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Highly Stereoselective Grignard Reaction of an Aldopyranose: A Simple Synthesis of 6-Deoxy-D-idose from D-Xylose[1]

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Grignard reaction of 2,3,4-tri-*O*-benzyl-D-xylopyranose yielded a single product with very high stereoselectivity. A *threo* relationship of the newly created chiral center with respect to C_2 was established by converting the product into the δ-lactone of D-*ido* configuration, then to the unsaturated lactone of *threo* configuration. The result made possible a stereoselective synthesis of 6-deoxy-D-idose from D-xylose in a small number of steps. Models accounting for the high stereoselectivity in the Grignard reaction of aldoses are discussed.

Keywords——Grignard reaction; stereoselectivity; conformation of unsaturated lactones; 2,3,4-tri-*O*-benzyl-D-xylose; 1-deoxy-D-sorbose; 6-deoxy-D-idono-1,5-lactone; 6-deoxy-D-idose; stereocontrol models

We report here a short and highly stereoselective synthesis of 6-deoxy-D-idose from D-xylose. The synthesis utilizes the latent symmetry of D-xylose, based on the fact that conversions of its alcoholic terminus (C_5) to an aldehyde and of the other terminus (C_1) to an alcohol produce a compound of the enantiomeric series. The synthesis involves highly stereoselective Grignard reaction at the anomeric carbon of an aldopyranose as a key step.

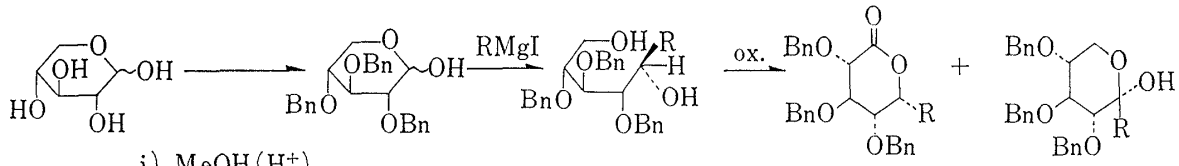
Grignard reaction of an anomeric mixture of 2,3,4-tri-*O*-benzyl-D-xylopyranose (**1**)[prepared from D-xylose in the usual way] with an excess of methyl magnesium iodide in tetrahydrofuran yielded the diol (**2a**) in 90% yield. In the ^{1}H-nuclear magnetic resonance (PMR) spectrum, it showed a doublet *C*-methyl peak at δ 1.10 ppm (J=6.5 Hz) which did not show any further separation on addition of Eu(dpm)$_3$, suggesting that a single compound was produced with almost 100% stereoselectivity. Stereochemical homogeneity of the product was confirmed by the following experiment. Lithium aluminum hydride reduction of 3,4,5-tri-*O*-benzyl-1-deoxy-D-sorbose (**4a**, see below) yielded a mixture of stereoisomeric diols, as expected, one of which showed a doublet *C*–Me peak identical with that of **2a**, whereas the other isomer exhibited a doublet peak at δ 1.20 ppm (J=6.5 Hz). Similarly, Grignard reaction of **1** with EtMgI gave the diol (**2b**) in 98% yield, also with high stereoselectivity.

Jones oxidation of **2a** yielded the δ-lactone (**3a**) and the hemiacetal (**4a**). Oxidation of **2b** similarly gave **3b** and **4b**. The ratio of the δ-lactone (**3**) and the hemiacetal (**4**) changed from *ca.* 1:5 to 2:1 depending on the nature of the oxidizing agent used, as illustrated in Table I.

The δ-lactone (**3a**) showed infrared (IR) absorption at 1750 cm^{-1}, and in the PMR spectrum a *C*–Me signal appeared at δ 1.35 ppm as a doublet (J=6.5 Hz), confirming the assigned structure except for the configuration of the methyl (or ethyl for **3b**) group.

The hemiacetal (**4a**) had no CO but had OH (3400 cm^{-1}) absorption in the IR spectrum. It also had a singlet *C*–Me peak at δ 1.32 ppm in the PMR spectrum. Therefore it is 3,4,5-tri-*O*-benzyl-1-deoxy-D-sorbose. The configuration of the anomeric center was elucidated as α for the following reasons. Aldopyranoses usually show two easily recognizable anomeric carbon signals corresponding to the α- and β-anomers in ^{13}C nuclear magnetic resonance (CMR)

1) Part V of "Utilization of Sugars in Organic Synthesis." Part IV: K. Yoshimoto, Y. Itatani, and Y. Tsuda, *Chem. Pharm. Bull.*, **28**, 2065 (1980).
2) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*



Bn : CH_2Ph
a : R=Me
b : R=Et

Chart 1

TABLE I. Oxidation of the Diols **2a** and **2b**

Procedure	Substrate	Product, isolation yield (%) δ-Lactone (3)	Hemiacetal (4)
Jones ox.	**2a**	(**3a**) 12	(**4a**) 44
Jones ox.	**2b**	(**3b**) 12	(**4b**) 59
PPC/Jones ox.	**2a**	(**3a**) 22	(**4a**) 52
Sarett/Jones ox.	**2a**	(**3a**) 23	(**4a**) 50
DMS–NCS/Jones ox.	**2b**	(**3b**) 40	(**4b**) 23

spectra. In fact, **1** shows signals at δ 91.4 and 99.0 ppm for the α- and β-anomer, respectively. In contrast, the hemiacetal (**4a**) showed only one anomeric carbon signal at δ 97.7 ppm, indicating that it exists as only one anomer in pyridine-d_5. Assuming that the anomeric carbons of the α- and β-anomers of **1** are substituted by equatorial and axial methyl groups, respectively, the chemical shifts of the α- and β-anomers of **4a** were calculated by adding the contribution of *eq.* —Me (+5.96 ppm) and *ax.* —Me (+1.4 ppm)[3] to the observed chemical shifts of **1**, yielding δ 97.4 for the α- and 100.4 ppm for the β-anomer. The calculated value for the α-anomer showed excellent agreement with the observed chemical shift of **4a**. The result is in accord with the generally accepted view that sorbopyranose has the most stable conformation (α-anomer).[4] The ethyl derivative (**4b**) also showed only one anomeric carbon signal at δ 99.0 ppm. Analogously, this was assigned to the α-anomer.

