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Catalytic Enantioselective Reactions Part 7. Synthesis of New β-Aminoalcohols Derived from α-D-Glucose as Chiral Catalysts for the Catalytic Enantioselective Addition of Diethylzinc to Aldehydes

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CATALYTIC ENANTIOSELECTIVE REACTIONS PART 7. SYNTHESIS OF NEW β-AMINOALCOHOLS DERIVED FROM α-D-GLUCOSE AS CHIRAL CATALYSTS FOR THE CATALYTIC ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES

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Abstract: A series of new 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-*N*,*N*-dialkylamino-α-D-glucofuranoses **1** and 1,2-*O*-isopropylidene-3,6-dideoxy-6-*N*,*N*-dialkylamino-α-D-glucofuranoses **1'** were prepared from α-D-glucose and their enantioselectivities compared as chiral catalysts for the ethylation of benzaldehyde and heptanal with diethylzinc.

The catalytic enantioselective addition of diorganozincs to aldehydes is a potentially important method for the preparation of optically active alcohols.[1] Accordingly, a wide variety of chiral catalysts for the enantioselective addition

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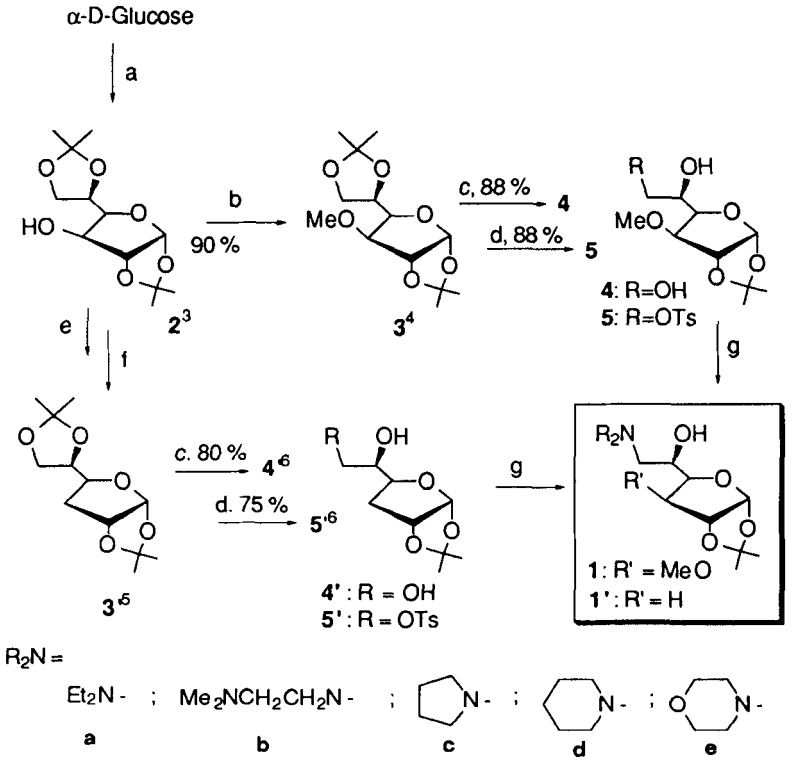
reaction has been extensively developed.[1a] Among them, most of highly effective chiral catalysts for the reaction are β-aminoalcohols derived from natural products, such as camphor, α-amino acids, norephedrine and cinchona alkaloids. And also several kinds of unnatural chiral aminoalcohol derivatives proved to be potentially chiral catalysts to afford high optical induction for such reaction. Recently we have reported that γ-aminoalcohol derivatives obained from α-D-xylose can catalyze highly enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes.[2] In continuation with our study on the preparation of new chiral catalysts from carbohydrate for such reaction, we wish hereby to report the preparation of chiral β-aminoalcohols derived from α-D-glucose and their enantioselectivities as new catalysts for the catalytic enantioselective addition of diethylzinc to aldehydes.

We initially prepared a series of 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-*N*,*N*-dialkylamino-α-D-glucofuranose derivatives **1** possessing a variety of dialkylamino substituents at the 6-position of the aminoalcohol moiety.

