NH_4^+)

Anal Calcd for $C_{29}H_{34}O_{10}$ C,64 20, H, 6 32 Found C, 63 97, H, 6 42

Aldol Reaction With 3-Benzyloxy-2-(S)-methylpropanal (34) The same procedure used for aldehyde **10** was followed using 215 mg of uloside **1** (0 816 mmol) and 160 mg (0 898 mmol) of aldehyde **34** [20] The crude product obtained was purified by flash chromatography (ethyl acetate petroleum ether= 2 1) to give a mixture of 7-(S) and 7-(R) aldols, **36a** and **36b** (3 2) Relatively pure sample of each isomer could be obtained and the structure of both isomers were unambiguously assigned by ^1H NMR

36a ^1H NMR (300 MHz, $CDCl_3$) δ 0 97 (d, $J_{CH_3,8}$=6 9 Hz, 3H, CH_3), 1 85-1 95 (m, 1H, 8-H) 2 91 (d, $J_{2,7}$=4 6 Hz, 1H, 2-H), 3 34 (s, 3H, OCH_3), 3 45 (dd, $J_{8,9}$=8 1, $J_{9,9}$=9 3 Hz, 1H, 9-H), 3 66

(dd, $J_{8,9}$=3 6, $J_{9,9}$=9 3 Hz, 1H, 9-H), 3 93 and 3 86-3 96 (t over m, J=10 0 Hz, 2H, 6-Ha and 7-H), 4 12 (dt, $J_{4,5}$=$J_{5,6}$=10 0, $J_{5,6}$=4 6 Hz, 1H, 5-H), 4 29 (b d, J=2 3 Hz, 1H, OH), 4 34 (dd, $J_{5,6}$=4 6, $J_{6,6}$=10 0 Hz, 1H, 6-He), 4 47 (d, J=11 8 Hz, 1H, benzyl CH_2), 4 52 (d, J=11 8 Hz, 1H, benzyl CH_2), 4 68 (d, $J_{4,5}$=10 0 Hz, 1H, 4-H), 4 94 (s, 1H, 1-H), 5 58 (s, 1H, benzylidene H), 7 24-7 38 and 7 45-7 52 (m, 5H, aromatic H's) MS, m/e 412 ($M+NH_4^+$)

36b ^{1}H NMR (300 MHz, $CDCl_3$) δ 0 99 (d, $J_{CH3,8}$=7 1 Hz, 3H, CH_3), 1 62-1 72 (m, 1H, 8-H), 2 86 (d, $J_{2,7}$=10 5 Hz, 1H, 2-H), 3 02 (b d, J=3 1 Hz, 1H, OH), 3 63 (s, 3H, OCH_3), 3 50 (dd, $J_{8,9}$=5 7, $J_{9,9}$=9 2 Hz, 1H, 9-H), 3 59 (dd, $J_{8,9}$=3 5, $J_{9,9}$=9 2 Hz, 1H, 9-H), 3 90 (t, J=10 0 Hz, 1H, 6-Ha), 4 13 (dt, $J_{5,6}$=4 4, $J_{4,5}$=$J_{5,6}$=10 0 Hz, 1H, 5-H), 4 19 (d, J=9 7 Hz, 1H, 4-H), 4 29 (b d, $J_{2,7}$= 10 5 Hz, 1H, 7-H), 4 36 (dd, $J_{5,6}$=4 4, $J_{6,6}$=10 0 Hz, 1H, 6-He), 4 51 (s, 2H, benzyl CH_2), 5 26 (s, 1H, 1-H), 5 49 (s, 1H, benzylidene H), 7 27-7 40 and 7 43-7 51 (m, 5H, aromatic H's) MS, m/e 412 ($M+ NH_4^+$)

Reduction of 16 with DIBAL in CH_2Cl_2 (Table 2) To a cooled (O°C) solution of adduct **16** (0 12 g, 0 305 mmol) in dry CH_2Cl_2 (3 mL), diisobutylaluminum hydride (0 38 mL of 1M solution in THF, 0 38 mmol), was added dropwise The resultant clear solution was allowed to warm to room temperature and stirred for 20 minutes The reaction mixture was then cooled in an ice bath and quenched by the addition of saturated ammonium chloride solution (2 mL) The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the extracts combined with the original dichloromethane layer The combined extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* The resulting colorless oil was chromatographed (ethyl acetate petroleum ether = 1 1), to provide the C3-equatorial alcohol **24(eq)** a colorless crystal (0 095 g, 79% yield) and the more polar C3-axial epimer **24(ax)** (0 011 g, 9 % yield) as a solid