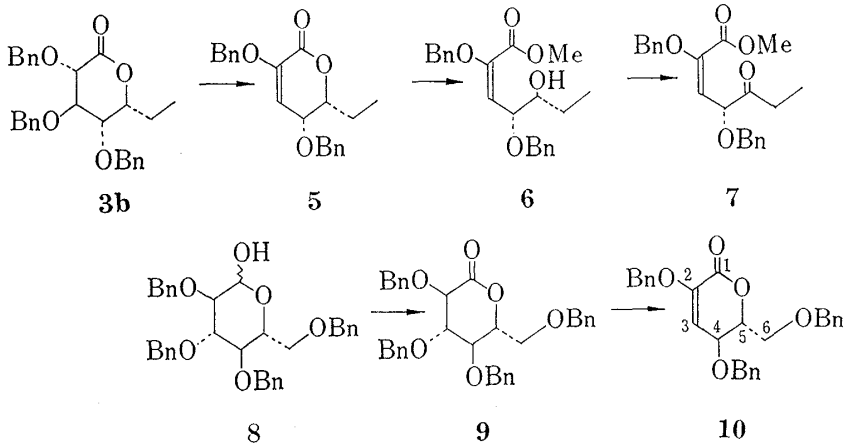


Chart 2

3) D.K. Dalling and D.M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967).
4) L. Hough and A.C. Richardson, in "Chemistry of Carbon Compounds," IF, 253 (1967).

When the δ-lactone (**3b**) was treated with NaOMe at room temperature, β-elimination took place with great ease to give the unsaturated lactone (**5**), which, on further treatment with NaOMe followed by methylation with methyl iodide in *N*,*N*-dimethylformamide (DMF), afforded the methyl ester (**6**). Jones oxidation of **6** gave the keto-ester (**7**).

The stereochemistry of the unsaturated lactone (**5**), and hence that of the δ-lactone (**3b**), was clarified by comparison of its PMR spectrum with that of the unsaturated lactone (**10**)

TABLE II. PMR Data for the α,β-Unsaturated δ-Lactones **5**, **10**, **11**, and **12** (100 MHz)

Compound	Chemical shifts (ppm) and first-order coupling constants (Hz)				Ref.
	H-3	*H*-4	*H*-5	*H*-6	
5[a]	5.73(d) $J_{3,4}$=6.3	3.98(dd) $J_{3,4}$=6.3 $J_{4,5}$=2.7	4.25(td) $J_{4,5}$=2.7 $J_{5,6}$=7.5	1.90(m)	This work
10[a]	5.63(d) $J_{3,4}$=4.0	4.47(dd) $J_{3,4}$=4.0 $J_{4,5}$=6.0	4.48—4.58	3.68	This work
11[a]	6.43(d) $J_{3,4}$=4.6	5.60(dd) $J_{3,4}$=4.6 $J_{4,5}$=5.2	4.71(m)	4.30	5)
12[b]	6.62(dd) $J_{3,4}$=5.9 $J_{3,5}$=1.0	5.45(m) $J_{3,4}$=5.9 $J_{4,5}$=2.3, 3.1	4.56(m) $J_{3,5}$=1.0 $J_{4,5}$=2.3, 3.1 $J_{5,5}$=13.0		5)

a) Solvent, chloroform-*d*.
b) Solvent, acetic acid-d_4.

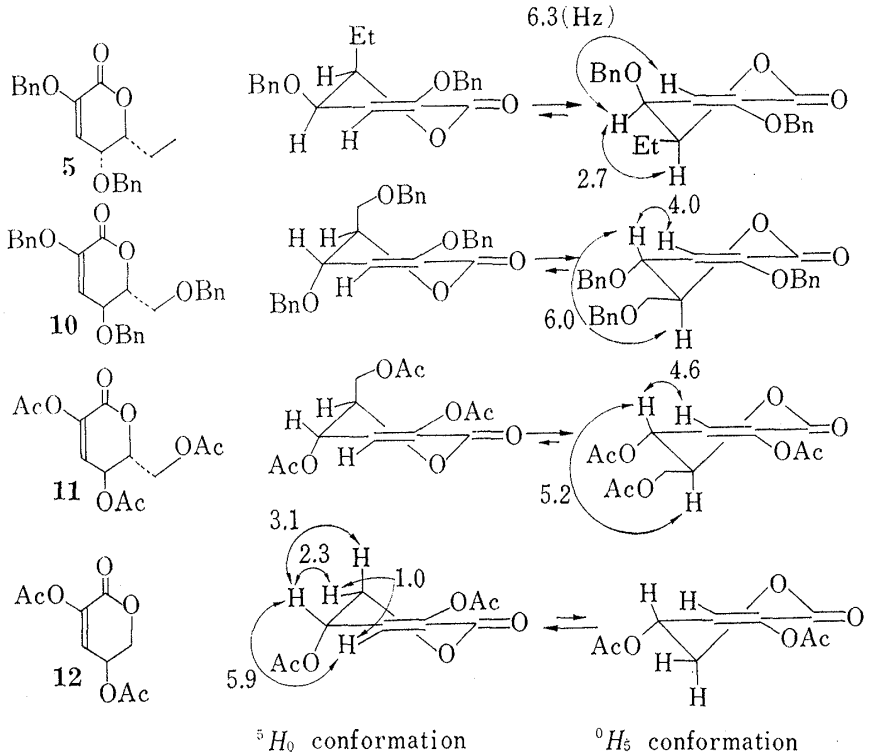


Fig. 1

prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**) by oxidation and β-elimination[5] and with the reported data[6] for the analogous compounds **11** and **12** (see Table II).

