Asymmetric Reactions. VII. Stereoselectivities in Phenyllithium and Grignard Reactions with Tetrahydrofurfural Derivatives

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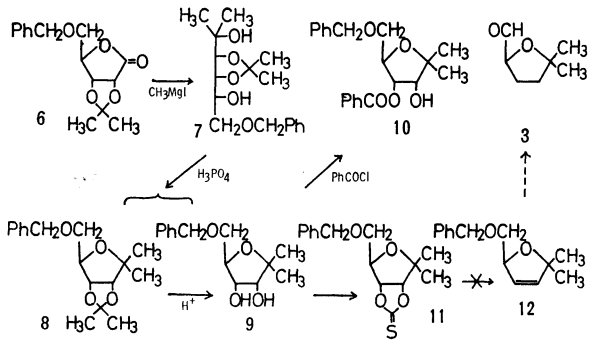
Stereoselectivities in the phenyllithium and phenylmagnesium bromide reactions with tetrahydrofurfural (**1**), its diacetate (**2**) and 5,5-dimethyl-(*S*)-tetrahydrofurfural (**3**) were examined, in order to clarify the cause of anomalous stereoselectivity of Grignard reactions with *N*-substituted 2,3-*O*-isopropylidene-D-glyceraldimine and the carbonyl analogue(giving *erythro* product predominantly). The presumption that the anomalous stereoselectivity might be caused by coordination ability of magnesium to C_3-oxygen, together with C_1-oxygen or C_1-nitrogen, and C_2-oxygen, was solidified from the present results that no stereoselectivity difference was observed between both reactions with substrates having no C_3-oxygen. Detailed discussion on the stereoselectivity differences between substrates was also made.

The authors have previously reported on the stereoselectivity difference between Grignard and phenyllithium reactions with 2,3-*O*-isopropylidene-D-glyceraldimines, and related compounds, and the difference was explained by assuming that the presence or absence of a coordinative interaction between C_3-oxygen and metal atoms in Grignard or phenyllithium reaction, respectively.[2-4]

In this paper, the presumption was solidified by comparison of the stereoselectivities of tetrahydrofurfural (**1**), its diacetate (**2**), and 5,5-dimethyl-(*S*)-tetrahydrofurfural (**3**) with the previous results.

Results

Synthesis of 5,5-Dimethyl-(S)-tetrahydrofurfural. At first, the synthesis was attempted by process shown in Scheme 1, starting from 2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribonolactone (**6**).[5] Methylation of **6** by methylmagnesium iodide gave the corresponding dimethylated product (**7**) in a good yield. The ring-closure of **7** was attained by heating with anhydrous orthophosphoric acid to give 1,1-dimethyl-1,4-anhydro-2,3-*O*-isopropylidene-D-ribitol (**8**) and its deacetonated derivative (**9**) which was benzoylated for identification to give a monobenzoate with mp 94—96°C. Among two possible structures, it was shown to be 3-*O*-benzoate (**10**) by NMR spectrum (Fig. 1). The doublet at 7.55 τ (J=6.3 Hz) and the triplet at 5.93 τ were assigned to the hydroxyl proton and C_2-proton, respectively, because they changed to a singlet and a doublet (J=6.3 Hz) by addition of a few drop of trifluoroacetic acid. Consequently, other proton signals were easily determined from the coupling constants. Treatment of **9** with thiocarbonylimidazole gave the corresponding



Scheme 1.

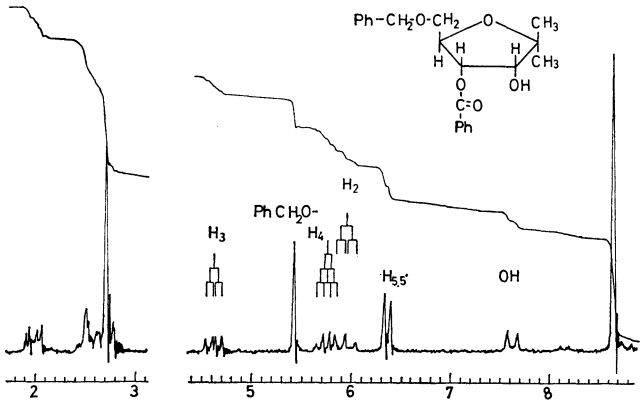


Fig. 1. NMR spectrum of **10** in $CDCl_3$ (τ).

