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SHORT-STEP SYNTHESIS OF CHIRAL C_2-SYMMETRIC 2,3,4,5-TETRASUBSTITUTED PYRROLIDINES FROM D-MANNITOL AND THEIR USE AS CHIRAL LIGANDS IN THE REACTION OF DIETHYLZINC AND BENZALDEHYDE

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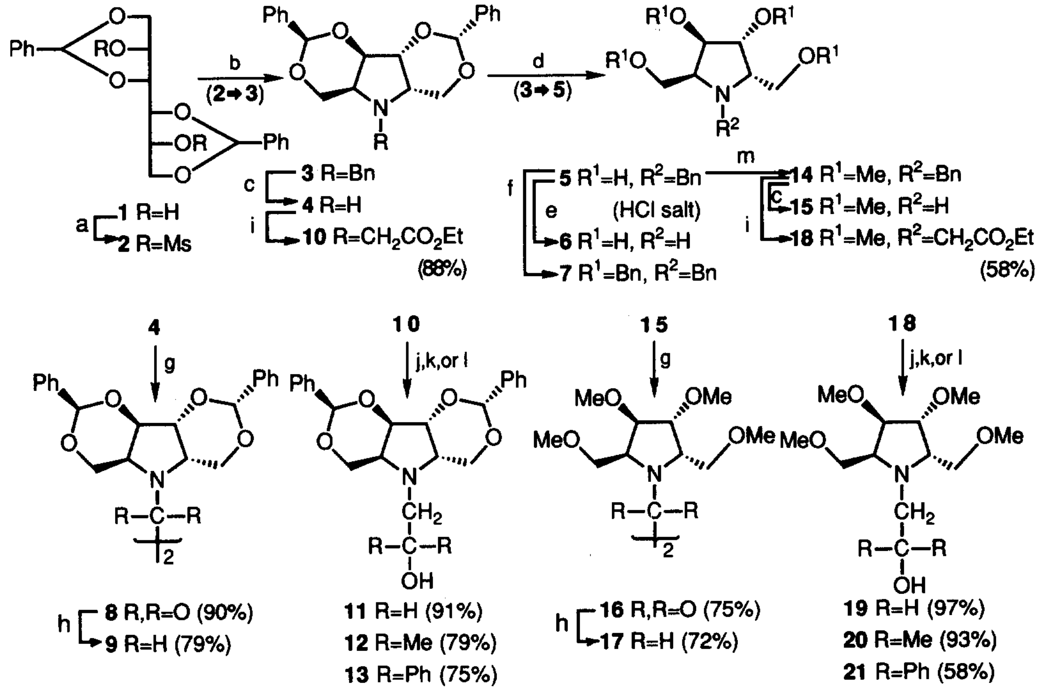
Summary: (3*R*,4*R*)-Bis(hydroxy)-(2*S*,5*S*)-bis(hydroxymethyl)-pyrrolidine and related chiral C_2-symmetric pyrrolidines including D_2-symmetric 1,2-bis(1-pyrrolidino)-ethanes and N-hydroxyethylpyrrolidines were synthesized highly practically from D-mannitol and a high chiral induction of 82% ee was observed in investigation of efficiency of these amines as chiral catalyst ligands in the addition reaction of diethylzinc to benzaldehyde.

High efficiencies of C_2-symmetric chiral reagents including auxiliaries and catalyst ligands in the chiral inductions have attracted much attentions in asymmetric synthesis.1) In the context, chiral C_2-symmetric five-membered heterocycles such as pyrrolidines,2) borolanes,3) and phospholanes4) have been claimed to be potential as the chiral auxiliary in C-C bond forming reactions,2a,b,f-i,3b,c) the stoichiometric chiral ligand for OsO_4 oxidation,2e) the chiral hydroboration reagent,3a) and chiral ligands for catalytic hydrogenation.2c,d,4) All of these five-membered 1-heterocycles utilized in asymmetric synthesis have been condensed into 3,4- and 2,5-disubstituted types. Although D-mannitol is recognized as the most easily available starting material for C_2-symmetric chiral 2,3,4,5-tetra-substituted five-membered 1-heterocycles, transformations of D-mannitol in the sense have been very limited,5) one of which, given by T.K.M. Shing,5a) appears to be short-step and practical, while the contents of his report are partially erroneous.6) We disclose here a short-step and highly practical synthesis of (3*R*,4*R*)-bis(hydroxy)-(2*S*,5*S*)-bis-(hydroxymethyl)-pyrrolidine (**6**) and related C_2-symmetric pyrrolidines from D-mannitol via facile cyclization of 1,3;4,6-di-O-benzylidene-2,5-di-O-mesyl-D-mannitol (**2**) with benzylamine and derivation to D_2-symmetric 1,2-bis(1-pyrrolidino)ethanes and N-hydroxyethylpyrrolidines, and the first application of these C_2-symmetric pyrrolidines to catalytic chiral ligands in the addition reaction of benzaldehyde and diethylzinc.

