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Preparation of 1,2-Isopropylidene-5-deoxy-5-dialkylamino-α-D-xylofuranose Derivatives as Chiral Catalysts for Enantioselective Addition of Diethylzinc to Aldehydes

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PREPARATION OF 1,2-ISOPROPYLIDENE-5-DEOXY-5-DIALKYLAMINO-α-D-XYLOFURANOSE DERIVATIVES AS CHIRAL CATALYSTS FOR ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES[1]

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Abstract: A series of new 1,2-isopropylidene-5-deoxy-5-dialkylamino-α-D-xylofuranose derivatives were prepared from α-D-xylose and compared their enantioselectivities as chiral catalysts for the ethylation of benzaldehyde with diethylzinc.

The catalytic enantioselective alkylation of carbonyl compounds is a potentially important method for the preparation of optically active alcohols. Considerable attention has been focused on the addition of diorganozinc reagents to aldehydes mediated by a wide range of chiral catalysts affording the products alcohols with high asymmetric induction.[2] Among them, it is generally realized

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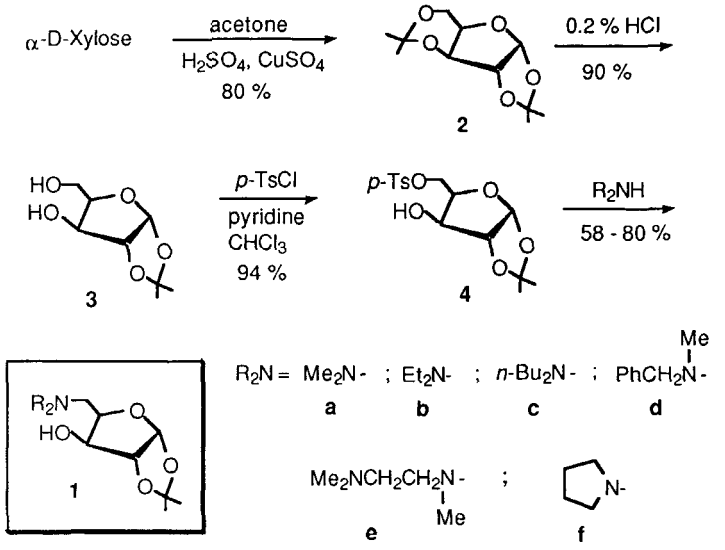
Scheme 1



that sterically congested β-aminoalcohols able to form a five membered ring are the most successful catalysts to provide high enantioselectivities for such reactions.

In our preliminary results[3], we found that a γ-aminoalcohol, 1,2-isopropylidene-5-deoxy-5-mopholino-α-D-xylofuranose, was a very effective catalyst for the ethylation of aldehydes with diethylzinc leading to optically active secondary alcohols with high enantioseletivities. In order to gain a better understanding of the catalytic effects and with the hope of developing improved chiral catalysts for the enantioselective alkylation of aldehydes, we prepared a series of new 1,2-isopropylidene-5-deoxy-5-dialkyamino-α-D-xylofuranose derivatives **1** possessing a variety of dialkylamino substituents at the 5-position of the xylofuranose ring moiety and compared their enantioselectivities as chiral catalysts for such reactions. Thus, the reactions of 1,2-isopropylidene-5-*p*-toluenesufonyl-

Table 1. Synthesis of 1,2-Isopropylidene-5-Deoxy-5-Dialkylamino-α-D-Xylofuranose Derivatives **1**[a,b]

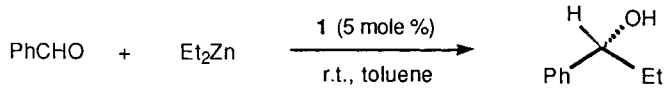
Cpds.	Yield[c] (%)	B.p.(°C / mmHg) or M.p. (°C)	$[\alpha]_D^{24}$ (*c* 1, $CHCl_3$)
1a	70[d]	(78 / 0.2)	2.54
1b	74	(80 / 0.15)	17.10
1c	61	(146-149 / 0.2)	10.66
1d	77	(164-165 / 0.15)	11.57
1e	58	(132 / 0.01)	-58.67
1f	80	94 - 95	7.06

[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**, satifactory results were obtained from IR, NMR (^1H and ^{13}C) spectroscopic and analytical analyses data: see experimental part. [c] Isolated yields. [d]The reaction was carried out with excess 50 % dimethylamine in water in a pressure bottle at 100 °C.