24(eq) mp 174-176°C, $[\alpha]_D$ +41 53° (*c* 0 73, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 35, 1 42 (s, 3H ea, isopropylidene CH_3), 2 34 (t, $J_{2,3}$=$J_{2,7}$=6 1 Hz, 1H, 2-H), 2 54 (b s, 1H, 3-OH), 2 64 (d, J=4 2 Hz, 1H, 7-OH), 3 37 (s, 3H, OCH_3), 3 72-3 85 (m, 3H, 4-H, 5-H, 6-Ha), 3 90 (dd, $J_{8,9}$=6 2, $J_{9,9}$=8 4 Hz, 1H, 9-H), 4 05 (dd, $J_{8,9}$=6 8, $J_{9,9}$=8 4 Hz, 9-H), 4 16 (m, 1H, 7-H), 4 24 (dd, $J_{5,6}$=1 7, $J_{6,6}$=8 1 Hz, 1H, 6-He), 4 31 (b t, $J_{2,3}$=$J_{3,4}$=6 1 Hz, 1H, 3-H), 4 42 (m, 1H, 8-H), 5 06 (s, 1H, 1-H), 5 56 (s, 1H, benzylidene H), 7 32-7 40 and 7 41-7 50 (m, 5H, aromatic H's) MS, m/e 414 ($M+ NH_4^+$)

Anal Calcd for $C_{20}H_{28}O_8$ C, 60 57, H, 7 12 Found C, 60 40, H, 7 18

24(ax) mp 156-158°C, $[\alpha]_D$ +62 9° (*c* 0 55, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 40, 1 47 (s, 3H ea, isopropylidene CH_3), 2 02 (dd, $J_{2,3}$=2 1, $J_{2,7}$=8 8 Hz, 1H, 2-H), 2 73 (dd, $J_{3,4}$=2 4, $J_{4,5}$=10 0 Hz, 1H, 4-H), 3 80 (t, $J_{5,6}$=$J_{6,6}$=10 0Hz, 1H, 6-Ha), 3 87-3 97(m, 2H, 3-H and 8-H), 4 00-4 07 (m, 2H, 9-H's), 4 13 - 4 28 (m, 2H, 5-H and 7-H), 4 33 (dd, $J_{5,6}$=4 1, $J_{6,6}$=10 0 Hz, 1H, 6-He), 5 05 (s, 1H, 1-H), 5 62 (s, 1H, benzylidene H), 7 29-7 39 and 7 43-7 51 (m, 5H, aromatic H's)

Anal Calcd for $C_{20}H_{28}O_8$ C, 60 57, H, 7 12 Found C, 60 77, H, 6 96

Reduction of Aldol 16 with $LiAlH_4$ in THF Similar experimental procedure used above was followed using 16 5 mg of aldol **16**, lithium aluminium hydride (3 mg, 0 05 mmol) and THF as solvent (1 mL) It provided 1 mg of **24(eq)** (6% yield) and 11 mg of **24(ax)** (66% yield)

Reduction of Aldol 16(eq) With DIBAL in CH_2Cl_2 and $LiAlH_4$ in THF (Table 2) The similar procedure used for **16** was performed The reduction with DIBAL in CH_2Cl_2 gave 60% yield of 3-axial alcohol (**26**) as the only product The reduction with LAH in THF gave 80% yield of the same product mp 173-174°C, $[\alpha]_D$ +74 2° (*c* 0 73, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 34, 1 38 (s, 3H ea, isopropylidene CH_3), 2 03-2 07 (m, 1H, 2-H), 3 21 (d, J=5 0 Hz, 1H, OH), 3 31 (d, J=3 1 Hz, 1H, OH), 3 42 (s, 3H, OCH_3), 3 57 (dd, $J_{3,4}$=2 8, $J_{4,5}$=10 0 Hz, 1H, 4-H), 3 74 (t, $J_{5,6}$=$J_{6,6}$=10 0 Hz, 1H, 6-Ha), 3 93-3 99 (m, 2H, 7-H and 9-H), 4 07-4 13 (m, 2H, 8-H