The chiral ligands **1** were synthesized from α-D-glucose in five steps. Thus, anhydrous α-D-glucose was reacted with acetone in the presence of concentrated sulfuric acid to give 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2**[3] in a 80 % yield. And then **2** was methylated with dimethyl sulfate to give 1,2-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **3**[4] in a 90 % yield. 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **4** obtained from partial hydrolysis of **3** with 0.2 % hydrochloric acid was reacted with *p*-toluenesulfonyl chloride in the presence of pyridine to provide 1,2-*O*-isopropylidene-3-*O*-methyl-6-*p*-toluenesufonyl-α-D-glucofuranose **5** in a 88 % yield. Finally, **5** was reacted with excess dialkylamines, such as *N*,*N*-diethylamine, *N*,*N*,*N*′-



Scheme 1

trimethylethylenediamine, pyrrolidine, piperidine and morpholine in 2-propanol at reflux temperature to give the corresponding β-aminoalcohols **1a-e** in 45-75 % yields. Similarly we also prepared1,2-*O*-isopropylidene-3,6-dideoxy-6-*N*,*N*-dialkylamino-α-D-glucofura-nose derivatives **1'd-e** from the amination of 1,2-*O*-isopropyli-dene-3-*deoxy*-*p*-toluenesufonyl-α-D-glucofuranose **4'**[6] with excess of piperidine and morpholine. The results are summarized in Scheme 1 and Table 1.

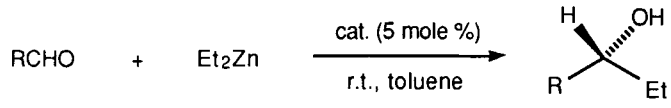
Table 1. Synthesis of 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-*N,N*-dialkylamino-α-D-glucofuranoses **1** and 1,2-*O*-isopropylidene-3,6-dideoxy-6-*N,N*-dialkylamino-α-D-glucofuranoses **1'** [a,b]

Cpds.	Yield[c] (%)	B.p.(° C / mmHg) or M.p. (°C)	$[\alpha]_D^{24}$ (*c* 1, $CHCl_3$)
1a	75	(106-108 / 0.8)	- 17.42
1b	45	(129-130 / 0.25)	- 21.25
1c	75	(130-132 / 0.8)	- 14.36
1d	54	(124-126 / 0.25)	- 9.36
1e	64	(151-152 / 0.6)	- 11.34
1'd	65	73-74	8.52
1'e	60	54-55	9.65

[a] Obtained from the reaction of **4** (1 eq) with dialkylamines (4 eq) in 2-propanol at reflux temperature, unless otherwise indicated. [b] For the structures of **1** and **1'**, satifactory results were obtained from IR, NMR (^1H and ^{13}C) spectroscopic and analytical analyses data: see experimental part. [c] Isolated yields.

Next, we compared their enantioselectivities of the β-aminoalcohols using **1** and **1'** as chiral catalysts for the enantioselective addition of diethylzinc to aldehydes. Thus, benzaldehyde and heptanal were chosen as representative. Diethylzinc (2 eq) was treated with the aldehyde in the presence of 5 mole % of each of **1a-e** and **1'd-e** in toluene at room temperature (ca. 25 °C). All the reactions examined proceeded smoothly to afford the corresponding alcohols in high yields. The optical purities of the product alcohols were determined by capillary GC analyses of their MTPA esters.[7] Unfortunately, all the catalysts examined afforded low optical inductions (0-48 % ee) for both benzaldehyde

Table 2. Comparison of Enantioselective Addition of Diethylzinc to Benzaldehyde and Heptanal in the Presence of 5 Mole % of **1** and **1'** in Toluene at Room Temperature[a]



Cat.	1-phenyl-1-propanol				3-nonanol			
	time	yield[b]	% ee[c]	confg.[d]	time	yield[b]	% ee[c]	confg.[d]
1a	10 h	93	14	S	10 h	80	18	S
1b	10 h	92	9	S	10 h	78	0	
1c	10 h	94	43	S	10 h	85	33	S
1d	10 h	95	48	S	10 h	85	41	S
1e	10 h	92	42	S	10 h	83	45	S
1'd	10 h	98	47	S	10 h	86	43	S
1'e	10 h	94	46	S	10 h	80	47	S