The small coupling constant between *H*-4 and *H*-5 ($J_{4,5}$=2.7 Hz) of **5** compared with the large $J_{4,5}$ (6.0 Hz) of **10**, in which the two substituents have a *trans* relationship, indicates that the substituents of **5** are in a *cis* relationship. Since it is reasonable to assume that the ethyl or $-CH_2OR$ group in **5** and **10** adopts an equatorial orientation due to an anchoring effect of these groups, and since the coupling constant $J_{4,5}$=6.0 Hz in **10** is too large for *quasi*-diequatorial coupling, which must be of the order of 3 Hz, we consider that the preferred conformations of **5** and **10** are $^{\circ}H_5$. Comparison of the coupling constant $J_{3,4}$ of **5** with that of **10** supported the above argument. Larger coupling (6.3 Hz) in the former indicates that the dihedral angle between *H*-4 and *H*-3 of **5** is smaller than that of **10**; that is, *H*-4 of the former is in *quasi*-equatorial and that of the latter is in *quasi*-axial orientation. The coupling pattern of **11** was almost the same as that of **10**. Mackie and Perlin[6] suggested the $^5H_0$ conformation for **11**. Obviously they were over-estimating both the *quasi*-diaxial and *quasi*-diequatorial couplings in such a half-chair δ-lactone. In fact, they were giving coupling constants of 2.3 and 3.1 Hz for *quasi*-axial–equatorial and *quasi*-diequatorial coupling in **12** ($^5H_0$ conformation). $J_{3,4}$=5.9 Hz of **12** is compatible with 6.3 Hz in **5**. Long-range coupling (1 Hz) between *H*-5 (equatorial) and *H*-3 reported in **12**[6] was not observed in **5**, **10**, and **11**, indicating that there is no W-type arrangement in these compounds.

The CD spectra (Fig. 2) of the δ-lactones (**3b** and **9**) and of the unsaturated lactones (**5** and **10**) also supported the above conclusion on the configuration. The opposite sign of the Cotton effects of **5** and **10** shows that the configurations adjacent to the unsaturated lactone system (C_4) are opposite to each other, as expected. However, the marked difference in amplitude indicated that they are not in antipodal configurations. The opposite Cotton effects of **3b** and **9** again indicated that the configurations at the carbon adjacent to the lactone carbonyl (C_2) are opposite in these compounds.

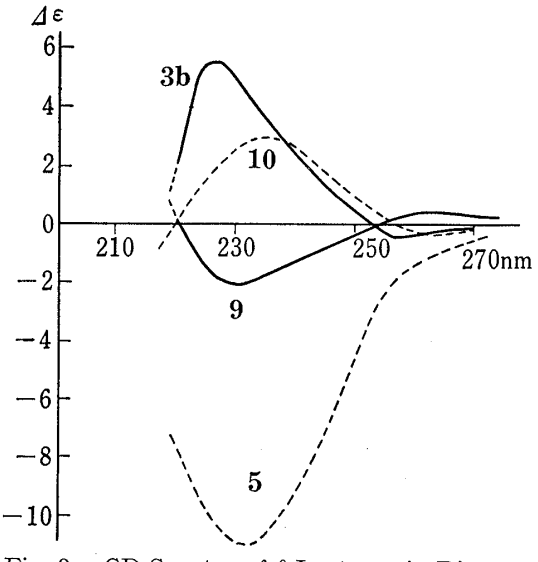


Fig. 2. CD Spectra of δ-Lactones in Dioxane

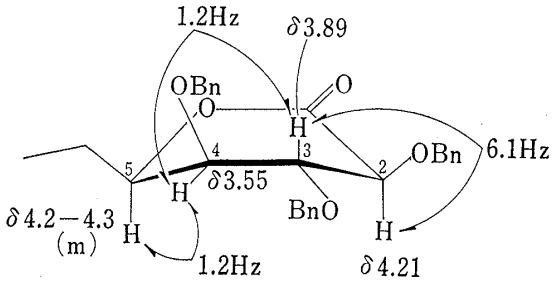


Fig. 3

The configuration of C-5 in **5** is therefore determined as [*R*] (*threo* with respect to the C_4-benzyloxy group), and thus the δ-lactone (**3b**) is 2,3,4-tri-*O*-benzyl-6,7-dideoxy-D-*ido*-heptonic acid-1,5-lactone.

5) β-Elimination of the lactone (**9**) under the same conditions was very slow, in contrast to the rapid elimination of **3b**.

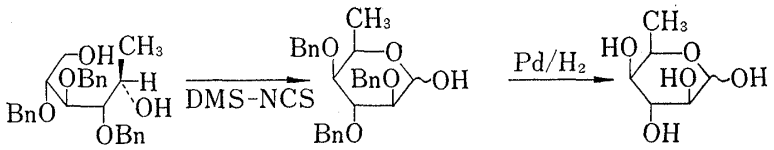
6) D.M. Mackie and A.S. Perlin, *Carbohydr. Res.*, **24**, 67 (1972).

Interestingly, the favored conformation of **3b** was suggested to be a boat form (Fig. 3), since the coupling constants $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ were 6.1, 1.2, and 1.2 Hz, respectively. In contrast, it was reported[7] that the favored conformation of 1,2,3,4,6-penta-*O*-acetyl-D-idose was a $^4C_1$ chair form, in which the corresponding coupling constants were 3.6, 3.5, and 2.1 Hz, respectively.

