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Asymmetric Reactions. III. Stereoselectivity Difference between Grignard and Alkyllithium Reactions with 2,3-*O*-Substituted-D-glyceraldehydes

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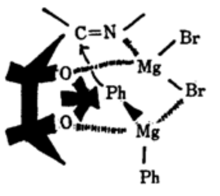
Stereoselectivity has been investigated in addition reactions of 2,3-*O*-isopropylidene-D-glyceraldehyde (I) or 2,3-di-*O*-benzyl-D-glyceraldehyde (II) with phenylmagnesium bromide or phenyllithium. Stereoselectivity difference between the Grignard and phenyllithium reactions occurred in the case of compound (I): the phenyllithium reaction gives *threo* and the Grignard reaction *erythro* products predominantly. On the other hand, no difference in stereoselectivity has been observed between the reactions with 2,3-di-*O*-benzyl-D-glyceraldehyde (II): both reactions gave *threo* product predominantly.

In a previous paper,[1] it has been reported that the asymmetric induction of *N*-substituted 2,3-*O*-isopropylidene-D-glyceraldimines with alkyllithium produced *threo* compound, and that with the Grignard reagent gave *erythro* product predominantly.

The steric direction of the alkyllithium reaction can be explained by Cram's rigid model.[2] Stereoselectivity of the Grignard reaction which was incompatible with the Cram's model was explained by assuming a coordinative interaction between C_3-oxygen and magnesium.



A

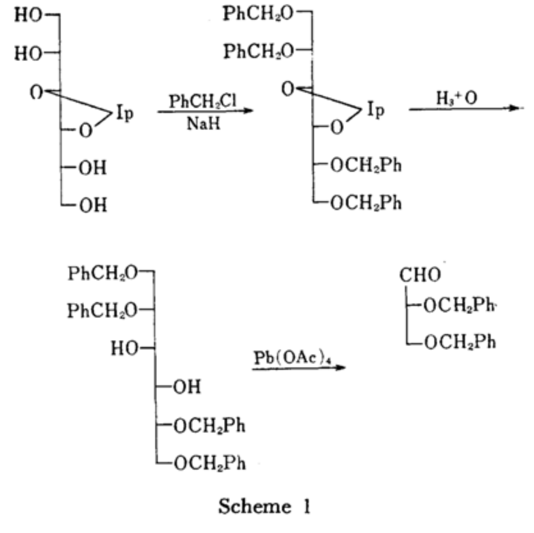
This paper reports that the same steric difference was observed in the reaction with 2,3-*O*-isopropylidene-D-glyceraldehyde and the fixation of oxygen atoms at 2- and 3-position by ketal ring is an essential factor for the occurrence of the stereoselectivity difference between the Grignard and alkyllithium reactions.

Materials

2,3-*O*-Isopropylidene-D-glyceraldehyde was prepared according to the method established by Baer and Fisher.[3] Freshly distilled material was used in each experiment.

2,3-*O*-Benzyl-D-glyceraldehyde was synthesized as follows.

Benzylation of 3,4-*O*-isopropylidene-D-mannitol with benzyl chloride and sodium hydride in dimethyl sulfoxide afforded 1,2;5,6-tetrabenzyl-3,4-*O*-isopropylidene-D-mannitol which was subjected to acid hydrolysis to give 1,2;5,6-tetra-*O*-benzyl-D-mannitol. Oxidative scission of the tetrabenzyl derivative with lead tetraacetate in benzene solution gave 2,3-di-*O*-benzyl-D-glyceraldehyde (bp 143—144°C/0.004 mmHg, $[\alpha]_{578}=+52°$) in a comparatively high yield (see experimental part). The structure was confirmed by means of IR data and microanalysis.



