Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2149–2157

TETRAHEDRON:
ASYMMETRY

Catalytic enantioselective reactions. Part 18:[1] Preparation of 3-deoxy-3-*N*,*N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol derivatives from D-mannitol and their applications for catalytic enantioselective addition of dialkylzinc to aldehydes

Byung Tae Cho,* Yu Sung Chun and Weon Ki Yang

Department of Chemistry, Hallym University, Chunchon 200-702, South Korea

Received 27 March 2000; accepted 8 May 2000

Abstract

A series of new chiral β-aminoalcohols, 3-deoxy-3-*N*,*N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol derivatives **2**–**4** possessing a variety of amine substituents at the 3-position and thiol or acetylthio group at the 4-position was prepared from D-mannitol and enantioselective additions of diethylzinc to aldehydes using them as chiral catalysts were examined. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantioselective carbon–carbon bond formation is one of the most interesting challenges in organic synthesis. In recent years the catalytic enantioselective addition of dialkylzinc to aldehydes has attracted much attention because of its potential in the preparation of optically active secondary alcohols.[2] Although several kinds of chiral alcohols, amines and aminoalcohols have been developed as chiral catalysts for the enantioselective addition of dialkylzinc to aldehydes, it was found that most of the successful results to exhibit high enantioselectivity were achieved by the use of sterically constrained β-aminoalcohols,[3] amino sulfur compounds,[4] diamines[5] and diols.[6] In the course of developing new chiral catalysts for the reaction from inexpensive chiral pool, compounds such as α-D-xylose,[7] α-D-glucose[8] and L-tartaric acid,[9] we found that 3-deoxy-3-*N*,*N*-di-*n*-octylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol **2b** obtained from D-mannitol served as highly effective chiral catalysts for the ethylation to both aromatic and unhindered aliphatic aldehydes to afford high enantioselectivity.[10] In order to gain a better understanding of the catalytic effect and with the hope of developing improved chiral catalysts for the enantioselective alkylation

---

* Corresponding author. E-mail: btcho@sun.hallym.ac.kr

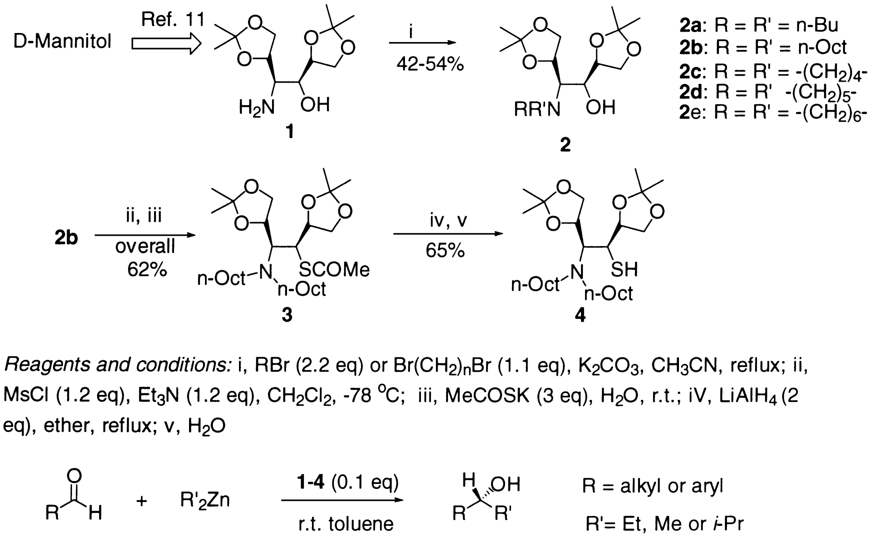
PII: S0957-4166(00)00183-X

of aldehydes, we prepared a series of new 3-deoxy-3-*N*,*N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol derivatives **2**–**4** possessing a variety of amine substituents at the 3-position and a thiol or acetylthio group at the 4-position and compared their enantioselectivities as the catalysts for such reactions. In this paper, we describe details of our preliminary reports and the scope and limitations of these reactions.