Simple Synthesis of 6-Deoxy-D-idose

The above results indicate that if we stop the oxidation of the diol (**2a**) at the aldehyde stage, 2,3,4-tri-*O*-benzyl-6-deoxy-D-idose (**13**) will be obtained.

N-Chlorosuccinimide-dimethyl sulfide oxidation[8] of the diol (**2a**) and chromatographic separation of the product gave, in 36% yield, the desired 2,3,4-tri-*O*-benzyl-6-deoxy-D-idopyranose (**13**), which was an anomeric mixture of α- and β-anomers, as shown by the CMR spectrum. The anomer ratio (β to α) varied depending on the solvent (*ca.* 1: 1 in $CDCl_3$ and 1: 3 in pyridine-d_5) as indicated by the intensity ratio of C_5–Me signals in the PMR spectra. Debenzylation of this compound by catalytic hydrogenation over palladium-black yielded 6-deoxy-D-idose (**14**) ($[\alpha]_D$ +12° in H_2O) as a gum[9]; its identity was confirmed by converting it to the crystalline phenylosazone. The overall yield of 6-deoxy-D-idose (**14**) from **1** was 16%.



2a **13** **14**

Chart 3

6-Deoxy-D-idose is an unnatural deoxy sugar, obtainable only by synthetic means. Three syntheses have been reported so far.[10–12] Two of them are syntheses of the L-isomer from D-glucose.[11,12] Application of these methods for the synthesis of the D-isomer requires L-glucose. Perry and Daoust[12] reported the synthesis of 6-deoxy-D-idose from 5-deoxy-D-xylose by condensation with nitromethane followed by Nef reaction of the resulting product (8 steps from D-xylose). Their synthesis however, completely lacks stereoselectivity, producing a 1: 1 mixture of 6-deoxy-D-idose and 6-deoxy-D-gulose. In contrast, our synthesis of 6-deoxy-D-idose from D-xylose is highly stereoselective with fewer steps (total 6 steps), and thus should be of great practical value.

Steric Course of the Grignard Reaction of Aldoses

Few reports exist on the Grignard reaction at the anomeric carbon of aldoses with determination of the configuration of the product. Two examples involving furanose derivatives have appeared in the literature,[13,14] both of which provided considerable stereoselectivity (Chart 4). Including these, the high stereoselectivity of the Grignard reaction with aldoses can be understood from either of the following two models: model A and model B (see Fig. 4).

7) N.S. Bhacca, D. Horton, and H. Paulsen, *J. Org. Chem.*, **33**, 2484 (1968).
8) E.J. Corey and C.U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).
9) The CMR spectrum of **14** in pyridine-d_5 suggested that it is a mixture of pyranose and furanose forms. This point will be fully discussed in a future communication.
10) A.S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29** 139 (1946).
11) M.L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27**, 1800 (1962).
12) M.B. Perry and V. Daoust, *Can. J. Chem.*, **51**, 3039 (1973).
13) J.G. Buchanan, A.R. Edgar, and M.J. Power, *J. Chem. Soc. Chem. Commun.*, **1972**, 346.
14) W.S. Chilton, W.C. Lontz, R.B. Roy, and C. Yoda, *J. Org. Chem.*, **36**, 3222 (1971).

Model A is essentially identical with that presented in Cram's second rule[15]: the Grignard reagent forms a chelate between the aldehyde and the neighboring oxygen function, and an alkyl group is introduced from the less hindered side of the molecule. The considerable stereoselectivities of Grignard reactions of α-alkoxyketones[16] and fully protected sugar derivatives with an aldehyde group at the terminus[11] are well explained by this model, in which the kind of organometallic reagent, the kind of alkoxy function, and the nature of the solvent are important factors influencing the stereoselectivity. The Grignard reagent as a reactant, the benzyloxy group as a protecting group, and THF as a solvent may be one of the best combinations.[16]