[a] [aldehyde] : [catalysts] : [Et_2Zn] = 1 : 0.05 : 2. [b] GC yields. [c] Determined by capillary GC analyses of (+)-MTPA esters. [d] Based on the sign of optical rotations and elution orders of peaks in GC.

and heptanal. However, the absolute configurations of all the product alcohols obtained are consistently enriched in the S enantiomers. The comparison study on the catalytic enantioseletive addition to the same aldehydes with **1** and **1'**, showed that the substituent group attached at the C-3 position of the furanose ring in the chiral ligands used did not provide any significant effect on the asymmetric induction for the catalytic ethylation reaction. The results are summarized in Table 2.

In conclusion, we synthesized new β-aminoalcohols from α-D-glucose for the enantioselective ethylation to aldehydes and compared the enantioselective addition of diethylzinc to benzaldehyde and heptanal using the aminoalcohols as

chiral catalysts. Further applications of these chiral catalysts to other asymmetric reaction are now under investigation.

Experimental

General. All reactions with air sensitive materials were carried out under static pressure of nitrogen. Liquid materials were transferred with a double-ended needles. ^{1}H NMR spectra were conducted on Varian Gemini 300 (300 MHz) spectrometer with Me_4Si as an internal standard. IR measurements were recorded on a Shimadzu IR-435 ratio recording spectrophotometer equipped with a Shimadzu data recorder. Optical rotations were measured with a Rudolph polarimeter Autopol III. All Gc analyses were carried out with Shimadzu GC-7A gas chromatograph and Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 3390A intergrater / plotter. Enantiomeric excesses (% ee) were determined by capillary Gc analyses of the corresponding MTPA ester of product alcohol using a Hewlett-Packard 5890 gas chromatograph equipped with a 50 m methyl silicon capillary column.

Materials. Most of the organic compounds utilized in this study were commercial products of the higest purity. They were further purified by distillation when necessary. Diehylzinc and commercially available dialkyamines were purchased from Aldrich Chemical Company. 1,2-*O*-isopropylidene-3-*O*-methyl-6-*p*-toluenesufonyl-α-D-glucofuranose **5** was prepared by tosylation of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **4** obtained by a partial hydroysis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **3**[4], with *p*-toluene-sulfonyl chlroride using a usual manner. 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-*p*-toluenesufonyl-α-D-glucofuranose **5'** was prepared by the literature[6]

from the 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranose **3'**.[5] (R)-MTPA was purchased from Aldrich Chemical Company and was converted to the acid chloride.

Preparation of 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-*N*,*N*-dialkylamino-α-D-glucofuranose. The preparation of 1,2-isopropylidene-3-*O*-methyl-6-deoxy-6-pyrrolidino-α-D-glucofuranose **1c** is representative. The mixture of **5** (10 mmol) and pyrroridine (40 mmol) in 2-propanol (20 ml) was heated to reflux for 24 h. After evaporation of solvent and excess amine *in vacuo*, the residue was treated with saturated $NaHCO_3$ and extracted with ether. The extracts were concentrated to dryness and the product **1c** was isolated by a bulb-to-bulb distillation in a 75 % yield : pale yellow oil ; b.p. 130-132 °C / 0.8 mmHg ; $[\alpha]_D^{24}$ - 14.36 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}), 3425, 2926, 2927, 1457, 1380, 1304; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32(s, 3 H, $C\underline{H}_3$), 1.48(s, 3 H, $C\underline{H}_3$), 1.64-1.80(m, 4 H, $\overline{CH_2C\underline{H}_2C\underline{H}_2CH_2N}$), 2.46-2.84(m, 6 H, $\overline{C\underline{H}_2CH_2CH_2C\underline{H}_2N}$ and <u>H-6</u>), 3.50(s, 3 H, OCH_3), 3.83-4.24(m, 3 H, <u>H-3, 4</u> and <u>5</u>), 4.57(d, 1 H, J = 2.0 Hz, <u>H-2</u>), 5.88 (d, 1 H, J =2.1 Hz, <u>H-1</u>); ^{13}C NMR(75.46 MHz, $CDCl_3$, TMS) δ 112.0 , 105.5, 84.2, 82.6, 82.9, 81.9, 65.3, 60.1, 58.3, 54.5, 26.9, 26.3 and 23.7 ; Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52 ; H, 8.77 ; N, 4.87. Found: C, 59.01 ; H, 9.01 ; N, 4.76. Using the same procedure, 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-N,N-diethylamino-α-D-glucofuranose **1a**, 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-N,N-N'-trimethylamino-α-D-glucofuranose **1b**, 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-piperidino-α-D-glucofuranose **1d** and 1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-morpholino-α-D-glucofuranose **1e** were prepared. 1,2-*O*-isopropylidene-3,6-dideoxy-6-piperidino-α-D-glucofuranose **1'd** and 1,2-*O*-isopropylidene-3,6-dideoxy-6-morpholino-α-D-glucofuranose **1'e** was obtained from the reaction of