α-D-xylofuranose **4**[4], which was obtained from tosylation of 1,2-isopropylidene-α-D-xylofuranose **3**[5], with excess dialkylamines, such as N,N-dimethylamine, N,N-diethylamine, N,N-di-*n*-butylamine, N-methylbenzylamine, N,N,N'-trimethylethylenediamine and pyrrolidine were carried out. The reactions proceeded smoothly to give the corresponding γ-aminoalcohols **1a-f** in 58 - 80 % yields (Scheme 1 and Table 1).

Next, to compare the reactivities and the effectiveness of these γ-aminoalcohols **1** as chiral catalysts for the enantioselective addition of diethylzinc to aldehydes, we selected benzaldehyde as representative. Diethylzinc (2 eq) was treated with the aldehyde in the presence of 5 mole % of each of **1a-f** in toluene at room temperature (ca. 25 °C). With one exception (**1e**), all the reaction examined proceeded smoothly to afford the corresponding alcohols in high yields. Although

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



Catalysts (**1**)	Time (h)	1-phenyl-1-propanol		
		Yield[b] (%)	% ee[c]	Abs. confg.[d]
a	24	88	86	R
b	10	90	81	R
c	10	86	64	R
d	10	85	75	R
e	2[e]	98	30	R
f	10	90	90	R

[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. [e] At 70 °C.

the reaction with **1e** proceeded very slowly at room temperature, the reaction is complete within 2 h at 70 °C. Enantiomeric excesses of the products alcohols were determined by capillary GC analyses of their MTPA esters.[6] The catalysts **1a** and **1f** were highly effective for the enantioselective addition to benzaldehyde to give 1-phenyl-1-propanol with 86 and 90 % ee, respectively. The catalyst **1e** afforded low stereoselectivity (30 % ee). The results are summarized in Table 2.

In conclusion, we synthesized new chiral catalysts from α-D-xylose for enantioselective ethylation and compared the catalytic enantioselective addition of diethylzinc to benzaldehyde with them. Further application 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. Melting points were determined with a Fisher-Johns melting point apparatus. 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.

Preparation of 1,2-isopropylidene-5-deoxy-5-dialkyamino-α-D-xylofuranose. The preparation of 1,2-isopropylidene-5-deoxy-5-pyrrolidino-α-D-xylo-furanose **1f** is representative. The mixture of **4** (10 mmol) and pyrrolidine (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 **1f** was obtained by crystallization with hexane in the yield of 80 %: m.p. 94-95 °C ; $[\alpha]_D^{24}$ 7.06 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}), 3296, 3182, 2953, 2800, 1457, 1379; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32(s, 3 H, CH_3), 1.47(s, 3 H, CH_3), 1.71-1.76(m, 4 H, $CH_2CH_2CH_2CH_2N$), 2.55-2.58(m, 2 H, $CH_aH_bCH_2CH_2CH_aH_bN$), 2.80-2.83(m, 2 H, $CH_aH_bCH_2CH_2CH_aH_bN$), 3.02(dd, 1 H, $J_{Ha,H4}$ = 3.0 Hz, J_{gem} = 14.1 Hz, H-5a), 3.24(dd, 1 H, $J_{Hb,H4}$ = 2.5 Hz, J_{gem} =