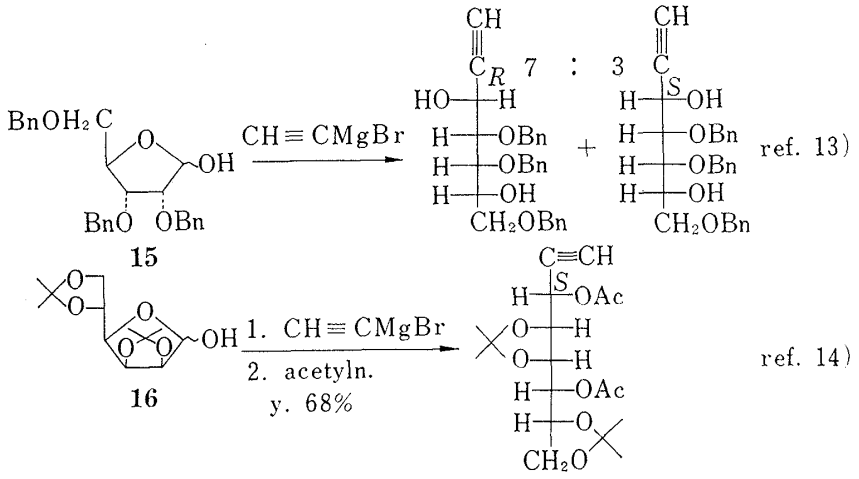


Chart 4. Reported Grignard Reactions of Aldose Derivatives

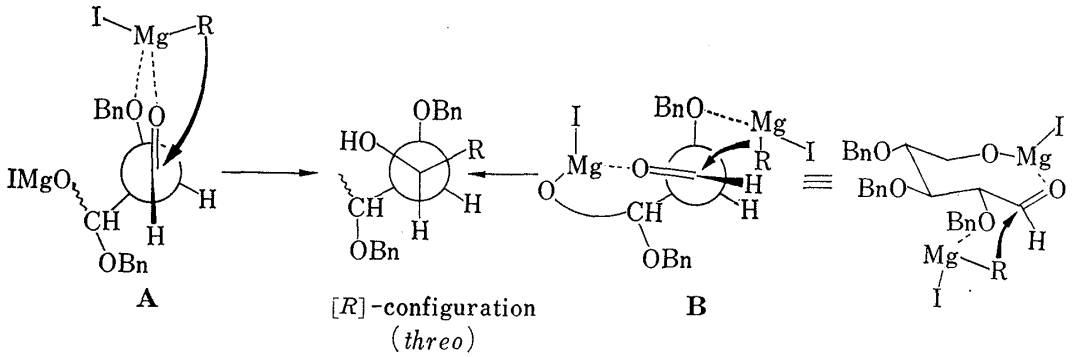


Fig. 4. Stereoselectivity of the Grignard Reaction of Aldoses

The other model B may also be considered to explain the very high stereoselectivity in the reaction of an aldose; in this model, a hydroxy group, which can readily form a chelate, is produced at the other terminus of the molecule. In model B, the first mole of Grignard reagent is consumed by a hydroxy function to form the cyclic intermediate by chelation between -OMgX and the aldehyde group. The second mole of Grignard reagent approaches the aldehyde group from the side of the adjacent benzyloxy group through chelation of the Grignard reagent to the oxygen function.

Either model leads to the conclusion that the configuration of the newly created chiral center is *threo* with respect to C_2–OR (or [*R*] from **1**). The reported stereoselectivities of the Grignard products of the aldofuranose derivatives **15**[13] and **16**[14] agree well with the predic-

15) D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
16) W.C. Still and J.H. McDonald, III, *Tetrahedron Lett.*, **1980**, 1031.

tion, being of [*R*] and [*S*] configuration, respectively. We therefore conclude that the steric course of the Grignard reaction at the anomeric center of an aldose is governed by the configuration of the adjacent oxygen function and that the compound of *threo* configuration is produced.

Experimental

Unless otherwise stated, mp's were taken on a Yanagimoto micro hot-stage mp apparatus, and CD spectra were measured with a Jasco J-20 spectrometer in dioxane solution (concentrations are given in g/ml). IR spectra were taken as KBr discs using a Jasco IR-G spectrometer and are given in cm^{-1}. NMR spectra were recorded on a JNM-PMX-60 (60 MHz) spectrometer with TMS as an internal reference. For 100 MHz PMR and CMR measurements, a JEOL FX-100 FT NMR spectrometer was used. Optical rotations were measured with a Jasco DIP-SL automatic polarimeter. MS were taken on a JMS-01SG spectrometer at 70 eV. Wakogel C-200 (silica gel) was used for column chromatography. All organic extracts were dried over Na_2SO_4 before concentration. Identities were confirmed by TLC, IR, and PMR comparisons.

2,3,4-Tri-*O*-benzyl-D-xylopyranose[17]——i) Methyl D-Xylopyranoside: D-Xylose (30 g) and Dowex-50 (H^+) (10 g) in dry MeOH (200 ml) were heated under reflux for 6 hr, then the reaction mixture was filtered. Concentration of the filtrate left a residue which was chromatographed on Florisil, eluting with $CHCl_3$–MeOH (5: 1) to give an anomeric mixture of methyl D-xylopyranosides (29 g), from which methyl β-D-xylopyranoside (3.3 g), mp 158—159° (lit.[18] mp 156—157°), separated out as colorless prisms on standing in acetone-methanol. The mother liquor was used for further processing without further purification.

ii) Methyl 2,3,4-Tri-*O*-benzyl-D-xylopyranoside: The above mixture (20 g) in DMSO (60 ml) was added dropwise to a stirred solution of dimsyl carbanion (prepared from 13 g of NaH and 40 ml of DMSO). After stirring for 1 hr, benzyl chloride (70 g) in DMSO (60 ml) was added dropwise to the mixture. After stirring for 3 hr at room temperature, the mixture was poured into ice-water, and extracted with Et_2O. The extract was concentrated to dryness. Chromatography of the residue, eluting with benzene, gave methyl tri-*O*-benzyl-D-xyloside (50 g) as an oil.

iii) 2,3,4-Tri-*O*-benzyl-D-xylopyranose (**1**): The above D-xyloside (50 g) in 2 N H_2SO_4 (140 ml)–AcOH (160 ml)–dioxane (150 ml) was heated under reflux for 10 hr. On cooling the mixture, the separated precipitate was collected by filtration and crystallized from *n*-hexane–Et_2O to give **1** (21 g, 41% from D-xylose) as colorless needles, mp 139—142°. $[\alpha]_D^{15}$ +12° (c=1.49 in $CHCl_3$). IR: 3400. PMR: δ 3.0—4.0 (6H), 4.6—6.8 (6H, $-OC\underline{H}_2Ph\times3$), 7.20 (15H, Ph×3). CMR: δ 91.4 (C_1, α-anomer) and 99.0 (C_1, β-anomer) (ratio *ca.* 4: 1).

The tosylhydrazone was formed on heating **1** with tosylhydrazide in MeOH for 3 hr at 70°. It crystallized in colorless needles from EtOH, mp 145—146°. IR: 3400 (br), 3250, 3170, 1600. *Anal.* Calcd for $C_{33}H_{36}N_2O_6S$: C, 67.32; H, 6.16; N, 4.76. Found: C, 67.07; H, 6.14; N, 4.83.