2,3-*O*-thiocarbonate (**11**), however, several trials for elimination of thiocarbonic acid from **11** by refluxing with trimethylphosphite[6] in order to obtain the corresponding unsaturated compound (**12**) gave unsuccessful results.

The successful synthesis of **3** was accomplished by another process shown in Scheme 2, starting from 2,3-*O*-isopropylidene-D-glyceraldehyde. It was converted to ethyl 4,5-*O*-isopropylidene-(4*S*), 5-dihydroxypentenoate-2 (**13**) by Wittig reaction,[7] which was then hydrogenated to the corresponding saturated ester (**14**).

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2) J. Yoshimura, Y, Ohgo, and T. Sato, *J. Amer. Chem. Soc.*, **86**, 3858 (1964).

3) Y. Ohgo, J. Yoshimura, and T. Sato, This Bullletin **42**, 728 (1969).

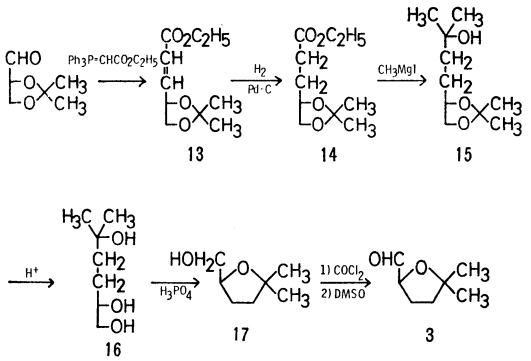
4) Y. Ohgo, J. Yoshimura, M. Kono, and T. Sato, *idid.* **42**, 2957 (1969).

5) J. Baddiley, J. G. Buchanan, and F. E. Hardy, *J. Chem. Soc.*, 1961, 2180.

6) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2667 (1965); A. H. Hains, *Carbohydrate Res.*, **1**, 214 (1965); S. D. Horton and W. N. Turner, *ibid.*, **1**, 444 (1966).

7) H. J. Bestmann and O. Kratzer, *Chem. Ber.*, **95**, 1894 (1962).

Treatment of **14** with an excess amount of methylmagnesium iodide gave 1,2-*O*-isopropylidene-5-methyl-1,(2*S*),5-trihydroxy-*n*-hexane (**15**) which was deacetonated with Amberlite IR-120 to **16**. Treatment of **16** with 85% phosphoric acid[8] gave an anhydride with bp 74—75.5°C/15 mmHg. Both five and six-membered ring structures are possible for the anhydride, however, it was confirmed to be 5,5-dimethyl-(*S*)-tetrahydrofurfuryl alcohol (**17**) by the facts that the chemical shifts of CH_2OH and H_2, and splitting patterns of signals in NMR spectra (Fig. 2) are closely similar to those of tetrahydrofurfuryl alcohol,[9] and that the oxidation of it gave an aldehyde. The oxidation product of 5-*O*-chloroformyl derivative of **17** by dimethyl sulfoxide showed an characteristic absorption of aldehyde at 1715 cm^{-1} in IR spectrum, and a signal of it at 0.4 τ (d, J=1.8 Hz) in the NMR spectrum. The elemental analysis of its 2,4-dinitrophenylhydrazone derivative agreed with theoreticals.



Scheme 2.

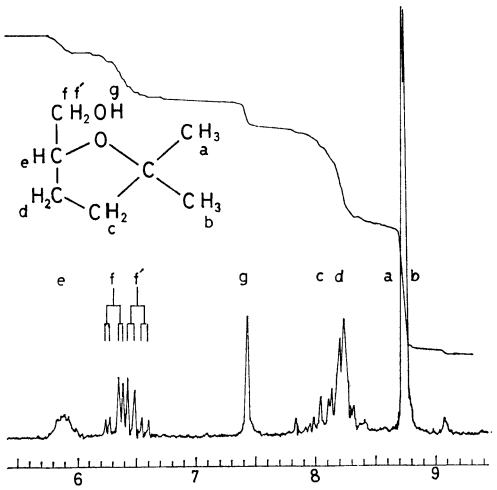
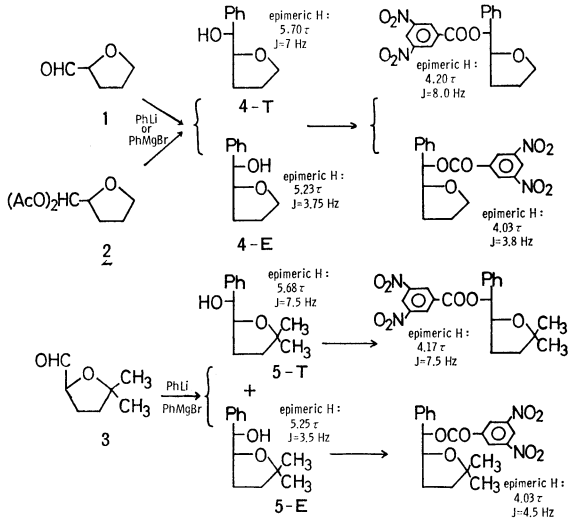


Fig. 2. NMR spectrum of **17** in $CDCl_3$.

