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STEREOSELECTIVE SYNTHESIS OF MESO(OR ERYTHRO) 1,3-DIOLS FROM β-HYDROXYKETONES

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Meso(or erythro) 1,3-diols are prepared in high stereoselectivity from β-hydroxyketones by the treatment with tributylborane and the successive reduction with sodium borohydride.

Recent surge of interest in new solution to the problem of stereocontrolled synthesis of acyclic compounds have been generating various useful and stereoselective reactions and they were successfully applied to the syntheses of macrolides or ionophore antibiotics.[1] The stereoinductions in the relationships between adjacent carbon atoms (1,2-relationship) have been widely studied, however, there are few reports on the reactions establishing 1,3-relationships.[2] Recently, effective methods for 1,3-stereoinductions have been strongly required in synthetic chemistry, therefore, some attempts have been tried for the preparation of 1,3-diols from β-hydroxyketones accompanying 1,3-asymmetric induction.[3] But they are not so highly stereoselective and have limited utility. In this communication, we wish to report the effective method for stereoselective synthesis of 1,3-diols from β-hydroxyketones.

We expected that stable chelate complex(2) would be formed when β-hydroxyketone(1) is converted to the corresponding dibutylborinic acid ester and be sufficiently rigid to control the direction of the attack of nucleophiles to carbonyl group. Based on this assumption, the formation of dibutylborinic acid ester of β-hydroxyketone and the stereochemistry in the successive reduction was examined.

To a THF (3.5 ml) solution of tributylborane (1.1 mmol) and 7-hydroxy-5-undecanone (1b, 1.0 mmol) was bubbled a small amount of air(3 ml) and the solution was stirred for 2 h at room temperature.[4] Then the solution was cooled (temp. of cooling bath, -100°C), and a solid sodium borohydride (1.1 mmol) was added at once. The reaction mixture was stirred for 6 h, and quenched with a mixture of 30% hydrogen peroxide (5 ml), pH 7 buffer (10 ml) and methanol. Almost all the organic solvent was evaporated, and the residual water solution was extracted with methylene chloride. The extract was dried over Na_2SO_4 and condensed under reduced pressure. To the residue was added 5 × 4 ml of 1% conc. HCl in methanol and evaporated each under reduced pressure to decompose the small amount of remaining boric acid ester of diols.[5] Then resulting oily substance was chromatographed on silica gel (hexane:ether(6:1) mixture as eluent) to give meso 1,3-diol (3b) and

dl 1,3-diol (4b) in 72% and 2% yields respectively.

The reduction of 3-hydroxy-1,3-diphenyl-1-propanone(1a) and 1,3-dicyclohexyl-3-hydroxy-1-propanone(1c) were also carried out according to the same procedure and the results are summarized in Table.

As shown in Table, high stereoselectivity was achieved when the reduction was carried out at -100°C, and in all cases, meso diols(3) were obtained almost exclusively.

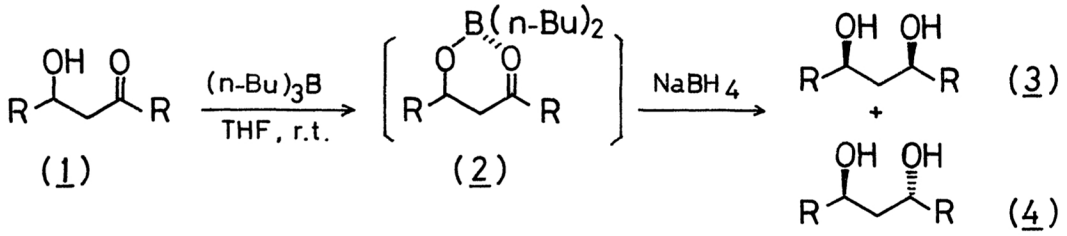
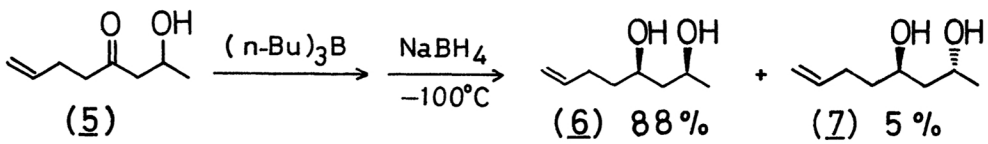


Table. Preparation of meso 1,3-diols*

1		Reaction temp. (Reaction time)	Ratio of meso(3):dl(4), (Total yield)
1a	R=C_6H_5	-78°C (2 h)	98: 2 (94%)[6]
1b	R=n-C_4H_9	-100°C (5 h)	96: 4 (74%)[7]
		-78°C (2 h)	88:12 (73%)
1c	R=cyclo-C_6H_{11}	-100°C (6 h)	84:16 (90%)[8]
		-78°C (6 h)	73:27 (94%)

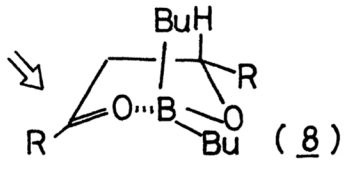
* All the products showed satisfactory IR and NMR spectra.