2,3,4-Tri-*O*-benzyl-6-deoxy-D-iditol (**2a**)——Tri-*O*-benzyl-D-xylopyranose **1** (3 g) in THF (30 ml) was added dropwise to a stirred ethereal solution of MeMgI (prepared from 3 g of Mg and 15.3 g of MeI in 100 ml of dry Et_2O) under ice-cooling. The mixture was stirred for 1 hr at room temperature and for a further 1 hr under reflux, and was then decomposed by addition of a saturated solution of NH_4Cl. The water layer was extracted repeatedly with Et_2O. The combined ethereal layer was concentrated to give a residue which was chromatographed in $CHCl_3$, affording the diol **2a** as an oil (2.9 g, 90%). $[\alpha]_D^{15}$ +13° (c=2.07 in MeOH). IR (film): 3400. MS *m/e*: 436 (M^+), 391 (M^+-CH_3CHOH), 345 (M^+-PhCH_2). PMR: δ 1.10 (3H, d, J= 6.5 Hz, $>CHC\underline{H}_3$) 2.24 (2H, bs, OH[19]), 3.35—3.93 (6H), 4.40—4.86 (6H, $-OC\underline{H}_2Ph\times3$), 7.23 (15H, Ph×3).

2,3,4-Tri-*O*-benzyl-6,7-dideoxy-D-*ido*-heptitol (**2b**)——**1** (6 g) in THF (70 ml) was allowed to react with EtMgI (prepared from 5 g of Mg and 30 g of EtI in 160 ml of Et_2O) and worked up as above to give **2b** as an oil (6.1 g, 98%). $[\alpha]_D^{15}$ +17° (c=1.63 in MeOH). IR: 3400. MS *m/e*: 450 (M^+), 391 ($M^+-C_2H_5CHOH$), 359 (M^+-PhCH_2). PMR: δ 0.84 (3H, t, J=6.5 Hz, $-CH_2C\underline{H}_3$), 1.48 (2H, m, $>CHC\underline{H}_2CH_3$), 2.16 (2H, bs, OH), 3.30—4.00 (6H), 4.40—4.90 (6H, $-OC\underline{H}_2Ph\times3$), 7.23 (15H, Ph×3).

Oxidation of the Diol 2a——i) Jones Oxidation: The diol **2a** (0.5 g) in acetone (30 ml) was oxidized with the Jones reagent (30 drops) for 20 min at 0°. The mixture was poured into water and extracted with Et_2O. Removal of the solvent from the extract and crystallization of the residue from Et_2O gave 2,3,4-tri-*O*-benzyl-6-deoxy-D-idono-1,5-lactone **3a** (55 mg). It formed colorless needles, mp 120—122°, on recrystallization from *n*-hexane–acetone. $[\alpha]_D^{15}$ −48° (c=1.45 in $CHCl_3$). IR: 1750. MS *m/e*: 341 (M^+-PhCH_2). PMR: δ 1.35 (3H, d, J=6.5 Hz, $>CHCH_3$), 3.45 (1H, bs, H-4), 3.76—5.10 (9H), 7.23 (15H, Ph×3). *Anal.* Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.62; H, 6.47.

17) S. Tejima, R.K. Ness, R.L. Kaufman, and H.G. Fletcher, Jr., *Carbohydr. Res.*, **7**, 485 (1968).
18) "Methods in Carbohydrate Chemistry," Vol. II, ed. by R.L. Whistler and M.L. Wolfrom, Academic Press, 1963, p. 375.
19) The signals due to OH disappeared on addition of D_2O.

Chromatography of the mother liquor, eluting with $CHCl_3$, gave a further crop of the δ-lactone **3a** (5 mg) and 2,3,4-tri-*O*-benzyl-1-*C*-methyl-α-D-xylopyranose (3,4,5-tri-*O*-benzyl-1-deoxy-α-D-sorbopyranose) **4a** (220 mg), mp 71—73°. $[\alpha]_D^{15}$ +19° (c=2.18 in $CHCl_3$). IR: 3400. MS *m/e*: 434 (M^+), 416 (M^+-H_2O), 343 (M^+-PhCH_2), 325 ($M^+-H_2O-PhCH_2$). PMR: δ 1.32 (3H, s, $-\overset{|}{C}C\underline{H}_3$), 2.66 (1H, bs, OH), 3.13—4.0 (5H), 4.46—5.03 (6H, $-OC\underline{H}_2Ph\times3$), 7.20 (15H, Ph×3). CMR (pyridine-d_5): δ 26.4 (CH_3), 60.9 (C_5), 97.7 (C_1).

ii) Sarett Oxidation–Jones Oxidation: The diol **2a** (0.5 g) and CrO_3–pyridine complex (prepared from 0.4 g of CrO_3 and 4 ml of pyridine) in CH_2Cl_2 (5 ml) were stirred for 20 hr at room temperature. After addition of water, the mixture was extracted with Et_2O, and the product in Et_2O was passed through a short column of SiO_2. The gummy residue obtained from the eluate was dissolved in acetone (30 ml) and oxidized with Jones reagent (15 drops) for 15 min at 0°. On work-up as usual, the product was crystallized from *n*-hexane–acetone to give the δ-lactone **3a** (0.1 g). Crystallization of the mother liquor from *n*-hexane–Et_2O gave **4a** (0.18 g). Chromatography of the mother liquor from **3a** and **4a** gave further crops of **3a** (10 mg) and **4a** (80 mg). Yield: **3a** (110 mg, 22%) and **4a** (260 mg, 52%).

iii) PCC Oxidation–Jones Oxidation: The diol **2a** (0.35 g) and pyridinium chlorochromate (0.53 g) in CH_2Cl_2 (5 ml) were stirred overnight at room temperature. Et_2O was added to the mixture and the inorganic precipitate was separated by decantation, then washed several times with ether. The combined ethereal extract was poured onto a column of Florisil and eluted with ether. The residue obtained from the eluate was dissolved in acetone (30 ml) and oxidized with Jones reagent as described above. On work-up, the product gave the δ-lactone **3a** (80 mg, 23%) and the hemiacetal **4a** (173 mg, 50%).