Stereoselectivities in the Phenyllithium and Grignard Reactions with Substrates 1, 2, and 3. Substrates **1** and **2** prepared by the method of Scheibler *et al.*,[10] or **3** were treated with an excess amount of phenyllithium or phenylmagnesium bromide by the procedure mentioned in a previous paper.[4] In the case of **1** and **2**, the reaction product was distilled at 80—99°C/0.3 mmHg or purified by column chromatography on silica gel C-100 column, respectively, whose analytical values agreed with those calculated for 2-(hydroxybenyl)tetrahydrofuran (**4**). Although *threo* and *erythro* isomers in **4** could not be isolated, the ratio of them was estimated by glpc and NMR techniques.



Scheme 3.

Table 1. Diastereomer ratios produced by the reactions of tetrahydrofurfural derivatives with phenyllithium or phenylmagnesium bromide

Substrate	PhLi Product threo : erthro (%)		PhMgBr Product threo : erythro (%)		
1	72.5[e]	27.5[b]	70[a]	30[b]	A
	72.7[a]	27.3[b]	70.5[a]	29.5[b]	B
2	66[a]	34[b]	66[a]	34[b]	C
3	57[c]	43[d]	57.4[c]	42.6[d]	
	(58	42)	(58.7	41.3)	
			58.9[c]	41.1[d]	
			(62	38)	

The diastereomeric ratios except for those in parentheses were estimated by glpc with 20% PEG-6000-Chromosorb AW column, and those in parentheses were estimated from NMR peak areas of epimeric H_1-signals.

A: Fraction 2 of distillates with bp 85—99°C/0.28—0.3 mmHg (PhLi reaction) or with bp 80—99°C/0.28—0.3 mmHg (PhMgBr reaction).

B: Fraction 2′ with bp 99°C/0.3 mmHg which was interceptedly taken. Analytical values of these fractions agreed with those of expected products (see experimental part).

C: The results shwon are of crude products, and the sample purified by silica gel C-100 column chromatography gave analytical values agreed with those of the expected product (see experimental part.)

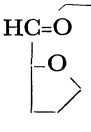
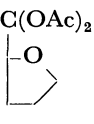
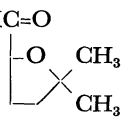
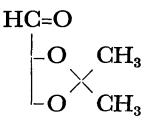
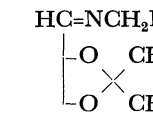
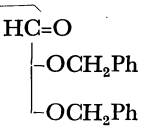
a) Faster fraction with retention time 633 sec on glpc.
b) Slower fraction with retention time 689 sec on glpc.
c) Faster fraction with retention time 528 sec on glpc.
d) Slower fraction with retention time 556 sec on glpc.

8) J. Colonge and G. Clerc, *Bull. Soc. Chim. Fr.*, **835** (1955).

9) The NMR spectrum of tetrahydrofurfuryl alcohol was taken for comparison with that of 5,5-dimethyl-(S)-tetrahydrofurfuryl alcohol: 5.92 τ (m, H_2); 6.28 τ (q, $J_{HH'}$=12 Hz, J_{HH_2}=4Hz——CH of hydroxymethyl); 6.475 τ (q, $J_{HH'}$=12Hz; $J_{H'H_2}$=6Hz——CH′ of hydroxymethyl).

10) H. Scheibler, F. Sotsckeik, and H. Friese, *Ber.*, **57**, 1443 (1924).