2. Results and discussion

2.1. *Synthesis of chiral ligands* **2**–**4**

In order to investigate their structure–selectivity relationships, we first prepared a series of new 3-deoxy-3-*N*,*N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-D-altritols **2** in 42–54% yield by refluxing 3-amino-3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-altritol **1**[11] with 2.2 mol equiv. of alkyl bromide (or 1.1 mol equiv. of α,ω-dibromoalkane) in the presence of excess potassium carbonate in acetonitrile. Next, we synthesized the β-amino thioacetate **3** and thiol **4** from the corresponding β-amino-alcohol **2b**. Thus, **2b** was treated with 1.2 mol equiv. of methanesulfonyl chloride in the presence of 1.2 mol equiv. of triethylamine in dichloromethane at –78°C. The resulting mesyloxy compound was directly reacted with 3 mol equiv. of potassium thioacetate in water at room temperature to give the corresponding thioacetate **3** with retention of configuration in 62% yield.[4a] Subsequent treatment of **3** with lithium aluminum hydride provided the β-amino thiol **4** in a 65% yield (Scheme 1).



Reagents and conditions: i, RBr (2.2 eq) or $Br(CH_2)_nBr$ (1.1 eq), K_2CO_3, CH_3CN, reflux; ii, MsCl (1.2 eq), Et_3N (1.2 eq), CH_2Cl_2, -78 °C; iii, MeCOSK (3 eq), H_2O, r.t.; iV, $LiAlH_4$ (2 eq), ether, reflux; v, H_2O

Scheme 1.

2.2. *Effect of the structure of the chiral catalysts* **2**–**4**

To examine effect of the structure of the chiral catalysts **2**–**4** on asymmetric induction, we compared the catalytic enantioselective addition of diethylzinc to benzaldehyde and heptanal chosen as a representative aromatic and aliphatic aldehyde, respectively. Thus, the reaction was carried out by addition of 2 mol equiv. of diethylzinc in toluene to the aldehydes in the presence of 0.1 mol equiv. of the catalyst at 0°C. As shown in Table 1, all the reactions except the cases with **3** and **4** proceeded smoothly to give the corresponding alcohols in good yields. The reaction with **3** was very slow even at 25°C, although the one with **4** provided good yields at the same temperature. With respect to enantioselectivity, the catalyst **2b** afforded the best results to give 92% ee and 85% ee for benzaldehyde and heptanal, respectively (entry 2). Catalyst **4** substituted with a thiol group instead of hydroxy group of **2b** gave somewhat lower enantioselectivity compared to those obtained with **2b** (entry 9). The corresponding thioacetate **3** provided low enantioselectivity (entry 8).

Table 1
Enantioselective addition of diethylzinc to benzaldehyde and heptanal using various chiral ligands (**2**–**4**) as catalyst[a]

		1-Phenylpropan-1-ol				3-Nonanol			
Entry	Cat	Time (h)	Yield[b] (%)	% ee[c]	Confg.[d]	Time (h)	Yield[b] (%)	% ee[h]	Confg.[d]
1	**2a**	12	83	90	*R*-(-)	12	81	78	*R*-(-)
2	**2b**	12	87	92	*R*-(-)	10	83	85	*R*-(-)
3	**2b**[e]	3	97	83	*R*-(-)	[g]			
4	**2b**[f]	24	62	47	*R*-(-)	[g]			
5	**2c**	14	85	87	*R*-(-)	12	80	70	*R*-(-)
6	**2d**	12	86	89	*R*-(-)	12	88	74	*R*-(-)
7	**2e**	12	82	90	*R*-(-)	12	82	78	*R*-(-)
8	**3**[e]	10	76	43	*R*-(-)	10	76	45	*R*-(-)
9	**4**[e]	6	97	82	*R*-(-)	12	80	73	*R*-(-)

[a] [Aldehyde] : [catalyst] : [Et_2Zn] = 1 : 0.1 : 2. [aldehyde] = 0.3 M. The reactions were carried out in toluene at 0 °C, unless otherwise indicated. [b] Isolated yield. [c] Determined by capillary GC analyses using a Chiraldex B-PH column (Astec Inc.). [d] Determined by the sign of optical rotation and the elution order of GC or HPLC analyses of the known compounds. [e] at 25 °C. [f] at –20 °C. [g] The reaction is not carried out. [h] Determined by capillary GC analyses of (*R*)-MTPA ester[13] of the corresponding alcohol.