14.2 Hz, H-5b), 4.14(dd, 1 H, J = 5.3 and 2.65 Hz, H-4), 4.31(d, 1 H, J = 2.75 Hz, H-3), 4,49 (d, 1 H, J = 3.6 Hz, H-2), 5.97 (d, 1 H, J =3.6 Hz, H-1); ^{13}C NMR(75.46 MHz, $CDCl_3$, TMS) δ 111.7 ($\underline{C}Me_2$), 105.3 (C-1), 86.3 (C-2), 78.5 (C-3), 77.3 (C-4), 55.9 (C-5), 55.4 ($\underline{C}H_2CH_2CH_2\underline{C}H_2N$), 26.9 and 26.2 [$(\underline{C}H_3)_2C$], 23.7($\underline{C}H_2CH_2\underline{C}H_2CH_2N$); Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24 ; H, 8.69 ; N, 5.76. Found: C, 59.95 ; H, 8.69 ; N, 5.82.

Using the same procedure, 1,2-isopropylidene-5-deoxy-5-N,N-diethylamino-α-D-xylofuranose **1b**, 1,2-iso-propylidene-5-deoxy-5-N,N-dibutylamino-α-D-xylofuranose **1c**, 1,2-isopropylidene-5-deoxy-5-N-benzyl-N-methylamino-α-D-xylofuranose **1d** and 1,2-iso-propylidene-5-deoxy-5-N,N,N'-trimethylethylenediamino-α-D-xylofuranose **1e** were prepared. 1,2-isopropylidene-5-deoxy-5-N,N-dimethylamino-α-D-xylofuranose **1a** was obtained from the reaction of **4** (10 mmol) and dimethylamine (50 wt. % solution in water, 10 ml) for 6 h at 100 °C in a pressure bottle. The physical and spectroscopic data of **1a-d** are as follws:

1a : 70 % yield ; colorless oil ; bp 78 °C/0.2 mmHg ; $[\alpha]_D^{24}$ 2.54 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3319, 3191, 2975, 2858, 1452, 1380 ; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H, $C\underline{H}_3$), 1.47 (s, 3 H, $C\underline{H}_3$), 2.36 (s, 6 H, $C\underline{H}_3NC\underline{H}_3$), 2.89 (dd, 1 H, J_{HaH4} = 2.8 Hz, J_{gem} = 14.3 Hz, H-5a), 2.98 (dd, 1 H, J_{HbH4} = 3.1 Hz, J_{gem} = 14.4 Hz, H-5b), 4.12 (dd, 1 H, J_{H4H5} = 5.74 Hz, J_{H4H3} = 3.0 Hz, H-4), 4.31 (d, 1 H, J_{H3H4} = 2.7 Hz, H-3), 4.50 (d, 1 H, J_{H2H1} = 3.85 Hz, H-2), 5.97 (d, 1 H, J_{H1H2} = 3.85 Hz, H-1) ; ^{13}C NMR ($CDCl_3$) δ 111.7 ($\underline{C}Me_2$), 105.3 (C-1), 86.1 (C-2), 78.4 (C-3), 77.4 (C-4), 58.6 (C-5), 47.4 ($H_3\underline{C}N\underline{C}H_3$), 26.8 and 26.3 ($H_3\underline{C}C\underline{C}H_3$) ; Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.29 ; H, 8.81 ; N, 6.45. Found: C, 55.27 ; H, 9.02 ; N, 6.55.