Table 2. Comparison of stereoselectivities in organometallic reactions with several aldehydes and aldimine

	Substrate						
							
	B	B	B	A[a]	B[b]	A	A
T/E(PhLi)	3.5	1.94	1.33	1.7	1.8	1.7	1.66
T/E(PhMgBr)	2.8	1.94	1.35	0.9	1.1	0.28	1.56
R_{Li}/R_{Mg}	1.25	1.0	0.99	1.8	1.6	6.0	1.06

A: By optical rotation.
B: By gas-liquid partition chromatography using 20% PEG-6000-Chromosorb AW.
a) This Bulletin, **42**, 2957 (1969).
b) Stereoselectivities were reexamined by glpc analysis; NMR analysis gave the same results; signals of the proton attached to carbinol carbon in *erythro* and *threo* isomer appear at 5.2τ (d, J=5 Hz) and 5.5τ (d, J=8 Hz) respectively. The ratio was given by the intergrals of peak areas.
T/E(PhLi): The ratio of *threo* to *erythro* in the PhLi reaction. T/E(PhMgBr): The same ratio in the PhMgBr reaction.
R_{Li}/R_{Mg}: The ratio of T/E(PhLi) to T/E(PhMgBr).

The glpc showed two peaks, of which the amount of faster fraction was larger than that of slower in both the products in organometallic reactions. The NMR spectrum showed two sets of doublet at 5.23 τ (J=3.8 Hz) and 5.70 τ (J=7 Hz), due to epimeric hydrogen attached to carbinol carbon. 3,5-Dinitrobenzoate of **4**, which could not also be isolated, showed the corresponding signals in lower field; at 4.03 τ (J=3.8 Hz) and 4.2 τ (J=8 Hz). It is known that the *erythro* isomers in analogous compounds give a smaller coupling constant than that of *threo* isomers,[4,11-13] and therefore, both the doublets mentioned are assigned to that of *erythro* and *threo* isomers, respectively. These results were presented in Scheme 3 with one presentative structural formula.

In the case of **3**, the product was distilled at 158—160°C/21 mmHg, which showed analytical values consisted with that of 2-(hydroxybenzyl)-5,5-dimethyltetrahydrofuren (**5**). The glpc and NMR analyses of the diastereomeric mixture and the corresponding 3,5-dinitrobenzoate showed the similar results to those in the cases of substrates **1** and **2**, and moreover, two diastereomers of **5** were successfully separated by column chromatography on silica gel C-100 column. Consequently, the relative configurations of the major and the minor products were concluded to be *threo* and *erythro*, respectively.

The diastereomeric ratios in **4** and **5** measured by methods mentioned above were summarized in Tables 1 and 2. These results indicate that there are no substantial differences in stereoselectivities between phenyllithium and phenylmagnesium bromide reactions with **1**, **2**, or **3**. This fact gave a positive support to our previous assumption that Grignard reagents have a coordinative interaction with C_3-oxygen of substrates, but phenyllithium cannot have such an interaction in the transition state of the reaction.

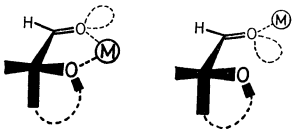
Discussion

For comparison, stereoselectivities of organometallic reactions with *N*-substituted 2,3-*O*-isopropylidene-D-glyceraldimine, its carbonyl analogue and related aldehydes were summarized in Table 2. R_{Li}/R_{Mg} is regarded as an indicator of stereoselectivity difference between phenyllithium and phenylmagnesium bromide reactions. As already pointed out,[4] stereoselectivity difference between phenyllithium and Grignard reactions is brought about when C_3-*O* (or C_β-*O*) of a substrate is sterically fixed at a certain position. The stereoselectivity of phenyllithium reaction should be explained by Cram's model.[14] On the other hand, anomalous stereoselecitvity of the Grignard reactions with aldehydes and aldimines having 2,3-dioxolane ring was explained by assuming that dimeric Grignard species (or two monomeric species) could coordinate to C_3-*O* together with C_2-*O* and imino nitrogen or carbonyl oxygen.[2-4] The validity of the assumption was solidified by the present results that there was no substantial difference in stereoselectivity between phenyllithium and phenylmagnesium bromide reactions with substrate **1**, **2**, and **3** in which C_3-*O* of 2,3-*O*-isopropylidene-D-glyceraldehyde was substituted with methylene group.