On the other hand, to examine effect of temperature on enantioselectivity, we carried out the same reaction using **2b** as the catalyst at 25 and –20°C. In both cases, we observed lower enantioselectivity than those obtained at 0°C, although the reason is unclear (entries 3–4).

2.3. Enantioselective addition of dialkylzinc to some other aldehydes

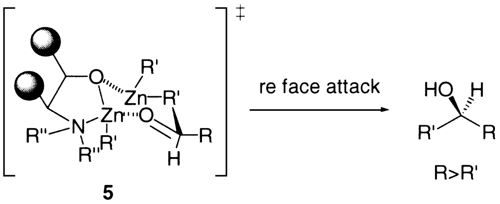
Based on the results in Table 1, we carried out the catalytic enantioselective addition of diethylzinc to other aldehydes using 0.1 mol equiv. of **2b** as the catalyst at 0°C. As shown in Table 2, it was found that the catalyst was highly effective for the ethylation of relatively unhindered aliphatic aldehydes, such as butanal, hexanal, undecanal and 3-phenylpropanal, leading to the corresponding alcohol with enantiomeric excesses in the range of 82–94% ee (entries 1–4). The reaction for a hindered aliphatic aldehyde, 2,2-dimethylpropanal, does not occur even at room temperature, although the same reaction for 3-methylbutanal and cyclohexanecarboxaldehyde proceeded smoothly to give the product alcohol with high enantioselectivity (entries 5–7). In the case of the α,β-unsaturated aldehyde, (*E*)-cinnamaldehyde, the reaction proceeded more slowly to produce the desired alcohol with low enantioselectivity (entry 8). However, the catalyst afforded high enantioselectivities (88–91% ee) for all the aromatic aldehydes examined. In this reaction, it is observed that the steric effect of the *o*-substituent of the aromatic ring on asymmetric induction is not significant (entries 9 vs 10; 12 vs 13). We also tested the same reaction for heterocyclic aldehydes. In all the cases examined, the reaction proceeded much more rapidly to produce the corresponding alcohols in good yields, although it afforded low enantioselectivity (entries 14–16).

Table 2
Catalytic enantioselective addition of dialkylzinc to aldehydes in the presence of 10 mol% of **2b**[a]

Entry	RCHO		Product alcohols			
		R'_2Zn	Time (h)	Yield[b] (%)	%ee	Confg.[d]
1	Butanal	Et_2Zn	10	88	82[g]	*R*-(-)
2	Hexanal	Et_2Zn	10	90	84[g]	*R*-(-)
3	Undecanal	Et_2Zn	12	92	94[h]	*R*-(-)
4	3-Phenylpropanal	Et_2Zn	12	81	90[i]	*R*-(-)
5	3-Methylbutanal	Et_2Zn	8	92	81[g]	*R*-(-)
6	Cyclohexanecarboxaldehyde	Et_2Zn	9	78	86[g]	*R*-(+)
7	2,2-dimethylpropanal	Et_2Zn	*m*			
8	(*E*)-Cinnamaldehyde	Et_2Zn	12	82	32[j]	*R*-(+)
9	*o*-Tolualdehyde	Et_2Zn	12	85	89[i]	*R*-(+)
10	*p*-Tolualdehyde	Et_2Zn	12	83	90[g]	*R*-(+)
11	*p*-Chlorobenzaldehyde	Et_2Zn	12	93	89[i]	*R*-(+)
12	1-Naphthaldehyde	Et_2Zn	18	82	88[j]	*R*-(+)
13	2-Naphthaldehyde	Et_2Zn	18	85	90[j]	*R*-(+)
14	2-Pyridinecarboxaldehyde	Et_2Zn	6	84	22[j]	(+)[n]
15	2-Furaldehyde	Et_2Zn	3	92	25[g]	*R*-(+)
16	2-Thiphenecarboxaldehyde	Et_2Zn	3	90	23[g]	*R*- (+)
17	Heptanal	Me_2Zn[e,f]	24	64	53[k]	*R*-(-)
18	Heptanal	*i*-Pr_2Zn	8	82	92[l]	(-)[n]
19	Benzaldehyde	Me_2Zn[e,f]	42	55	29[c]	*R*-(+)
20	Benzaldehyde	*i*-Pr_2Zn	4	95	92[c]	*R*-(+)