1b : 74 % yield ; colorless oil ; bp 84 °C/0.15 mmHg ; $[\alpha]_D^{24}$ 17.10 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3346, 3082, 2965, 2817, 1455, 1380 ; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 6 H, J = 7.2 Hz, $C\underline{H}_3CH_2NCH_2C\underline{H}_3$), 1.32 (s, 3 H, $C\underline{H}_3$),

1.47 (s, 3 H, $C\underline{H}_3$), 2.50 (dq, 2 H, J = 7.0 Hz, J_{gem} = 13.0 Hz, $CH_3C\underline{H}_aH_bNC\underline{H}_aH_b$-$CH_3$), 2.82 (dq, 2 H, J = 7.0 Hz, J_{gem} = 13.0 Hz, $CH_3CH_a\underline{H}_bNCH_a\underline{H}_bCH_3$), 2.95 (dd, 1 H, J_{HaH4} = 3.0 Hz, J_{gem} = 14.8 Hz, H-5a), 3.14 (dd, 1 H, J_{HbH4} = 2.7 Hz, J_{gem} = 14.8 Hz, H-5b), 4.11 (dd, 1 H, J_{H4H5} = 5.5 Hz, J_{H4H3} = 2.8 Hz, H-4), 4.29 (d, 1 H, J_{H3H4} = 2.5 Hz, H-3), 4.48 (d, 1 H, J_{H2H1} = 3.8 Hz, H-2), 5.97 (d, 1 H, J_{H1H2} = 3.6 Hz, H-1) ; ^{13}C NMR ($CDCl_3$) δ 111.7 ($\underline{C}Me_2$), 105.3 (C-1), 86.1 (C-2), 78.1 (C-3), 77.4 (C-4), 52.9 (C-5), 48.5 ($H_3\underline{C}N\underline{C}H_3$), 26.9 and 26.2 ($H_3\underline{C}C\underline{C}H_3$), 23.7 ($\underline{C}H_3CH_2NCH_2\underline{C}H_3$) ; Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.76 ; H, 9.45 ; N, 5.63. Found: C, 58.64 ; H, 9.47 ; N, 5.63.

1c : 61 % yield ; pale yellow oil ; bp 146-149 °C/0.2 mmHg ; $[\alpha]_D^{24}$ 10.66 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3348, 3109, 2953, 2820, 1466, 1370 ; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6 H, J = 7.3 Hz, $C\underline{H}_3$), 1.24-1.34 (m, 4 H, $C\underline{H}_2$), 1.32 (s, 3 H, $C\underline{H}_3$), 1.35-1.48 (m, 4 H, $C\underline{H}_2$), 1.47 (s, 3 H, $C\underline{H}_3$), 2.33-2.42 (m, 2 H, $CH_3CH_2CH_2C\underline{H}_aH_bNC\underline{H}_aH_bCH_2CH_2CH_3$), 2.68-2.78 (m, 2 H, $CH_3CH_2CH_2$-$CH_a\underline{H}_bNCH_a\underline{H}_bCH_2CH_2CH_3$), 2.95 (dd, 1 H, J_{HaH4} = 2.9 Hz, J_{gem} = 14.8 Hz, H-5a), 3.12 (dd, 1 H, J_{HbH4} = 2.9 Hz, J_{gem} = 14.8 Hz, H-5b), 4.11 (dd, 1 H, J_{H4H5} = 5.45 Hz, J_{H4H3} = 2.76 Hz, H-4), 4.29 (d, 1 H, J_{H3H4} = 2.5 Hz, H-3), 4.48 (d, 1 H, J_{H2H1} = 3.6 Hz, H-2), 5.96 (d, 1 H, J_{H1H2} = 3.6 Hz, H-1) ; ^{13}C NMR ($CDCl_3$) δ 111.7 ($\underline{C}Me_2$), 105.3 (C-1), 86.0 (C-2), 78.1 (C-3), 77.6 (C-4), 55.4 (C-5), 54.2 (-$H_2\underline{C}N\underline{C}H_2$-), 28.7 (-$\underline{C}H_2CH_2NCH_2\underline{C}H_2$-), 26.8 and 26.2 ($H_3\underline{C}C\underline{C}H_3$), 20.6 (-$\underline{C}H_2CH_2$-$CH_2NCH_2CH_2\underline{C}H_2$-), 14.7 ($\underline{C}H_3CH_2CH_2$-$CH_2NCH_2CH_2CH_2\underline{C}H_3$) ; Anal. Calcd for $C_{16}H_{31}NO_4$: C, 63.75 ; H, 10.38 ; N, 4.65. Found: C, 63.80 ; H, 10.60 ; N, 5.15.