$LiAlH_4$ Reduction of 2,3,4-Tri-*O*-benzyl-1-*C*-methyl-α-D-xylopyranose (4a)——The hemiacetal **4a** (65 mg) and $LiAlH_4$ (50 mg) in THF (3 ml) were heated under reflux for 4 hr. After addition of a few drops of water, the mixture was repeatedly extracted with Et_2O. The combined ethereal extract gave, on removal of the solvent, a mixture of the diols **2a** and the D-*gulo*-isomer (60 mg), which were not separated by column chromatography. TLC: one spot. PMR: δ 1.10 and 1.20 (—$CHC\underline{H}_3$, each d, J=6.5 Hz, intensity ratio *ca.* 1:1).

Oxidation of the Diol 2b——i) Jones Oxidation: The diol **2b** (0.3 g) was oxidized with Jones reagent and worked up as described for **2a** to yield 2,3,4-tri-*O*-benzyl-6,7-dideoxy-D-*ido*-heptonic acid-1,5-lactone **3b** (935 mg, 12%) and 2,3,4-tri-*O*-benzyl-1-*C*-ethyl-α-D-xylopyranose (4,5,6-*O*-benzyl-1,2-dideoxy-α-D-*xylo*-3-heptulopyranose) **4b** (175 mg, 59%).

The δ-lactone **3b** gave mp 118—120° (colorless needles from *n*-hexane–Et_2O). $[\alpha]_D^{15}$ −34° (c=1.42 in $CHCl_3$). IR: 1740. MS *m/e*: 355 (M^+-PhCH_2). PMR (100 MHz): δ 0.86 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.78 (2H, m, $>CHC\underline{H}_2CH_3$), 4.44 (2H, ABq, $\Delta\delta$=0.30 ppm, J=11.8 Hz), 4.63 (2H, ABq, $\Delta\delta$=0.14 ppm, J=11.5 Hz), and 4.85 (2H, ABq, $\Delta\delta$=0.43 ppm, J=11.5 Hz) ($-OC\underline{H}_2Ph\times3$); other protons, see Fig. 3. CD ($c=0.582\times10^{-3}$) $\Delta\varepsilon$ (nm): +2.21 (220), +5.57 (226), 0 (261), −0.04 (265), 0 (277).

The hemiacetal **4b** was an oil. $[\alpha]_D^{15}$ +21° (c=3.57 in $CHCl_3$). IR (film): 3430. MS *m/e*: 448 (M^+), 430 (M^+-H_2O), 357 (M^+-PhCH_2), 339 ($M^+-H_2O-PhCH_2$). PMR: δ 0.83 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.70 (2H, q, J=7.0 Hz, $-CC\underline{H}_2CH_3$) 2.80 (1H, bs, OH), 3.22—4.08 (5H), 4.46—5.0 (6H, $-OC\underline{H}_2Ph\times3$), 7.20 (15H, Ph×3). CMR (pyridine-d_5): δ 7.9 (q, CH_3), 31.8 (t, CH_2), 60.9 (t, C_5), 99.0 (s, C_1).

ii) NCS–DMS Oxidation–Jones Oxidation: DMS (3.5 ml) was added to a cooled solution (0°) of NCS (4.5 g, excess) in toluene (90 ml) and the mixture was stirred for 30 min at −25°. The diol **2b** (3 g) in toluene (10 ml) was added dropwise to the above reagent and the mixture was stirred for a further 2 hr, then decomposed by adding Et_3N (1 ml) in toluene (5 ml) and stirring for 10 min. Acidification of the mixture with 1% HCl and extraction with Et_2O gave, on concentration of the extract, a solid residue which was crystallized from *n*-hexane–Et_2O to afford the δ-lactone **3b** (1 g). The mother liquor from **3b** was oxidized in acetone (50 ml) with Jones reagent and worked up as usual. Chromatography of the product gave the δ-lactone **3b** (0.2 g) and the hemiacetal **4b** (0.7 g, 23%).

[4*R*,5*R*]-2,4-Dibenzyloxy-5-hydroxyhept-2-enoic Acid-1,5-lactone (5)——The heptonic acid-1,5-lactone **3b** (340 mg) and 0.24 N NaOMe–MeOH (3.4 ml, 1.2 eq.) in MeOH (10 ml) were stirred together for 30 min at room temperature. Acidification of the mixture with 2% HCl and extraction with Et_2O gave the unsaturated lactone **5** (310 mg), mp 64—67°, colorless prisms from EtOH. IR (film): 1730, 1640. MS *m/e*: 338 (M^+), 280 ($M^+-CH_3CH_2CHO$), 247 (M^+-PhCH_2). PMR (100 MHz): δ 1.00 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.41 (2H, ABq, $\Delta\delta$=0.18 ppm, J=11.8 Hz, $-OC\underline{H}_2Ph$), 4.92 (2H, d, J=1 Hz, $-OC\underline{H}_2Ph$), 7.2—7.4 (10H, Ph×2); other protons, see Table II. CMR ($CDCl_3$): δ 9.6 (q, CH_3), 23.4 (t, CH_2), 68.3 (d, C_4), 82.3 (d, C_5), 109.1 (d, C_3), 146.4 (s, C_2), 160.4 (s, C_1), 70.3 (t), 69.9 (t). CD ($c=0.60\times10^{-3}$) $\Delta\varepsilon$ (nm): −7.77 (220), −10.75 (231), −1.45 (260), −0.51 (277). *Anal.* Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.35; H, 6.60.