1,2-*O*-isopropylidene-3-*O*-methyl-6-deoxy-6-N,N-diethylamino-α-D-glucofuranose **5'** with the corresponding amines using the same methods as described above. The physical and spectroscopic data of **1a-b, 1d-e** and **1'd-e** are as follows:

1a : 75 % yield ; pale yellow oil ; bp 106-108 °C / 0.8 mmHg ; $[\alpha]_D^{24}$ - 17.42 (*c* 1, $CHCl_3$) ; IR (neat, cm^{-1}) 3441, 2964, 2818, 1455, 1380, 1316 ; ^1H NMR ($CDCl_3$) δ 1.05 (t, 6 H), 1.32(s, 3 H), 1.49 (s, 3 H), 2.45-2.78 (m, 6 H), 3.50 (s, 3 H), 3.84-3.92 (m, 3 H), 4,57 (d, 1 H, J = 3.9 Hz), 5.88 (d, 1 H, J = 3.6 Hz) ; ^{13}C NMR ($CDCl_3$) δ 111.6, 105.1, 83.9, 82.6, 81.6, 63.1, 58.1, 57.0, 46.9, 26.5, 25.9 and 11.6 ; Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11 ; H, 9.41 ; N, 4.84. Found: C, 58.24 ; H, 9.93 ; N, 4.79.

1b : 45 % yield ; pale yellow oil ; bp 129-130 °C / 0.25 mmHg ; $[\alpha]_D^{24}$ - 21.25 (*c* 1, $CHCl_3$) ; IR (neat, cm^{-1}), 3368, 3141, 2969, 2812, 1458, 1378, 1302 ; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.49 (s, 3 H), 2.25 (s, 6 H), 2.38 (s, 3 H,), 2.27-2.70 (m, 6 H), 3.50 (s, 3 H), 3.86-3.97 (m, 3 H), 4,57 (d, 1 H, J = 3.8 Hz), 5.87 (d, 1 H, J = 3.8 Hz) ; ^{13}C NMR ($CDCl_3$) δ 111.9, 105.5, 84.1, 82.2, 82.1, 65.5, 59.9, 58.5, 57.3, 55.2, 45.1, 44.6, 26.9 and 26.3 ; Anal. Calcd for $C_{15}H_{30}N_2O_5$: C, 56.58 ; H, 9.50 ; N, 8.80. Found: C, 56.84 ; H, 9.65 ; N, 8.34.

1d : 54 % yield ; pale yellow oil ; bp 124-126 °C / 0.25 mmHg ; $[\alpha]_D^{24}$ - 9.36 (*c* 1, $CHCl_3$) ; IR (neat, cm^{-1}), 3416, 2975, 2852, 1378, 1305 ; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 1.26-1.57 (m, 6 H), 2.25-2.61 (m, 6 H), 3.50 (s, 3 H), 3.81-3.98 (m, 3 H), 4.57 (br. s, 1 H), 5.87 (br. s, 1 H) ; ^{13}C NMR ($CDCl_3$) δ 112.0, 105.5, 84.2, 82.9, 81.9, 63.1, 62.6, 58.4, 54.9, 26.8, 26.3, 26.2, 24.3 ; Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.77 ; H, 9.03 ; N, 4.65. Found: C, 60.47 ; H, 9.25 ; N, 4.83.