1d : 77 % yield ; pale yellow oil ; bp 164-165 °C/0.15 mmHg ; $[\alpha]_D^{24}$ 11.57 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3317, 2893, 1494, 1452, 1380 ; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H, $C\underline{H}_3$), 1.47 (s, 3 H, $C\underline{H}_3$), 2.32 (s, 3 H, $C\underline{H}_3N$), 3.00 (dd, 1 H, J_{HaH4} = 3.0 Hz, J_{gem} = 14.3 Hz, H-5a), 3.09 (dd, 1 H, J_{HbH4} = 3.0 Hz, J_{gem} = 14.6

Hz, H-5b), 3.42 (d, 1 H, J_{gem} = 12.7 Hz, NCH_aH_bPh), 3.86 (d, 1 H, J_{gem} = 12.7 Hz, NCH_aH_bPh), 4.15 (dd, 1 H, J_{H4H5} = 5.7 Hz, J_{H4H3} = 3.0 Hz, H-4), 4.29 (d, 1 H, J_{H3H4} = 2.7 Hz, H-3), 4.52 (d, 1 H, J_{H2H1} = 3.8 Hz, H-2), 5.99 (d, 1 H, J_{H1H2} = 3.6 Hz, H-1), 7.25-7.37 (m, 5 H, aromatic- H) ; ^{13}C NMR ($CDCl_3$) δ 138 (aro-C-1), 129.7 (aro-C-3), 129.0 (aro-C-2), 128.0 (aro-C-4), 111.7 (CMe_2), 105.3 (C-1), 85.9 (C-2), 78.2 (C-3), 77.3 (C-4), 64.0 (NCH_2Ph), 56.4 (C-5), 44.1 (NCH_3), 26.9 and 26.2 (H_3CCCH_3) ; Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51 ; H, 7.90 ; N, 4.78. Found: C, 65.74 ; H, 7.90 ; N, 4.86.

1e : 58 % yield ; pale yellow oil ; bp 132 °C/0.01 mmHg ; $[\alpha]_D^{24}$ - 58.67 (*c* 1, $CHCl_3$) ; IR (KBr, cm^{-1}), 3089, 2974, 2841, 1454, 1378 ; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 2.03-2.09 (m, 1 H), 2.22 (s, 6 H, CH_3NCH_3), 2.33 (s, 3 H, CH_3N), 2.34-2.40 (m, 2 H), 2.56-2.66 (m, 1 H), 2.75-2.93 (m, 2 H), 4.23 (d, 1 H, J_{H3H4} = 2.5 Hz, H-3), 4.27-4.33 (m, 1 H, H-4), 4.51 (d, 1 H, J_{H2H1} = 3.78 Hz, H-2), 5.96 (d, 1 H, J_{H1H2} = 3.63 Hz, H-1) ; ^{13}C NMR ($CDCl_3$) δ 111.4 (CMe_2), 105.7 (C-1), 85.3 (C-2), 79.0 (C-3), 75.3 (C-4), 57.9, 54.9, 51.4, 44.9, 44.4 [C-5 and $(CH_3)_2NCH_2CH_2NCH_3$], 26.9 and 26.2 (H_3CCCH_3) ; Anal. Calcd for $C_{13}H_{26}N_2O_4$: C, 56.91 ; H, 9.55 ; N, 10.21. Found: C, 56.54 ; H, 9.70 ; N, 10.04.

Enantioselective addition of diethylzinc to benzaldehyde in the presence of 5 mole % of 1. The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (3.6 ml) of diethylzinc (4 mmol) was added to **1f** (243 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 90 % 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 95 (R) and 5 (S) (*i.e.*, 90 % ee).

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