However, there still exist questions why there is not so large difference in stereoselectivity between Grignard and phenyllithium reactions with 2,3-*O*-isopropylidene-D-glyceraldehyde[4] as those in the case of *N*-substituted 2,3-*O*-isopropylidene-D-glyceraldimines which are nitrogen analogues of the former and why the reaction with tetrahydrofurfural has higher stereoselectivity than that with 5,5-dimethyltetrahydrofurfural. This can be explained mainly in terms of dual directionality of lone pair orbitals of carbonyl oxygen as follows. As seen from comparison of stereoselectivities with substrate **1** and **3**, stereoselectivity is influenced by existence of methyl on C_5; the methyl group decreases stereoselectivity in either phenyllithium or Grignard reaction. This seems to be concerned with increased difficulty of

11) M. H. Delton and G. U. Yuen, *J. Org. Chem.*, **33**, 2473 (1968).
12) D. Horton and J. M. J. Tronchet, *Carbohyd. Res.*, **2**, 315 (1966).
13) D. Horton, J. B. Hughes, and J. K. Thomson, *J. Org. Chem.*, **33**, 728 (1968).
14) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2737 (1959).

bridged coordination between carbonyl and ring oxygen. Lone pair electron orbitals of carbonyl oxygen extend to two directions (C_2-*O* side and aldehydic *H* side) to which organometallics can coordinate. In the case of 2,3-*O*-isopropylidene-D-glyceraldehyde or 5,5-dimethyltetrahydrofurfural, metal may not necessarily make coordinative bridge between carbonyl oxygen and C_2-*O*, because of steric hindrance of methyl group. Both chelated and non-chelated coordination states, **A**



(A) (B)

and **B**, may exist in the transition states. Consequently, reaction may occur from both states and proportion of these two states will depend on the balance of the energy saved by the chelation and repulsion by methyl groups. Increase of non-chelated coordination state in the equillibrium is considered to cause lower stereoselectivity and also smaller difference in stereoselectivity between Grignard and phenyllithium reactions.

It can also be understood that both phenyllithium and Grignard reactions with tetrahydrofurfural have higher stereoselectivity than those with its 5,5-dimethyl derivative, because the substrate has no methyl group and therefore the chelated coordination state would be favored in the equillibrium; rigidity of the bridged coordination and proximity of asymmetry to the reaction center may afford higher stereoselectivity.

On the other hand, imino compounds have alkyl substituent on the nitrogen and the alkyl may be oriented to the sterically less-hindered hydrogen side so that the lone pair electron orbital is oriented to the C_2-*O* side and then dimeric organomagnesium compound may be compelled to form a bridged coordination between C=N, C_2-*O* and C_3-*O*, in spite of the repulsion by isopropylidene group. This allows to explain the unique reversal of stereoselectivity with change from phenyllithium to phenylmagnesium bromide reaction.

Experimental

The NMR spectra were taken with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 100 MHz in a deuteriochloroform or carbon tetrachloride solution, using tetramethylsilane as an internal standard. The IR spectra were recorded with a Hitachi Model EPI-G2 grating IR spectrophotometer. The optical rotations were measured with a Carl-Zeiss Photoelectric Precision Polarimeter (0.005°). The gas-liquid partition chromatographic analyses were performed with a Hitachi Model K-53 gas chromatograph using a column packed with 20%PEG-6000-Chromosorb AW (1 m column in the case of **4**; 2 m column in the case of **5**).

Reaction of Tetrahydrofurfural with Phenylmagnesium Bromide. To an ice-cooled solution of phenylmagnesium bromide prepared from magnesium (1.2 g) and bromobenzene (4.85 m*l*) in ether (50 m*l*) was added an ethereal solution of tetrahydrofurfural (2.1 g) with stirring. The reaction mixture was refluxed with stirring for 1.5 hr, and then poured into ice-water saturated with ammonium chloride. The ether layer was separated and the water layer was extracted with ether. The combined ether layer was washed, successively with *N*-NaOH, water, *N*-H_2SO_4 and water, and dried over anhydrous sodium sulfate, and concentrated to a syrup (3.2 g). The syrup was fractionally distilled;

Fr. 1 50—60°C/0.3 mmHg 0.8 g.
2 80—99°C/0.3 mmHg 2.2 g.
2′ 99°C/0.3 mmHg 0.2 g.

The fraction 2′ was one which was taken interceptedly only at the boiling point of 99°C/0.3 mmHg. The analytical values agreed with 2-(hydroxybenzyl)tetrahydrofuran.

Found: C, 74.49; H, 8.11%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%.

These fraction were analysed on glpc using 20% PEG-6000-Chromosorb AW (detector: FID, carrier gas: nitrogen with 0.67 kg/cm², oven temperature: 200°C). The results are shown in Table 1.

NMR: 8.1—8.7 τ (multiplet; H_3 and H_4 in tetrahydrofuryl group (THF group)), 6—6.45 τ (multiplet; H_2 and H_5 in THF group), 5.77 τ (singlet; OH), 5.7 τ (doublet, J=7 Hz; epimeric proton-*threo*), 5.23 τ (doublet, J=3.8 Hz; epimeric proton-*erythro*).