Scheme 1

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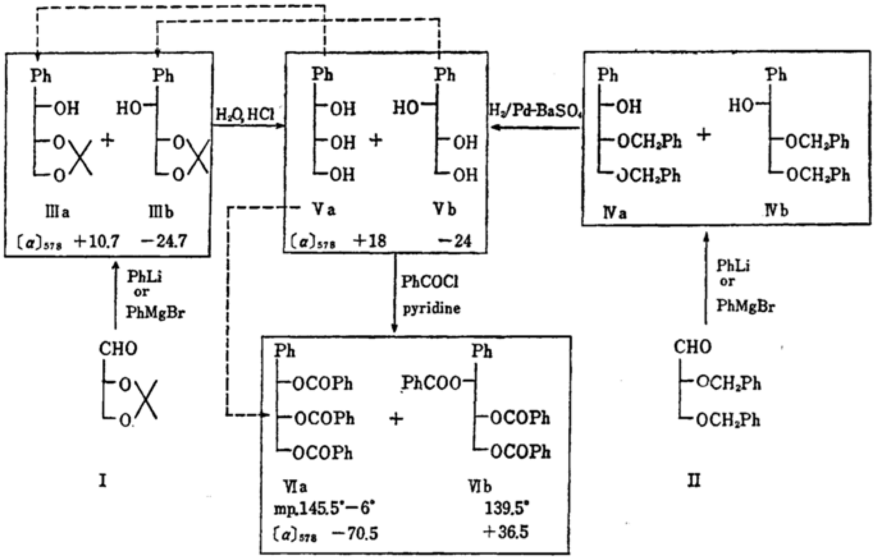
[1] a) J. Yoshimura, Y. Ohgo and T. Sato, *J. Am. Chem. Soc.*, **86**, 3858 (1964). b) Y. Ohgo, J. Yoshimura and T. Sato, This Bulletin, **42**, 728 (1969).

[2] D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2737 (1959).

[3] E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).



Scheme II

—— Sequence of asymmetric induction experiment.
---- Process carried out in order to establish stereochemical correlation.

Results and Discussion

2,3-*O*-Isopropylidene-D-glyceraldehyde (I)[3] or 2,3-di-*O*-benzyl-D-glyceraldehyde (II) was treated with 3 mol of phenyllithium or phenylmagnesium bromide in ether. The reaction mixture was decomposed with ice water, and from the ether layer a diastereomeric mixture of the corresponding addition products was obtained (IIIa, IIIb or IVa, IVb).

III and IV were respectively converted to a diastereomeric mixture of crystalline 1-*C*-phenyl-1,2,3-tri-*O*-benzoyl-glycerols (VIa and b) by acid hydrolysis of III or by catalytic hydrogenation of IV followed by benzoylation. The optical rotations and analytical results of the mixture are shown in Table 1. From the diastereomeric mixture two crystalline compounds were obtained by fractional crystallization, *i. e.*, mp 145.5—146°C, $[\alpha]_{578}$ −70.5°; mp 139.5°C, $[\alpha]_{578}$ +36.5°.

The isomer with mp 145.5—146°C has been reported by Tiffeneau and Neuberg.[4] However, no assignment of configuration was made.

The above diastereomers should have D-*threo* or D-*erythro* configuration. The configuration will be assigned as follows.

The de-acetonated product (Va+Vb) was distilled at 150—153°C/0.09 mmHg. It crystallized partially and the crystals with mp 103—105°C (Va) were separated from syrup (Vb). On the other hand, IIIa and IIIb were derived from Va and Vb by acetonation, respectively. The configuration of IIIa, IIIb, Va and Vb was presumed from comparison of optical rotational strength and sign with those of analogous compounds 1-*C*-phenyl-glycitols and their isopropylidene derivatives.[5,6]

The isomer bearing oxygen right in the Fischer Projection seems to have more positive rotation than the one bearing oxygen left. The analgous relation has been observed in the case of α-aminonitrile and 1-*C*-phenyl-1-alkylamino-1-deoxy-D-glycerols.[7,1a] Since Va and IIIa have positive values (+18° and +10.2°) [Vb and IIIb have negative (−24° and −24.7°)], it can be inferred that Va and IIIa have D-*erythro* configuration, and Vb and IIIb D-*threo*.