and 9-H), 4 23 (dt, $J_{5,6}$=5 0, $J_{4,5}$=$J_{5,6}$=10 0 Hz, 1H, 5-H), 4 34 (dd, $J_{5,6}$=5 0, $J_{6,6}$=10 0 Hz, 1H, 6-He), 4 49-4 51 (m, 1H, 3-H), 4 80 (d, $J_{1,2}$=3 9 Hz, 1H, 1-H), 5 59 (s, 1H, benzylidene H), 7 30-7 38 and 7 46-7 51 (m, 5H, aromatic H's)

Anal Calcd for $C_{20}H_{28}O_8$ C, 60 57, H, 7 12 Found C, 60 39; H, 7 04

Reduction of Aldol 18 (Table 2) To a solution of aldol (150 mg, 0 287 mmol) in suitable solvent (see Table 2) (5 mL) 2 equivalents of reducing agent was added at room temperature and stirred for 30 min , and then quenched with saturated ammonium chloride solution It was then extracted with EtOAc The EtOAc extract was dried over MgSO4 and the solvent was evaporated under reduced pressure The crude product was purified by flash chromatography (ethyl acetate petroleum ether = 1 2)

25(eq) mp $[\alpha]_D$ -7 5° (*c* 2 29, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 31, 1 36, 1 47, 1 52 (all s, 3H ea, isopropylidene CH_3), 2 56 (bt, $J_{2,3}$=$J_{2,7}$=6 1 Hz, 1H, 2-H), 3 23 (b d, J=4 0 Hz, 1H, OH), 3 34 (s, 3H, OCH_3), 3 75-3 88 (m, 3H, 6-Ha, 6-He, and 8-H), 4 03-4 20 (m, 3H, OH, 4-H, 7-H), 4 20-4 25 (m, 1H, 5-H), 4 30 (dd, $J_{10,11}$=2 4, $J_{11,12}$=5 1 Hz, 1H, 11-H), 4 40-4 48 (m, 1H, 3-H), 4 51 (dd, $J_{8,9}$=1 7, $J_{9,10}$=8 0 Hz, 1H, 9-H), 4 61 (dd, $J_{10,11}$=2 4, $J_{9,10}$=8 0 Hz, 1H, 10-H), 4 97 (s, 1H, 1-H), 5 53 (d, $J_{11,12}$=5 1 Hz, 1H, 12-H), 5 59 (s, 1H, benzylidene H), 7 32-7 39 and 7 44-7 50 (m, 5H, aromatic H) MS, m/e 542 ($M+NH_4^+$)

Anal Calcd for $C_{26}H_{36}O_{11}$ C,59 53 , H,6 92 Found C, 59 58, H, 7 05

25(ax) $[\alpha]_D$ -44 6° mp 195-196° (*c* 1 93, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 30, 1 35, 1 46, 1 50 (all s, 3H ea, isopropylidene CH_3), 2 47 (dd, $J_{2,3}$=2 1, $J_{2,7}$=7 3 Hz, 1H, 2-H), 2 68 (b s, 1H, OH), 3 40 (s, 3H, OCH_3), 3 75 (dd, $J_{8,9}$=2 0, $J_{7,8}$=7 8 Hz, 1H, 8-H), 3 79 (t, $J_{5,6}$=$J_{6,6}$=10 0 Hz, 1H, 6-Ha), 3 95 and 3 90-4 00 (dd over m, J=3 0, 9 5 Hz, 2H, 7-H and 4-H), 4 19-4 34 (m, 3H, 5-H, 6-He and 11-H), 4 41 (m, 1H, 3-H), 4 44 (dd, $J_{8,9}$=2 0, $J_{9,10}$=7 9 Hz, 1H, 9-H), 4 63 (dd, $J_{10,11}$=2 5, $J_{9,10}$=7 9 Hz, 1H, 10-H) 4 85 (s, 1H, 1-H), 5 53 (d, $J_{11,12}$=4 9 Hz, 1H, 12-H), 5 62 (s, 1H, benzylidene H), 7 30-7 38 and 7 45-7 50 (m, 5H, aromatic H's) MS, m/e 412 ($M+ NH_4^+$)