To a solution of Fr. 2 (0.3 g) and 3,5-dinitrobenzoyl chloride (0.5 g) in benzene (20 m*l*) was added 1.5 m*l* of pyridine, and the reaction mixture was poured into water after standing overnight and extracted with chloroform. The organic layer was washed successively with sodium carbonate solution, water, dil-HCl solution and water, and then was concentrated *in vacuo* to dryness. The NMR spectrum of the resulting diastereomeric mixture of 3,5-dinitrobenzoate showed two sets of doublet due to epimeric proton at 4.03 τ (J=3.8 Hz) and 4.2 τ (J=8 Hz).

Reaction of Tetrahydrofurfural (1) with Phenyllithium. The reaction was carried out with the same procedure as in the case of the Grignard reaction. The syrup obtained was fractionally distilled;

Fr. 1 50—85°C/0.28—0.3 mmHg
2 85—99°C/0.28—0.3 mmHg 3 g
2′ 99°C/0.3 mmHg 0.4 g
Yield (2+2′): 3.4 g (91%).

Anal. of fraction 2′. Found: C, 74.41; H, 7.67%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%.

The products were analysed on glpc under the same condition as in the case of Grignard reaction (Table 1).

Reaction of Tetrahydrofurfural Diacetate (2) with Organometallic Reagents. The reactions were carried out of tetrahydrofurfural diacetate (10 g) with phenyllithium prepared from lithium (4.52 g) and bromobenzene (34.4 m*l*) or phenylmagnesium bromide prepared from magnesium (12 g) and bromobenzene (48.5 m*l*) in ether. Thereafter, the reaction mixture was treated as usual method (described above). The reaction products were tried to purify by distillation, but the aimed products were not separated from diphenyl methyl carbinol. The products were purified by column chromatography using silica gel C-100. The adsorbed products mixtures were successively eluted by *n*-hexane, *n*-hexane-benzene, benzene, and benzene-acetone. Each fraction was analysed by glpc. The acetone-benzene fraction contained the addition products; 2-(hydroxybenzyl)tetrahdrofuran. Found: C, 74.10; H, 8.05%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%.

Reaction of 5,5-Dimethyl-(S)-tetrahydrofurfural with Phenylmagnesium Bromide or Phenyllithium. A solution of 5,5-dimethyl-(*S*)-tetrahydrofurfural (3.2 g) in 10 m*l* of ether was added with stirring at 0—5°C to an ethereal solution of phenylmagnesium bromide prepared from magnesium (1.8 g) and bromobenzene (11.8 g), and the reaction mixture was

refluxed for 2 hr, and then decomposed with 1N-HCl solution. The products were extracted with ether. The ether layer was concentrated *in vacuo* to a syrup. The syrup was distilled at 158—160°C/21 mmHg. Yield: 2.0 g (39%); $[\alpha]_D$+2.85° (*c* 2, ethanol). Found: C, 75.47; H, 9.06%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

A solution of 5,5-dimethyl-(*S*)-tetrahydrofurfural (3.3 g) was reacted with phenyllithium prepared from 1.1g of lithium and 12.5 g of bromobenzene in ether, and the reaction mixture was treated in the same procedure as in the Grignard reaction; bp 155—160°C/20 mmHg, yield: 2.5 g (48%); $[\alpha]_D$+2.54° (*c* 1.5, ethanol). Found: C, 75.63; H, 9.10%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

NMR spectrum of the diastereomeric mixture: 2.77 τ (Ph), 5.25 τ (doublet, J=3.5 Hz; epimeric proton-*erythro*), 5.68 τ (doublet, J=7.5 Hz; epimeric proton-*threo*), 5.8—6.2 τ (multiplet; H_2 in THF group), 6.85 τ (OH), 8.35—8.5 τ (multiplet; H_3 and H_4 in THF group).

The products were analysed on glpc using 20% PEG-6000-Chromosorb AW (Table 1).

The two diastereomers were separated with column chromatography using silica gel C-100 column and *n*-hexane-benzene (10: 1) as the eluting solvent: faster fraction contained *erythro* isomer and slower fraction contained *threo* isomer. The *erythro* isomer has $[\alpha]_D^{24}$−3.3° (*c* 0.45, ethanol). NMR spectrum: 2.76 τ (Ph), 5.25 τ (doublet, J=3.5 Hz; epimeric proton), 5.8—6.0 τ (multiplet; H_2 in THF group), 7.58 τ (OH), 8.2—8.5 τ (multiplet; H_3 and H_4 in THF group), 8.73 and 8.78 τ (methyl).