Their configurations are also deduced from comparison of the IR spectra of dilute solution of IIIa and IIIb (which were derived from Va and Vb by acetonation). The ratio of the bonded and free hydroxy stretching frequency (at 3630—3580 region) of IIIb is much greater than that of IIIa in dilute solution (see experimental). This implies that IIIb has *threo* configuration whose hydrogen bonding is stable.[8] The same conclusion may be derived from NMR spectra. Stable conformation of the *erythro* and the *threo* compound (IIIa,b)

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[4] M. Tiffeneau and I. Neuberg, *Compt. rend.*, **198**, 2174 (1934).

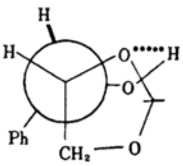
[5] W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3126 (1951).

[6] J. English, Jr., and P. H. Griswald, Jr., *ibid.*, **67**, 2039 (1945); *ibid.*, **70**, 1390 (1948).

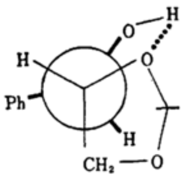
[7] J. Yoshimura, Y. Ohgo and T. Sato, This Bulletin, **34**, 1197 (1961).

[8] W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).

will be regulated by the balance of attractive force due to O_1H–O_2 hydrogen bonding and the repulsion between non-bonded groups. Most stable conformations of the *erythro* and *threo* may be represented by B and C respectively in which phenyl group is located in such a way that the non-bonded interaction may be minimized within the range making hydrogen bonding possible. If so, it can be expected from Karplus equations[9] that $J_{\mathrm{H_1H_2}}$ of *threo* is larger than that of the *erythro* compound. In the case of IIIa, signal at 5.15 due to H_1 splits in quartet (J=5 cps and 2.5 cps). By addition of H^+ the quartet changes to doublet with J=5 cps which is ascribed to $J_{\mathrm{H_1H_2}}$. The coupling constant ($J_{\mathrm{H_1H_2}}$) of IIIb is 8 cps. This fact is consistent with the above assumption.



B



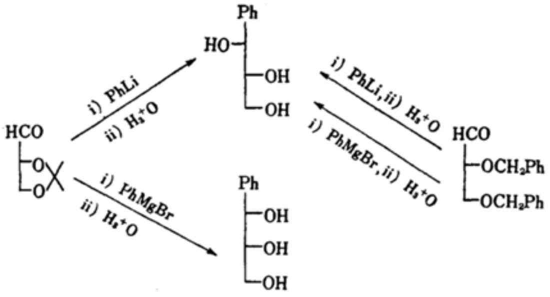
C

On the other hand, Va was correlated with VIa (mp 145.5°C) by benzoylation of the former. In consequence, series a (IIIa, Va, VIa) belongs to D-erythro type, and series b (IIIb, Vb, VIb) to D-threo type.[10]

The produced diastereomer ratio was calculated from optical rotations of *erythro* (VIa), *threo* (VIb) and the diastereomeric mixture produced in the reaction. The results are shown in Table 1.

As expected, the difference in stereoselectivity between the Grignard and phenyllithium reactions occurred with 2,3-*O*-isopropylidene-D-glyceraldehyde; the phenyllithium reaction gives *threo* and Grignard reaction *erythro* products predominantly.

On the other hand, the same reaction with 2,3-di-*O*-benzyl-D-glyceraldehyde gives no difference in stereoselectivity between the two reactions; *threo* product is predominant in both reactions. This may imply that C_3–O must be fixed in a certain steric position suitable to interaction with the reagent for the Grignard reaction to give *erythro* product.



Scheme 3

Experimental

The NMR spectrum was taken in deuteriochloroform solution with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 100 Mc/sec, using tetramethylsilane as an internal standard.