[4*R*,5*R*]-Methyl 2,4-Dibenzyloxy-5-hydroxyhept-2-enoate (6)——The unsaturated lactone **5** (56 mg) and 0.24 N NaOMe–MeOH (0.6 ml) in MeOH (1 ml) were stirred for 20 min at room temperature, then concentrated to dryness under reduced pressure. The residue was dissolved in DMF (1 ml) and stirred with MeI (0.5 ml) for 5 hr at room temperature. The mixture was diluted with water and extracted with Et_2O. Chromatography of the product, eluting with $CHCl_3$, gave **6** as an oil (37 mg). IR (film): 3550, 1720. MS *m/e*: 311 ($M^+-COOCH_3$). PMR: δ 0.90 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), 1.36 (2H, q. like, $C\underline{H}_2CH_3$) 2.56 (1H, bs, OH), 3.35 (1H, m, H-5), 3.71 (3H, s, $COOCH_3$), 4.33 (2H, ABq, $\Delta\delta$=0.24 ppm, J=12 Hz, $-OC\underline{H}_2Ph$), 4.53 (1H, dd, J=6.0 and 9.5 Hz, H-4), 4.80 (2H, s, $-OC\underline{H}_2Ph$), 5.04 (1H, d, J=9.5 Hz, H-3), 7.17 and 7.22

(10H, Ph×2).

[4*R*]-Methyl 2,4-Dibenzyloxy-5-oxohept-2-enoate (7)——The methyl ester **6** (35 mg) in acetone (8 ml) was oxidized with Jones reagent (5 drops) for 15 min at 0° and worked up as usual to yield **7** (31 mg) as an oil. IR (film): 1720, 1640. MS *m/e*: 368 (M^+), 311 ($M^+-COCH_2CH_3$), 309 ($M^+-COOCH_3$). PMR: δ 1.02 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.53 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 3.73 (3H, s, $COOC\underline{H}_3$), 4.43 (2H, d, J=1.7 Hz, $-OC\underline{H}_2Ph$), 4.80 (2H, s, $-OC\underline{H}_2Ph$), 5.02 (1H, d, J=9.0 Hz, H-4), 5.31 (1H, d, J=9.0 Hz, H-3), 7.20 and 7.26 (10H, Ph×2).

2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone (9)[20]——2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose **8** (500 mg) was oxidized with DMSO (3 ml)–Ac_2O (2 ml) and worked up as reported previously[20] to yield the oily δ-lactone **9** (quantitative yield). IR (film): 1750. CD ($c=0.435\times10^{-3}$) $\Delta\varepsilon$ (nm): −0.26 (220), −1.95 (228), 0 (253), +0.15 (275).

[4*S*,5*R*]-2,4,6-Tribenzyloxy-5-hydroxyhex-2-enoic Acid-1,5-lactone (10)——The glucono-lactone **9** (0.3 g) in MeOH (8 ml) was treated with 0.24 N NaOMe–MeOH (2.8 ml, 1.2 eq.) for 30 min at room temperature and worked up as described above. Chromatography of the product gave the starting material **9** (100 mg) and the unsaturated lactone **10** (40 mg) as an oil. IR (film): 1740, 1635. PMR: see Table II. CD ($c=0.326\times10^{-3}$) $\Delta\varepsilon$ (nm): 0 (220), +2.84 (238), 0 (255), −0.80 (264), −0.16 (275).

2,3,4-Tri-*O*-benzyl-6-deoxy-D-idopyranose (13)——A mixture of NCS (0.59 g, 1.2 eq.) and DMS (0.5 ml) in toluene (30 ml) was stirred for 30 min at −25° (dry ice-CCl_4 bath). The diol **2a** (1.6 g) in toluene (6 ml) was added dropwise to the above reagent and the mixture was stirred for 2 hr at the same temperature. Et_3N (0.37 g) in toluene (6 ml) was added and, after 10 min, the mixture was acidified with 1% HCl to separate the toluene from the water layer. The water layer was extracted with Et_2O and the combined extracts and toluene layer were concentrated to yield a gummy residue, which was purified by chromatography. Elution of the column with benzene–acetone (20: 1) gave tri-*O*-benzyl-6-deoxy-D-idopyranose **13** (570 mg, 35%), together with the hemiacetal **4a** (240 mg, 15%) and the starting material **2a** (410 mg). **13** was an oil. IR (film): 3400. PMR (100 MHz, $CDCl_3$): δ 1.27 and 1.28 (each d, J=6.6 Hz, ratio *ca.* 1: 1). PMR (100 MHz, pyridine-d_5): δ 1.40 and 1.54 (each d, J=6.8 Hz, ratio *ca.* 3: 1). CMR ($CDCl_3$): δ 15.1 and 16.7 (*ca.* 1: 1, CH_3), 92.4 and 93.5 (*ca.* 1: 1, C_1). CMR (pyridine-d_5): δ 14.2 and 17.7 (*ca.* 3: 1, CH_3), 93.8 (C_1).

Jones Oxidation of 13——**13** (57 mg) in acetone (15 ml) was oxidized with Jones reagent (5 drops) for 20 min at 0° and worked up as usual to yield the δ-lactone **3a** (51 mg).

6-Deoxy-D-idose (14)——Tri-*O*-benzyl-6-deoxy-D-idose **13** (270 mg) and Pd–black (300 mg) in EtOH (10 ml) were shaken for 3 hr under H_2. Removal of the solvent and the catalyst left a gummy residue, which was dissolved in $CHCl_3$–MeOH (5: 1) and passed through a short column of Florisil to afford **14** (52 mg) as a gum. $[\alpha]_D^{15}$ +12° (c=2.67 in H_2O) (lit.[12] gum, $[\alpha]_D$ +14.7° in H_2O).

14 (50 mg), phenylhydrazine (100 mg), and AcOH (3 drops) in H_2O (2 ml) were heated for 2 hr at 80°. The separated precipitate was collected by filtration and recrystallized from EtOH–H_2O to give the phenylosazone as yellow needles, mp 190—192° (lit.[12] mp 175—177°). *cf.* 6-deoxy-L-idose phenylosazone,[11] mp 182—184°. MS *m/e*: 342 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.46; H, 6.39; N, 16.59.

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