Threo isomer has $[\alpha]_D^{24}$+6.7° (*c* 1.3, ethanol). NMR: 2.76 τ (Ph), 5.68 τ (doublet, J=7.5 Hz; epimeric proton), 5.95—6.2 τ (multiplet, H_2 in THF group), 7.7 τ (OH), 8.2—8.5 τ (multiplet; H_3 and H_4 in THF group), 8.73 and 8.78 τ (methyl).

1,1-Dimethyl-2,3-O-isopropylidene-D-ribitol (7). 5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribonolactone (116.4 g) was reacted with 6 molar equivalent of methylmagnesium iodide in ether at 0—5°C. The reaction mixture was left standing overnight and poured into 3 *l* of ice-water. The water layer was extracted twice with 1 litre of ether which was washed with water. The combined ether layer was dried over anhydrous sodium sulfate, concentrated to give a syrup which was distilled at bp 162°C/0.005 mmHg. Yield: 100 g (88%). Found: C, 65.42; H, 8.30%. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44%.

1,4-Anhydro-5-O-benzyl-1,1-dimethyl-D-ribitol (9). 50.4 g (0.16 mol) of 1,1-dimethyl-2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribitol was treated with anhydrous orthophosphoric acid (0.12 mol) with stirring at 100°C for 50 min. The reaction mixture was extracted with 600 m*l* of ether, and the ether layer was washed with water, sodium bicarbonate solution and water, successively. The ether layer was concentrated to give a syrup (36 g). The syrup was fractionally distilled:

Fr. 1 119°C/0.007 mmHg 18.8 g.
2 149°C/0.007 mmHg 10.7 g.

Fr. 1 was dissolved in petroleum ether and extracted with a small amount of water. The evaporation of the petroleum layer gave 1,4-anhydro-1,1-dimethyl-2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribitol (14.8 g) which was hydrolysed with 70% acetic acid (50 m*l*) under reflux for 4 hr, and the reaction mixture was extracted with ether. The ether layer was washed with sodium bicarbonate and water, concentrated to give a syrup (12.8 g) which was distilled at 149°C/0.007 mmHg. Found: C, 66.34; H, 8.16%. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%.

1,4-Anhydro-1,1-dimethyl-3-O-benzoyl-5-O-benzyl-D-ribitol (10). The above distillate (1.2 g) with bp 149°C/0.007 mmHg was treated with benzoyl chloride (1.4 g) and pyridine (1 m*l*) in chloroform at room temperature. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with water and concentrated *in vacuo* to give crystals of mp 94—96°C. The product has absorption bands at 3400 cm^{-1} and 1735 cm^{-1} which correspond to OH and ester carbonyl absorptions, respectively. The structure was confirmed by NMR spectrum (Fig. 1).

1,4-Anhydro-1,1-dimethyl-2,3-O-thiocarbonyl-5-O-benzyl-D-ribitol (11). To a solution of 15.32 g of **9** in acetone (225 m*l*) was added thiocarbonyldiimidazole (16.3 g) and the solution was refluxed for 1 hr under nitrogen atmosphere. The reaction mixture was concentrated to give a syrup containing crystals which was extracted with ether (300 m*l*). The extract was washed with 400 m*l* of water. The water layer was extracted twice with 200 m*l* of ether. The combined ether solution was dried over anhydrous sodium sulfate. The ether layer was filtered and concentrated under reduced pressure to give a syrup (18 g). The syrup was distilled at bp 145—150°C/0.03 mmHg, yield 11.8 g. Found: C, 61.00; H, 6.68%. Calcd for $C_{15}H_{18}O_4S$: C, 61.22; H, 6.12%.

Elimination of thiocarbonyl group of **11**. 11.1 g of **11** was dissolved in 75 m*l* of trimethyl phosphite and refluxed under nitrogen atmosphere for 3 days. To the reaction mixture was added 6N-NaOH solution under powerful stirring till pH 10, and stirring was continued for 2 hr. The mixture was extracted twice with methylene chloride (200 m*l*), washed with water, and concentrated *in vacuo* to give a syrup. The syrup had no absorption in the region of stretching vibration of olefins.