The hydrogen bonding measurements were performed in dilute CCl_4 solution on a Perkin-Elmer 125

TABLE 1

Run	Substrate	Reagent	Products					
			Optical rotation		Analysis		Ratio	
			$[\alpha]_{546}$	$[\alpha]_{578}$	C	H	*threo*	*erythro*
1	I	PhLi	−3.0	−3.6	74.99	5.25	63	37
2	I	PhMgBr	−20.0	−23.0	74.07	6.13	47*	53*
3	I	PhMgBr	−18.2	−21.7	74.79	5.12	48	52
4	II	PhLi	+0.5	−1.0	76.38	5.99	65	35
5	II	PhLi	−6.4	−7.4	75.71	5.50	60	40
6	II	PhMgBr	−6.5	−8	74.84	5.27	60	40
7	II	PhMgBr	−4.0	−4.5	75.73	5.61	62	38

* During the course of preparation of our article, a similar study was reported by M. H. Delton and G. U. Yuen [*J. Org. Chem.*, **33**, 2473 (1968)]. According to their report, the Grignard reaction gives *threo* products in 58% and *erythro* in 42% yield. The difference between their results and ours may be due to the difference in experimental methods, particularly in measurements. Delton and Yuen determined the diastereomeric ratio by gas chromatography, while we carried it out by optical rotation. In view of this, further experiments are now in progress and the results will be published later.

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9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

10) This assignment was confirmed by preliminary experiment deriving IIIa and IIIb to L(+) and D(−)-1-methoxyphenylacetaldehyde[5] respectively. More precise experiments are under investigation and will be published later.

grating spectrophotometer. The optical rotations were measured on a Carl Zeis Photoelectric Precision Polarimeter (0.005°).

Addition Reaction of 2,3-*O*-Isopropylidene-D-glyceraldehyde with Phenylmagnesium Bromide. A solution of 14 g of 2,3-*O*-isopropylidene-D-glyceraldehyde in 20 m*l* of ether was slowly added to a well-stirred solution of phenylmagnesium bromide prepared from 51 g (0.32 mol) of bromobenzene and 7.93 g. of magnesium in 170 m*l* of ether. The mixture was stirred for 1 hr at 0—5°C and for four hours at reflux-temperature of the ether solution. The reaction mixture was poured into ice-water containing ammonium chloride. The ether layer was separated, and washed with water. The solution was dried and concentrated under reduced pressure to give a syrup (16.5 g, yield 74%, $[\alpha]_{578}$ −4.77). The syrup was dissolved in 300 m*l* of ethanol and to the solution was added 4.4 m*l* of concentrated hydrochloric acid and 142 m*l* of water. The mixture was refluxed for 2 hr. The reaction mixture was neutralized by potassium carbonate solution and concentrated under reduced pressure. The residue was extracted twice with 100 m*l* of ethyl acetate. The combined ethyl acetate solution was concentrated *in vacuo* to give 6.5 g of syrup (yield 49%).

The diastereomeric mixture (5 g) of 1-*C*-phenyl-D-*threo*- and D-*erythro*-glycerol was treated with benzoyl chloride (14.2 g) and pyridine (8 g) in chloroform (40 m*l*) at room temperature. The mixture was allowed to stand overnight and then poured into ice-water. The chloroform layer was separated and washed with water repeatedly until the layer became neutral. The chloroform layer was dried and concentrated under about 15 mmHg and then under 0.001 mmHg at 80—100°C for 5 hr to give colorless crystals (14 g, yield 98%). Analytical data agreed with those of the 1,2,3-tri-*O*-benzoyl-1-*C*-phenyl-D-glycerol (see Table 1). Optical rotation was measured (c=2.00, l=0.5, benzene). Fractional crystallization from an ethanol-benzene mixture gave two diastereomers; VIa (1,2,3-tri-*O*-benzoyl-1-*C*-phenyl-*erythro*-D-glycerol) mp 145.5—146°C; $[\alpha]_{578}$ −70.5, $[\alpha]_{546}$ −81 (c=2.00, l=0.5, benzene); VIb (1,2,3-tri-*O*-benzoyl-1-*C*-phenyl-*threo*-D-glycerol) mp 139.5°C, $[\alpha]_{578}$ +36.5 (c=2.028, l=0.5, benzene), $[\alpha]_{546}$ +41.5. Found: C, 74.57; H, 5.08%. Calcd for $C_{30}H_{24}O_6$: C, 74.99; H, 5.03%.