Anal Calcd for $C_{26}H_{36}O_{11}$ C,59 53 , H,6 92 Found C, 59 75, H, 7 06

The reduction of **18** (150 mg) with DIBAL in THF gave 122 mg (81% yield) of **25(eq)** and 9 mg (6 %) of **25(ax)** The reduction of **18** (200 mg) with superhydride in CH_2Cl_2 gave 86 mg (43% yield) of **25(ax)** only

Reduction of Aldol 23 The similar procedure used for **18** was performed on **23** (80 mg, 0 147 mmol) and DIBAL in THF The C3-equatorial alcohol **28** (71 mg, 88% yield) was isolated $[\alpha]_D$ +74 1° (*c* 1 35, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) d 1 34 and 1 57 (s, 3H ea, isopropylidene CH_3), 2 37 (b d, J=5 3 Hz, 1H, OH), 2 43 (dd, $J_{2,7}$=3 2, $J_{2,3}$=6 1 Hz, 1H, 2-H), 3 32 (s, 3H, OCH_3), 3 73-3 85 (m, 2H, 5-H and 6-Ha), 3 89 (dd, $J_{9,10}$=3 6, $J_{8,9}$=8 9 Hz, 1H, 9-H), 4 15-4 30 (m, 4H, 4-H, 6-He, 7-H and 8-H), 4 35 (dd, $J_{2,3}$=6 1, $J_{3,4}$=10 0 Hz, 1H, 3-H), 4 49 (t, $J_{9,10}$=3 6 Hz, 1H, 10-H), 4 61 (d, J=11 9 Hz, 1H, OCH_2), 4 74 (d, J=11 9 Hz, 1H, OCH_2), 5 19 (s, 1H, 1-H), 5 59 (s, 1H, benzylidene H), 5 72 (d, $J_{10,11}$=3 6 Hz, 1H, 11-H),7 26-0-7 42, 7 42-7 50 (m, 5H, aromatic H's) MS, m/e 562 ($M+ NH_4^+$)

Anal Calcd for $C_{29}H_{36}O_{10}$ C,63 95 , H,6 66 Found C, 63 89, H, 6 69

Acetonation of Diol 25(eq) Compound **25(eq)** (120 mg, 0 229 mmol) was dissolved in 3 ml of dry acetone To this solution catalytic amount of toluenesulphonic acid, 2,2-dimethoxypropane (1 mL) and Drierite (powder, 5 g) were added The mixture was stirred at room temperature for 4 hr, then quenched with 0 5 ml of dry Et_3N It was filtered and the filtrate was evaporated under reduced pressure The crude product was purified by flash chromatography (ethyl acetate petroleum ether = 1 5 then 1 2) to give 105 mg of **27** $[\alpha]_D$ -59 1° (*c* 0 73, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ 1 33, 1 38, 1 43, 1 48, 1 50, 1 54 (all s, 3H ea,

isopropylidene CH_3), 2 51 (ddd, $J_{1,2}$=1 0, $J_{2,3}$=6 0, $J_{2,7}$=8 8 Hz, 1H, 2-H), 3 35 (s, 3H, OCH_3), 3 73-3 80 (m, 2H, 6-Ha, 5-H), 3 95 (dd, $J_{8,9}$=1 3, $J_{7,8}$=9 3 Hz, 1H, 8-H), 4 11-4 29 (m, 3H, 4-H, 6-He,7-H), 4 31 (dd, $J_{10,11}$=2 3, $J_{11,12}$=5 0 Hz, 1H, 11-H), 4 35 (dd, $J_{2,3}$=6 0, $J_{3,4}$=9 9 Hz, 1H, 3-H), 4 44 (dd, $J_{8,9}$=1 3, $J_{9,10}$=8 0 Hz, 1H, 9-H), 4 62 (dd, $J_{10,11}$=2 3, $J_{9,10}$=8 0 Hz, 1H, 10-H), 5 05 (d, $J_{1,2}$=1 0 Hz, 1H, 1-H), 5 53 (d, $J_{11,12}$=5 0 Hz, 1H, 12-H), 5 60 (s, 1H, benzylidene H), 7 30-7 39 and 7 7-7 53 (m, 5H, aromatic H's) MS, m/e 582 (M+ NH_4^+)

References and Footnotes

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