Ethyl-4,5-O-isopropylidene-(4S),5-dihydroxypentenoate-2 (13). A solution of carboethoxymethylenetriphenylphosphonium bromide (400 g) in 700 m*l* of abs. ethanol was added with cooling and stirring into sodium alcoholate solution prepared from sodium (23 g) and 500 m*l* of abs. ethanol. To the solution was added 118 g of a freshly distilled 2,3-*O*-isopropylidene-D-glyceraldehyde with cooling and stirring. The reaction mixture was stirred for 48 hr at room temperature, and then concentrated. The resulting sodium bromide and triphenylphosphine oxide were filtered off, and the remainder was distilled at 115—117°C/12 mmHg; $[\alpha]_D^{21}$+83.4° (*c* 0.34, ethanol); yield 112 g (60%). Found: C, 60.59; H, 8.12%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.

Ethyl-4,5-O-isopropylidene-(4S),5-dihydroxypentanoate (14). A solution of **13** (14.4 g) in ethanol (50 m*l*) was shaken with hydrogen in the presence of Pd-C (3 g) for 1 hr during which the substrate absorbed 1.75 *l* of hydrogen at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to a syrup which was distilled at 119—120°C/25 mmHg; yield, 14 g (97%); $[\alpha]_D^{21}$−5° (*c* 0.42, ethanol). Found: C, 59.85; H, 9.02%. Calcd for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91%.

1,2-O-isopropylidene-5-methyl-1,(2S),5-trihydroxy-n-hexane (15). To a cooled ethereal solution of methylmagnesium iodide prepared from 400 g of methyl iodide and 70 g of magnesium was added dropwise **14** (70 g) with stirring. The mixture was refluxed for 30 min, poured into ice-water containing ammonium chloride, and the resulting solution was extracted with ether. The ether layer was concentrated to a syrup which was distilled at 108—110°C/9 mmHg; yield, 52 g (82%); $[\alpha]_D^{21}$−2.2° (*c* 0.50, ethanol). Found: C, 63.86; H, 10.80%. Calcd for $C_{10}H_{20}O_3$; C, 63.79; H, 10.71%.

5-Methyl-1,(2S),5-trihydroxy-n-hexane (16). A solution of **15** (9.4 g) in water (80 m*l*) and ethanol (20 m*l*) was stirred in the presence of Amberlite IR-120[H] (16 g) at room temperature for 2 hr. The solution filtered was treated with activated carbon and concentrated to give a syrup which was distilled at 110—113°C/0.005 mmHg; yield, 6 g (81%);

$[\alpha]_D^{21}-12.5°$ (*c* 1.0, ethanol). Found: C, 56.16; H, 11.14%. Calcd for $C_7H_{16}O_3$: C, 56.73; H, 10.88%.

5,5-Dimethyl-(S)-tetrahydrofurfuryl Alcohol (17). **16** (25.2 g) was heated with 85% orthophosphoric acid with stirring for 40 min. After cooling the reaction mixture was poured into water, and the resulting solution was extracted with ethyl acetate. The ethyl acetate layer was washed with sodium bicarbonate solution and water, and concentrated to a syrup which was distilled at 74—75.5°C/15 mmHg; yield, 15.7 g (71%); $[\alpha]_D^{18}+13.6°$ (*c* 0.6, ethanol). Found: C, 64.29; H, 11.00%. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84%.

5,5-Dimethyl-(S)-tetrahydrofurfural (3). To a cooled ether solution containing phosgen (3.3 g) was added 4 g of **17** under cooling and the solution was left standing for 2 hr at room temperature. The reaction mixture was concentrated to remove ether and phosgen, and the resulting syrup was distilled at 84—85°C/11 mmHg to give the chloroformate quantitatively. To a solution of 5.6 g of the chloroformate in benzene (10 m*l*) was added 5 g of dimethyl sulfoxide and the reaction mixture was stirred with cooling until carbon dioxide evolution ceased. To this solution 16 m*l* of triethylamine was added and the resulting precipitate of triethylamine hydrochloride was removed by filtration. The mixture was purified through Magnesol-Celite (1:3) column to give 5,5-dimethyl-(*S*)-tetrahydrofurfural. Aldehydic proton signal was observed at 0.4 τ (doublet, $J=1.8$ Hz) in the NMR spectrum.

The reaction of the aldehyde with 2,4-dinitrophenylhydrazin gave an yellow precipitate; mp 119°C. Found: C, 51.26; H, 5.07; N, 18.78%. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.64; H, 5.23; N, 18.18%.