Addition Reaction of I with Phenyllithium. A solution of 14 g of 2,3-*O*-isopropylidene-D-glyceraldehyde in 20 m*l* of ether was slowly added to a well-stirred solution of phenyllithium prepared from 51 g (0.32 mol) of bromobenzene and 4.48 g of lithium in 170 m*l* of ether. The same procedure as in the Grignard reaction gave a diastereomeric mixture of 1,2,3-tri-*O*-benzoyl-1-*C*-phenyl-*threo*-D- and *erythro*-D-glycerols in total yield of about 50%.

1-*C*-Phenyl-2,3-*O*-isopropylidene-*erythro*-D-glycerol (IIIa). 1-*C*-Phenyl-*erythro*-D-glycerol (Va) (12 g) was treated with 250 m*l* of acetone containing 19.3 g of zinc chloride at room temperature for 2 days. The reaction mixture was poured with stirring into a solution of K_2CO_3 (26 g) in 26 m*l* of water covered with 300 m*l* of ether. The acetone-ether solution was dried over potassium carbonate and then concentrated *in vacuo* to give 16 g of syrup. The syrup was distilled at 175—176°C/30 mmHg. Yield, 10 g, (67%). $[\alpha]_{578}$ +10.7, $[\alpha]_{546}$ +12.2 (c=2.052, ethanol).

Found: C, 69.22; H, 7.89%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

The infrared measurement was carried out in 0.013 molar carbon tetrachloride solution. The infrared spectrum shows free and bonded OH stretching vibrations at 3619 cm^{-1} and 3578 cm^{-1} respectively. The ratio of bonded OH to free OH absorption is about 2—2.5. NMR spectrum: CH_3, 8.55, 8.66; OH, 7.35 (doublet, J=2.5 cps, this doublet disappeared on addition of trifluoroacetic acid); H_3 and H_3', 6.15τ (multiplet); H_2, 5.72τ (multiplet); H_1, 5.15τ (quartet, $J_{H_1H_2}$=5 cps, J_{H_1OH}=2.5 cps); phenyl, 2.65τ.

1-*C*-Phenyl-2,3-*O*-isopropylidene-*threo*-D-glycerol (IIIb). Vb was converted to IIIb by the same procedure as above (Va to IIIa) (yield; 56%). $[\alpha]_{578}$= −24.7 (c=1.06, l=0.5, ethanol), $[\alpha]_{546}$=−27.5 (c= 1.06, l=0.5, ethanol).

Found: C, 68.85; H, 7.89%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

The infrared measurement was carried out in 0.0125 M carbon tetrachloride solution. The infrared spectum shows bonded OH stretching vibration at 3600 cm^{-1} but no substantial absorption at higher frequency region. NMR spectrum: CH_3, 8.5 and 8.46τ; H_3 and H_3', 6.2τ (unresolved multiplet); H_2, 5.75τ (multiplet); H_1, 5.5τ (doublet, $J_{H_1H_2}$=8 cps).

1-*C*-Phenyl-*erythro* and *threo*-D-glycerols (Va and Vb). The reaction of phenylmagnesium bromide (prepared from 17 g of magnesium and 7.35 m*l* of bromobenzene) in ether (350 m*l*) with an ether solution of 2,3-*O*-isopropylidene-D-glyceraldehyde followed by acid hydrolysis [with a mixture of ethanol (560 m*l*), water (270 m*l*) and 12 N HCl (20 m*l*)] gave a syrup (30 g) of a diastereomeric mixture of 1-*C*-phenyl-*erythro* and *threo*-D-glycerols. From the syrup 9.4 g of a crystalline compound was obtained: mp 103—105°C, $[\alpha]_{587}$ +18, $[\alpha]_{546}$ +20 (c=2, l=0.5, ethanol).

When the residual syrup was distilled at 150—153°C/ 0.09 mmHg and left standing at room temperature additional crystals (3 g) were obtained. Total yield of crystalline isomer is 12.4 g. The residual syrup weighed 12.7 g. The rotation of the residual syrup; $[\alpha]_{578}$ −24, $[\alpha]_{546}$ −28 (c=1.01, l=0.5, ethanol).