[a-e, g] See the corresponding footnotes in Table 1. [f] [RCHO] : [**2b**] : [Me_2Zn] = 1 : 0.1 : 5. [h] Determined by capillary GC analysis of trifluoroacetate of 3-tridecanol using Chiraldex B-PH column (Astec Inc.). [i] Determined by capillary GC analyses of (-)-menthyl carbonate[14]of the corresponding alcohol using a 50 m methylsilicon column. [j] Determined by HPLC analyses using a Chiralcel OD column (eluent: hexane : i-PrOH = 9 : 1). [k] Determined by capillary GC analysis of trifluoroacetate of 1-phenylethanol using Chiraldex G-TA column (Astec Inc.). [l] Determined by capillary GC analysis using a β-DEX 120 (Supelcowax) column. [m] No reaction. [n] Absolute configuration is unknown.

On the other hand, the catalytic enantioselective additions using dimethylzinc and diisopropylzinc instead of diethylzinc were compared under the same reaction conditions for benzaldehyde and heptanal. In both cases, the reaction with diisopropylzinc proceeded much more rapidly to provide the desired alcohols with high enantioselectivities (92% ee) compared to those obtained with diethylzinc (entries 18 and 20). In contrast, the addition of dimethylzinc proceeded much more slowly to give the product alcohol in low yields with low enantioselectivities, although the reaction was carried out even with 5 mol equiv. of dimethylzinc at room temperature (entries 17 and 19). The absolute configurations of all the product alcohols obtained are consistently enriched in the *R* enantiomers. The stereochemical course of the enantioselective addition can be explained by the proposed mechanism involving six-membered cyclic transition state **5**, in which *R′* in R'_2Zn is transferred to aldehydes on the *re* side to produce (*R*)-alcohols in the case of $R > R'$ (Scheme 2).[12]



Scheme 2.

3. Conclusions

We have established enantioselective additions of diethylzinc to aldehydes using new chiral β-aminoalcohols, 3-deoxy-3-*N*,*N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol derivatives **2**–**4** possessing a variety of amine substituents at the 3-position and thiol or acetylthio group at the 4-position prepared from D-mannitol as chiral catalysts. Of the catalysts examined, 3-deoxy-3-*N*,*N*-di-*n*-octylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol **2b** provides the best results to give high enantioselectivities for aromatic and relative unhindered aliphatic aldehydes. The reaction with diisopropylzinc under the same reaction condition proceeded much more rapidly to give the product alcohols with high enantioselectivities, whereas the case with dimethylzinc proceeded much more slowly to give the product alcohols with low enantioselectivities.

4. Experimental

4.1. General

All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230–400 mesh). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. *J*-Values are given in hertz. Optical rotations were measured with a high resolution digital polarimeter. Melting points were uncorrected. Enantiomeric excesses (% ees) of the product alcohols were determined by capillary GLC analyses of their (*R*)-MTPA esters [α-methoxy-α-[trifluoromethyl]phenylacetates][13] or (–)-menthyl carbonates[14] with a 25 m Spelcowax™ column or a 50 m methylsilicon column or by capillary GLC analyses using a 20 m Chiraldex G-TA, B-PH and β-Dex 120 chiral column or by a HPLC analysis using a 25 cm Chiralcel OD.

4.2. Materials

Most of the organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. Toluene was distilled over sodium and stored in an ampoule under nitrogen atmosphere. Diethylzinc, dimethylzinc, (*R*)-MTPA chloride and (–)-menthyl carbonyl chloride were purchased from Aldrich Chemical Company. Diisopropylzinc was prepared according to the literature procedure.[15]

*4.3. Preparation of 3-deoxy-3-*N,N*-dialkylamino-1,2;5,6-di-*O*-isopropylidene-*D*-altritols (**2**)*

4.3.1. General method

A mixture of 3-amino-3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-altritol[11] (5 mmol), alkyl bromide (11 mmol) or α,ω-alkyl dibromide (5.5 mmol), sodium iodide (15 mmol) and anhydrous potassium carbonate (15 mmol) in acetonitrile (25 ml) was heated to reflux for 24 h. After a usual work-up, the products obtained was further purified by flash chromatography on silica gel using appropriate eluents.