1e : 64 % yield ; pale yellow oil ; bp 151-152 °C / 0.6 mmHg ; $[\alpha]_D^{24}$ -11.34 (*c* 1, $CHCl_3$) ; IR (neat, cm^{-1}), 3437, 2923, 2818, 1452, 1372, 1303 ; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 2.45-2.53 (m, 3 H), 2.67-2.72 (m 3 H), 3.49 (s, 3 H), 3.70-3.78 (m, 4 H), 3.87-3.98 (m, 3 H), 4.58 (d, 1 H, J = 3.8 Hz), 5.88 (d, 1 H, J = 3.6 Hz) ; ^{13}C NMR ($CDCl_3$) δ 112.1, 105.5, 84.2, 82.4, 81.9, 67.2, 63.5, 62.6, 58.3, 54.0, 26.9, 26.3, 26.3 ; Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43 ; H, 8.38 ; N, 4.62. Found: C, 55.41 ; H, 8.38 ; N, 4.70.

1'd : 65 % yield ; m.p. 73-74 °C ; $[\alpha]_D^{24}$ 8.52 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3504, 3346, 2978, 2856, 1435, 1382, 1302 ; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.50 (s, 3 H), 1.41-1.60 (m, 6 H), 1.81-2.57 (m, 8 H), 3.77-3.84 (m, 1 H), 4.03-4.10 (m, 1 H), 4.74 (t, 1 H, J = 4.4 Hz), 5.81 (d, 1 H, J = 3.6 Hz) ; ^{13}C NMR ($CDCl_3$) δ 111.5, 105.9, 80.8, 80.4, 67.6, 61.8, 54.9, 34.4 26.9, 26.3, 26.2, 24.4 ; Anal. Calcd for $C_{14}H_{25}NO_5$: C, 61.97 ; H, 9.29 ; N, 5.16. Found: C, 62.61 ; H, 9.48 ; N, 5.07.

1'e : 60 % yield ; m.p. 54-55 °C ; $[\alpha]_D^{24}$ 9.65 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3449, 3335, 2988, 2885, 1456, 1376, 1316 ; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.51 (s, 3 H), 1.86-1.91 (m, 1 H), 2.12 (dd, 1 H, J = 13.5 and 4.5 Hz), 2.37-2.53 (m, 4 H), 2.57-2.67 (m, 2 H), 2.90-3.05 (br. s, 1 H), 3.66-3.74 (m, 4 H), 3.84-3.90 (m, 1 H), 4.58 (d, 1 H, J = 4.3 Hz), 5.82 (d, 1 H, J = 3.6 Hz) ; ^{13}C NMR ($CDCl_3$) δ 111.8, 105.9, 80.8 80.1, 67.6, 67.2, 61.7, 53.9, 34.2, 26.9, 26.3 ; Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.12 ; H, 8.48 ; N, 5.13. Found: C, 56.65 ; H, 8.40 ; N, 5.00.

Enantioselective addition of diethylzinc to benzaldehyde in the presence of 5 mole % of 1 or 1'. The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (3.6 ml) of diethylzinc (4 mmol) was added to **1c** (28.7 mg, 0.1 mmol) in toluene (0.4 ml) and stirred at room

temperature for 30 min. After benzaldehyde (212 mg, 2 mmol) was added to this, the mixture was stirred at the same temperature for 10 h and then diluted with ether (15 ml). The excess diethylzinc was destroyed by addition of 1. 5 N HCl (10 ml). The mixture was then extracted with ether (3 x 15 ml). GC analysis indicated the formation of 1-phenyl-1-propanol in 94 % yield. The extract was dried over anhydrous Na_2SO_4 and concetrated under reduced pressure. The product alcohol was isolated by bulb-to-bulb distillation and further purified with silica gel column chromatography. Enantiomeric excess was measured by GC analysis of its diastereoisomer of (+)-MTPA ester of the product alcohol using a 50 m methyl silicon capillary column. The diastereomeric ratio by GC analysis showed a composition of 71.5 (S) and 28.5 (S) (*i.e.*, 43 % ee).

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MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid.

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