Addition Reaction of 2,3-Di-*O*-benzyl-D-glyceraldehyde with Phenylmagnesium Bromide. A solution of 10 g (0.037 mol) of 2,3-di-*O*-benzyl-D-glyceraldehyde in 20 m*l* ether was added slowly into a stirred solution of phenylmagnesium bromide prepared from 17.5 g (0.11 mol) of bromobenzene and 2.7 g of magnesium in 100 m*l* ether at 0—5°C.

The same procedure as in the case of addition reaction of I with organometallic reagents gave 11.5 g of syrup (yield 89%) of addition products. The syrup (7.2 g) obtained above was hydrogenated with 10 g of palladium-barium sulfate catalyst in 260 m*l* of ethanol containing concd. hydrochloric acid (2.6 m*l*). The reaction mixture was neutralized with a 2 N sodium hydroxide solution and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The ethyl acetate solution was concentrated to a syrup (3.7 g). 3.7 g of the diastereomeric mixture of 1-*C*-phenyl-D-glycerols was benzoylated with the same procedure as described before to give 10 g of the tribenzoate (100%). Fractional crystallization from a mixture of ethanol and benzene afforded two crystalline compounds of mp 145—146°C and mp 138—139°C. These compounds were identified with VIa and VIb (mixed melting point).

Addition Reaction of 2,3-Di-*O*-benzyl-D-glyceraldehyde (II) with Phenyllithium. A solution of 10 g of II in 20 m*l* ether was added slowly to a well-stirred solution of phenyllithium prepared from 17.5 g of bromobenzene and 1.54 g of lithium at 0—5°C. The same procedure as in the Grignard reaction gave a diastereomeric mixture of 1,2,3-tri-*O*-benzoyl-1-*C*-phenyl-D-*threo* and D-*erythro* glycerol. Analytical results and optical rotations of diastereomeric mixtures are shown in Table 1.

2,3-Di-*O*-benzyl-D-glyceraldehyde. To a solution of 40 g of 3,4-*O*-isopropylidene-D-mannitol in 400 m*l* of dimethyl sulfoxide was slowly added 50 g of 50% sodium hydride and then 220 m*l* of benzyl chloride with vigorous stirring. The mixture was heated on a water bath for 30 min and left standing overnight. The reaction mixture was poured into ice-water, extracted with benzene, benzene layer was washed with water, dried over sodium sulfate and concentrated *in vacuo*. Last traces of benzyl chloride and dimethyl sulfoxide were removed in a high vacuum. The syrup thus obtained has no absorption due to OH stretching vibration. Yield; 90 g.

A suspension of 90 g of 1,2;5,6-tetra-*O*-benzyl-3,4-*O*-isopropylidene-D-mannitol in 200 m*l* of ethanol, 70 m*l* of water and 36 m*l* of concentrated hydrochloric acid was refluxed for 2 hr, and concentrated under reduced pressure to about 100 m*l* and extracted with benzene (400 m*l*). The benzene layer was washed first with a potassium carbonate solution and then water. The benzene layer was concentrated to a syrup. The syrup was washed with petroleum ether and dried *in vacuo*. Yield, 67 g (70%).

To a vigorously stirred solution of 40 g of 1,2;5,6-tetra-*O*-benzyl-D-mannitol in 500 m*l* of benzene was added 34 g of lead tetraacetate. The reaction mixture was stirred at room temperature for 3 hr. The resulting precipitate was filtered off. The mother liquor was dried over sodium sulfate and concentrated under reduced pressure to give a syrup. The syrup was distilled at 143—144°C/0.003 mmHg. $[\alpha]_{578}$ +52, $[\alpha]_{546}$ +58 (c=2.00, l=0.5, benzene). Yield, 20 g.

Found: C, 75.59; H, 7.04%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

The distillate has no substantial absorption in the OH region but has a remarkable absorption at about 1715 cm^{-1} which is due to aldehydic carbonyl stretching vibration.

The authors express their cordial thanks to Mr. K. Fukukawa for measurements of NMR spectra.