*4.3.2. 3-Deoxy-3-*N,N*-di-*n*-butylamino-1,2;5,6-di-*O*-isopropylidene-*D*-altritol* ***2a***

Yield: 48%; R_f 0.52 (EtOAc:Hex = 1:4); oil (found: C, 63.33; H, 10.34; N, 3.75. $C_{20}H_{39}NO_5$ requires: C, 64.34; H, 10.52; N, 3.75%); $[\alpha]_D^{20}$ = +37.65 (*c* 1.12, $CHCl_3$); ν_{max} (film)/cm^{-1} 3484, 2985, 2869, 1460, 1378, 1254, 1214, 1162, 1057, 857; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, *J* 7.2, 2×CH_3), 1.25–1.48 (8H, m, 4×CH_2), 1.34 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.40 (6H, s, 2×CH_3), 2.58–2.65 (2H, m, N-CH_2), 2.72–2.81 (3H, m, 3-*H* and N-CH_2), 3.33 (1H, br s, O*H*), 3.48 (1H, t, *J* 6.2, 1-H_a), 3.74 (1H, t, *J* 7.7, 6-H_a), 3.84–3.90 (1H, m, 4-*H*), 4.08–4.14 (3H, m, 5-*H*, 1 and 6-H_b), 4.54–4.60 (1H, m, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.60 (*C*Me$_2$), 108.78 (*C*Me$_2$), 76.61 (5-*C*), 76.26 (2-*C*), 71.32 (1-*C*), 68.51 (6-*C*), 67.68 (4-*C*), 65.49 (3-*C*), 53.17 (N-*C*H$_2$), 32.28 (N-CH$_2$*C*H$_2$), 27.10, 26.81, 25.94 and 25.49 [4×(*C*H$_3$)$_2$C], 20.93 (*C*H$_2$), 14.52 (*C*H$_3$).

*4.3.3. 3-Deoxy-3-*N,N*-di-*n*-octylamino-1,2;5,6-di-*O*-isopropylidene-*D*-altritol* ***2b***

Yield: 46%; R_f 0.58 (EtOAc:Hex = 1:4); oil (found: C, 69.11; H, 11.59; N, 2.64. $C_{28}H_{55}NO_5$ requires: C, 69.23; H, 11.41; N, 2.88%); $[\alpha]_D^{20}$ = +41.4 (*c* 1.13, $CHCl_3$); ν_{max} (film)/cm^{-1} 3482, 2985, 2859, 1466, 1378, 1255, 1214, 1160, 1056, 857; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* 7.0, 2×CH_3), 1.26–1.48 (24H, m, 12×CH_2), 1.34 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.40 (6H, s, 2×CH_3), 2.56–2.63 (2H, m, N-CH_2), 2.71–2.80 (3H, m, 3-*H* and N-CH_2), 3.30 (1H, br s, O*H*), 3.48 (1H, t, *J* 6.0, 1-H_a), 3.73 (1H, t, *J* 7.8, 6-H_a), 3.84–3.89 (1H, m, 4-*H*), 4.09–4.14 (3H, m, 5-*H*, 1-H_b and 6-H_b), 4.53–4.59 (1H, m, 2-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.22 (*C*Me$_2$), 108.41 (*C*Me$_2$), 76.23 (5-*C*), 75.89 (2-*C*), 70.93 (1-*C*), 68.14 (6-*C*), 67.31 (4-*C*), 65.15 (3-*C*), 53.05 (N-*C*H$_2$), 31.86 (N-CH$_2$*C*H$_2$), 29.69, 29.63, 29.37 and 27.42 [4×(*C*H$_3$)$_2$C], 26.74, 26.45, 25.58, 25.10 and 22.67 (5×*C*H$_2$), 14.11 (*C*H$_3$).