This procedure was also successfully applied to the synthesis of erythro 7-octene-2,4-diol(6), the synthetic intermediate of nonactic acid.[9] When 2-hydroxy-7-octen-4-one(5) was treated by the same procedure, the desired erythro-7-octene-2,4-diol(6) was obtained almost exclusively in 88% yield along with a small amount (5%) of threo isomer(7).[10]



The effective stereocontrol of the reduction may be explained by assuming either of following mechanisms. At the stage of boron chelate of β-hydroxy-ketone(2), two conformations are possible: i) When the chelate forms pseudo boat

conformation(8), the attack of hydride should proceed from less hindered side. ii) In the case where the chelate exists in pseudo chair conformation(9), the axial attack of hydride presumably occurs to allow maximum orbital overlap.[11] Hence, meso(or erythro) isomers are obtained predominantly.



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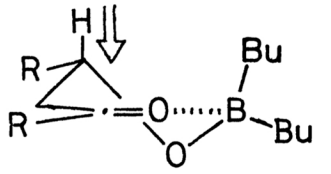

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In these days, a wide variety of β-hydroxyketones, the starting materials, are readily available by the directed aldol reactions. Therefore, the present procedure affords a synthetically useful method for the highly stereoselective preparation of meso(or erythro)diols from β-hydroxyketones.

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References and Notes

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4) The formation of the adduct(2) was ascertained by NMR study. The reaction mixture of 1a and tributylborane was condensed under reduced pressure and the

NMR spectrum of the residue showed the presence of two each of phenyl and butyl groups.

5) D. R. Knapp, "Handbook of Analytical Derivatization Reactions". John Wiley and Sons, Inc., P 545 (1979).

6) Meso and dl isomers were not separated by tlc or glpc. At the stage of $NaBH_4$ reduction, butylboronic acid ester (10) was formed in the reaction mixture. So the isomer ratio was determined based on glpc analysis of the reaction mixture by comparison with authentic sample. The NMR spectrum of crude product was indentical with that of meso isomer (3a),[12] and after recrystalization from benzene, pure meso isomer was obtained; mp 106-7°C.[3a, 12a]

7) 3b: bp 125°C/1 mmHg (bath temp.); Found, C, 70.04; H, 12.85%. Calcd for $C_{11}H_{24}O_2$, C, 70.16; H, 12.85%. 4b: mp 76-8°C. Found, C, 70.34; H, 13.15%. Calcd for $C_{11}H_{24}O_2$, C, 76.16; H, 12.85%. Stereochemistry was assigned by NMR study of phenylboronic acid esters(11) or 3b and 4b, which were prepared by the treatment with phenylboronic acid in the presence of molecular sieve in benzene at room temp.: 11 from 3b; NMR($CDCl_3$) δ 1.90 (1H; d×t; J=13, 3 Hz; -CH-C(H)H-CH-); 11 from 4b; NMR($CDCl_3$) δ 1.77 (2H; t; J=6 Hz; -CH-CH_2-CH-).

8) 3c: mp 109-110°C, Found, C, 75.00; H, 11.84%. Calcd for $C_{15}H_{28}O_2$, C, 74.95; H, 11.74%. 4c: mp 148-150°C; Found, C, 74.96; H, 11.86%. Calcd for $C_{15}H_{28}O_2$, C, 74.95; H, 11.74%. Each isomer (3c, 4c) was allowed to react with benzaldehyde in the presence of molecular sieve to prepare acetal. From the reaction of 3c, it is expected to obtain two isomers, but only one product was isolated: NMR($CDCl_3$) δ 3.44 (2H; d×d×d; J=10.2, 6.6, 3.3 Hz; Hex-CH-). Also one kind of acetal was obtained from 4c: NMR($CDCl_3$) δ 3.87-3.53 (m, 2H).

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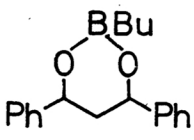

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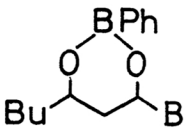

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