4.3.4. *3-Deoxy-3-(1-pyrrolidinyl)-1,2;5,6-di-*O*-isopropylidene-*D*-altritol* **2c**

Yield: 42%; R_f 0.36 (EtOAc:Hex = 1:1); oil (found: C, 61.00; H, 9.21; N, 4.71. $C_{16}H_{29}NO_5$ requires: C, 60.93; H, 9.28; N, 4.44%); $[\alpha]_D^{20}=+20.3$ (*c* 1.18, $CHCl_3$); ν_{max} (film)/cm^{-1} 3438, 2941, 1455, 1370, 1253, 1215, 1158, 1115, 1061, 856; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 1.41 (3H, s, C*H*$_3$), 1.64–1.75 (4H, m, 2×C*H*$_2$), 2.91–2.95 (4H, m, 2×N-C*H*$_2$), 3.01–3.11 (2H, m, 3-H and O*H*), 3.47 (1H, t, *J* 5.6, 1-*H*$_a$), 3.80 (1H, t, *J* 7.8, 6-*H*$_a$), 3.89–3.93 (1H, m, 4-H), 4.07–4.14 (3H, m, 5-*H*, 1-*H*$_b$ and 6-*H*$_b$), 4.52–4.58 (1H, m, 2-*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.61 (*C*Me$_2$), 107.65 (*C*Me$_2$), 73.51 (5-*C*), 72.12 (4-*C*), 67.67 (1- and 6-*C*), 64.32 (4-*C*), 62.14 (3-*C*), 51.27 (N-*C*H$_2$), 26.68, 25.91, 25.45 and 24.81 [4×(*C*H$_3$)$_2$C], 23.29 and 22.62 (2×*C*H$_2$).

4.3.5. *3-Deoxy-3-(1-piperidinyl)-1,2;5,6-di-*O*-isopropylidene-*D*-altritol* **2d**

Yield: 48%; R_f 0.48 (EtOAc:Hex = 1:2); oil (found: C, 61.78; H, 9.68; N, 4.24. $C_{17}H_{31}NO_5$ requires: C, 61.98; H, 9.48; N, 4.25%); $[\alpha]_D^{20}=+23.25$ (*c* 1.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3474, 2990, 1442, 1380, 1251, 1217, 1160, 1058, 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 1.41 (3H, s, C*H*$_3$), 1.43–1.52 (6H, m, 3×C*H*$_2$), 2.51–2.53 (1H, m, 3-*H*), 2.66–2.67 (2H, m, N-C*H*$_2$), 2.89 (2H, m, N-C*H*$_2$), 3.35 (1H, br s, O*H*), 3.54 (1H, t, *J* 5.7, 1-*H*$_a$), 3.75 (1H, t, *J* 7.8, 6-*H*$_a$), 3.85–3.90 (1H, m, 4-*H*), 4.08–4.11 (3H, m, 5-*H*, 1-*H*$_b$ and 6-*H*$_b$), 4.49–4.55 (1H, m, 2-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.31 (*C*Me$_2$), 107.53 (*C*Me$_2$), 75.12 (5-*C*), 74.34 (4-*C*), 69.59 (1 and 6-*C*), 66.87 (4-*C*), 66.14 (3-C), 51.97 (N-*C*H$_2$), 25.81, 25.41 and 24.81[(*C*H$_3$)$_2$C], 24.29 and 23.26 (*C*H$_2$).

4.3.6. *3-(1-Azepino)-3-deoxy-1,2;5,6-di-*O*-isopropylidene-*D*-altritol* **2e**

Yield: 54%; R_f 0.42 (EtOAc:Hex = 1:2); oil (found: C, 62.76; H, 9.78; N, 4.05. $C_{18}H_{33}NO_5$ requires: C, 62.95; H, 9.68; N, 4.08%); $[\alpha]_D^{20}=+36.4$ (*c* 1.11, $CHCl_3$); ν_{max} (film)/cm^{-1} 3483, 2990, 2882, 1452, 1381, 1252, 1216, 1157, 1068, 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, s, 2×C*H*$_3$), 1.40 (6H, s, 2×C*H*$_3$), 1.50–1.80 (8H, m, 4×C*H*$_2$), 2.60 (1H, t, *J* 8.0, 3-*H*), 2.73–2.79 (2H, m, N-C*H*$_2$), 2.99–3.02 (2H, m, N-C*H*$_2$), 3.58 (1H, t, *J* 6.7, 1-*H*$_a$), 3.73 (1H, t, *J* 7.9, 6-*H*$_a$), 3.88 (1H, t, *J* 7.7, 4-*H*), 4.09–4.14 (2H, m, 1- and 6-*H*$_b$), 4.18–4.25 (1H, m, 5-*H*), 4.48–4.53 (1H, m, 2-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.22 (*C*Me$_2$), 108.70 (*C*Me$_2$), 75.12 (5-*C*), 74.0 (2-*C*), 70.0 (1-*C*), 68.49 (6-*C*), 68.24 (3-*C*), 67.42 (4-*C*), 66.49 (N-*C*H$_2$), 65.46 (N-*C*H$_2$), 26.93, 26.82 and 26.46 (*C*H$_2$), 25.47, 25.40, 25.18 and 24.48 [(*C*H$_3$)$_2$C].

4.4. *3-Deoxy-3-*N,N*-di-*n*-octylamino-1,2;5,6-di-*O*-isopropylidene-*D*-acetylthioaltritol* **3**

To a mixture of **2b** (2 mmol) and triethylamine (2.4 mmol) in dichloromethane (10 ml) was added slowly methanesulfonyl chloride (2.4 mmol) in dichloromethane (2 ml) at –78°C. The reaction mixture was stirred for 2 h at –78°C and then warmed up to room temperature. After solvent was evaporated in vacuo, the residue was treated with potassium thioacetate (6 mmol) in water (2 ml) for 18 h at room temperature. The mixture was extracted with dichloromethane (3×10 ml). The extract was dried over anhydrous magnesium sulfate. After evaporation of solvent, the residue was purified by flash column chromatography on silica gel to give the product **3**; yield: 62%; R_f 0.47 (EtOAc:Hex = 1:9); oil (found: C, 66.21; H, 10.59; N, 2.64; S, 5.79. $C_{30}H_{57}NO_5S$ requires: C, 66.25; H, 10.56; N, 2.58; S, 5.90%; $[\alpha]_D^{20}=+44.6$ (*c* 1.13, $CHCl_3$); ν_{max} (film)/cm^{-1} 2987, 2858, 1693, 1466, 1378, 1255, 1216, 1157, 1064, 860; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* 7.0, 2×C*H*$_3$), 1.26–1.48 (24H, m, 12×C*H*$_2$), 1.34 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.40 (6H, s, 2×C*H*$_3$), 2.56–2.63 (2H, m, N-C*H*$_2$), 2.71–2.80 (3H, m, 3-*H* and N-C*H*$_2$), 3.30 (1H, br s, O*H*), 3.48 (1H, t, *J* 6.0, 1-*H*$_a$), 3.73 (1H, t, *J* 7.8, 6-*H*$_a$), 3.84–3.89 (1H, m, 4-*H*), 4.09–4.14 (3H, m, 5-*H*, 1 and 6-*H*$_b$), 4.53–4.59 (1H, m, 2-*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.80 (*C*OCH$_3$), 109.99 (*C*Me$_2$), 108.75 (*C*Me$_2$), 76.31 (2-*C*), 75.11 (5-*C*), 69.09 (6-*C*), 68.27 (1-*C*), 67.31 (3-*C*), 52.91 (N-*C*H$_2$), 49.37 (4-*C*), 31.91 (N-CH$_2$*C*H$_2$), 30.61 (CO*C*H$_3$), 29.75, 29.55, 29.43 and 27.48 [(*C*H$_3$)$_2$C], 26.74, 26.46, 25.84, 25.78, 25.62 and 22.67 (*C*H$_2$), 14.12 (*C*H$_3$).

4.5. 3-Deoxy-3-N,N-di-n-octylamino-1,2;5,6-di-O-isopropylidene-D-thioaltritol 4

To a suspension of lithium aluminum hydride (2 mmol) in dry ether (5 ml) was dropped a solution of **3** (1 mmol) in dry ether (3 ml). The reaction mixture was heated to reflux for 18 h. After a usual work-up, the residue was purified by flash column chromatography on silica gel to afford the product **4**; yield: 65%; R_f 0.38 (EtOAc:Hex = 1:9); mp 59–60°C (found: C, 67.21; H, 11.19; N, 2.74; S, 6.51. $C_{28}H_{55}NO_4S$ requires: C, 67.02; H, 11.05; N, 2.79; S, 6.39%); $[\alpha]_D^{20} = +56.0$ (*c* 1.01, CHCl$_3$); ν_{max} (KBr)/cm^{-1} 2984, 2855, 1465, 1378, 1217, 1214, 1060, 860; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (6H, t, *J* 6.6, 2×C*H*$_3$), 1.24–1.50 (24H, m, 12×C*H*$_2$), 1.35 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.40 (3H, s, C*H*$_3$), 1.41 (3H, s, C*H*$_3$), 2.60–2.66 (2H, m, N-C*H*$_2$), 2.71–2.79 (3H, m, H-4 and N-C*H*$_2$), 3.08 (1H, dd, *J* 8.7 and 3.65, H-3), 3.65 (1H, t, *J* 7.7, 1-*H*$_a$), 3.81 (1H, t, *J* 8.0, 6-*H*$_a$), 4.03–4.09 (1H, m, 5-*H*), 4.13–4.17 (2H, m, 1- and 6-*H*$_b$), 4.62–4.67 (1H, m, 2-*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 109.40 (*C*Me$_2$), 108.86 (*C*Me$_2$), 76.21 (5-*C*), 76.03 (2-*C*), 69.21 (1-*C*), 68.30 (6-*C*), 67.94 (4-*C*), 61.69 (3-*C*), 53.41 (N-*C*H$_2$), 31.88 (N-CH$_2$*C*H$_2$), 29.75, 29.67, 29.45 and 27.54 [(*C*H$_3$)$_2$C], 26.84, 26.58, 25.79, 25.75 and 22.68 (*C*H$_2$), 14.12 (*C*H$_3$).

4.6. Catalytic enantioselective addition of dialkylzinc to aldehydes

The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (2 ml) of diethylzinc (2 mmol) was added to **2b** (0.1 mmol) in toluene (1 ml) and stirred at 0°C for 30 min. After undecanal (1 mmol) was added to this, the mixture was stirred at the same temperature for 12 h and then diluted with ether (10 ml). The excess diethylzinc was destroyed by addition of 1N HCl and the reaction mixture was extracted with ether (3×10 ml). The ether extract was dried over anhydrous magnesium sulfate and concentrated in vacuo. The product alcohols was purified by flash column chromatography on silica gel to give 3-tridecanol; 92% yield; R_f 0.43 (EtOAc: Hex = 1:9); oil. Enantiomeric excess of the product alcohol was measured by capillary GC analysis of trifluoroacetate of the product alcohols using a Chiraldex B-PH capillary column. GLC analysis showed a composition of 97 (*R*) and 3 (*S*) (i.e. 94% ee, *R*) (Table 2).

Acknowledgements

This study was supported by the Basic Science Research Institute Program (BSRI 98-015-D00168), Korea Research Foundation, Korea.

References

1. Part 17: Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1999**, *10*, 1843.
2. For reviews, see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833 and references cited therein; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (c) *Modern Synthetic Methods*; Scheffold, R., Ed.;

Springer-Verlag: Berlin, 1989; pp. 115–198; (d) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; pp. 211–229.

3. (a) Lawrence, C. F.; Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Synlett* **1999**, 1571. (b) Reddy, K. S.; Solá, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969.
4. (a) Kang, J.; Kim, J. W.; Lee, J. W.; Kim, D. S.; Kim, J. I. *Bull. Korean Chem. Soc.* **1996**, *17*, 1135; (b) Anderson, J. C.; Cubbon, R.; Harding, M.; James, D. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3461; (c) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellog, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31; (d) Rejnberg, E.; Hovestad, N. J.; Kleij, A. W.; Jasterzebski, J. T. B. H.; Boersma, J.; Janssen, M. D.; Spek, A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2847; (e) Jin, M.-J.; Ahn, S.-J.; Lee, K.-S. *Tetrahedron Lett.* **1996**, *37*, 8767.
5. Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4169.
6. (a) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 497. (b) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364.
7. Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901.
8. Cho, B. T.; Kim, N. *Synth. Commun.* **1996**, *26*, 855.
9. Cho, B. T.; Kim, N. *Synth. Commun.* **1996**, *26*, 2273.
10. Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489.
11. (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655; (b) Baker, B. R.; Haines, A. H. *J. Org. Chem.* **1963**, *28*, 442.
12. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5237.
13. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543; MTPA = α-methoxy-α-(trifluoromethyl)-phenylacetic acid.
14. Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.
15. Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732.