1,3,4,6-Di-O-benzylidene-D-mannitol (**1**) 7) was mesylated to give qantitatively the corresponding 2,5-di-O-mesylate (**2**). The desired C_2-symmetric chiral tetra-substituted pyrrolidine (**3**) (mp. 110 °C ,$[\alpha]_D$ + 90.6 ° (c 0.32, $CHCl_3$) was obtained in high yield (94%) by cyclization of the dimesylate (**2**) on heating (135 °C/8 h) in benzylamine. Selective N-debenzylation of **3** was carried out by catalytic hydrogenolysis on 5% Pd/C in the presence of a trace of concentrated hydrochloric acid to afford the *sec*-amine (**4**) (mp. 130 °C ,$[\alpha]_D$ + 7.7° (c 1.41, $CHCl_3$).6) The structures and homochirality of the C_2-symmetric pyrrolidines (**3**) and (**4**) were established by derivation to and identification with the known compounds. Thus, the



(a) MsCl / Et_3N / CH_2Cl_2 / 0°C / 2hr (quant.) ; (b) $BnNH_2$ / 135°C / 8hr (94%) ; (c) 5%Pd/C / H_2 / EtOH / r.t. / 1hr (quant.) ; (d) c-HCl / MeOH / r.t. / 2days (98%) ; (e) 5%Pd/C / H_2 / c-HCl / EtOH / r.t. / 10hr (86%) ; (f) NaH / BnBr / DMF / r.t. / 12hr (67%) ; (g) $(COCl)_2$ / Et_3N / CH_2Cl_2 / r.t. / 1hr ; (h) LAH / THF / r.t. / 1hr ; (i) NaH / DMF / $BrCH_2CO_2Et$ / r.t. / 12hr ; (j) LAH / THF / r.t. / 0.5hr ; (k) MeMgBr / THF / r.t. / 0.5hr ; (l) PhMgBr / THF / r.t. / 12hr ; (m) NaH / MeI / DMF / r.t. / 12hr (98%)

<u>Table</u> Asymmetric Addition Reaction of Diethylzinc to Benzaldehyde in the Presence of Chiral Pyrrolidines as Catalyst Ligand

$$\underset{(1\,eq)}{\text{Ph-CHO}} + \underset{(2\,eq)}{Et_2Zn} \xrightarrow[\text{Hexane 0°-r.t. 5-60 h}]{\text{chiral ligand (0.06 eq)}} \underset{\mathbf{22}}{\text{PhCH(OH)Et}}$$

Entry	Catalyst	Yield (%)	%ee	Config.
1	**3**	52	1	R
2	**4**	53	8	S
3	**9**	55	10	R
4	**11**	48	42	S
5	**12**	96	28	S
6	**13**	100	34	S
7	**17**	58	2	R
8	**19**	73	19	R
9	**20**	96	38	R
10	**21**	90	82	R

acetal (**3**) was converted on successive treatments with conc. HCl in MeOH providing the N-benzyl-tetraol hydrochloride salt (**5**) followed by hydrogenolysis of N-benzyl group to the known tetrasubstituted (2*S*,3*R*,4*R*,5*S*)-pyrrolidine (**6**) (mp. 167 °C, $[\alpha]_D$ 16.2 ° (c 1.0, H_2O).[8] The tetraol (**5**) was also characterized by derivation to the known perbenzylated pyrrolidine (**7**) ($[\alpha]_D$ -29.3 °(c 1.81, CH_2Cl_2).[5b]

In order to exploit new chiral ligands, D_2-symmetric 1,2-bis(1-pyrrolidino)ethanes (**9**, **17**), and several N-hydroxyethylpyrrolidines (**11**-**13**, **19**-**21**) were synthesized. The D_2-symmetric 1,2-bis(1-pyrrolidino)ethane (**9**) was prepared by successive treatments of **4** with oxalyl chloride and Et_3N providing the diamide (**8**) and then with $LiAlH_4$.[2e] The N-ethoxycarbonylmethyl-pyrrolidine (**10**) obtained from **4** on treatment with $BrCH_2CO_2Et$ in the presence of NaH gave the N-2-hydroxyethyl derivative (**11**), N-2-methyl-2-hydroxypropyl derivative (**12**), and N-2,2-diphenyl-2-hydroxyethyl derivative (**13**) on treatments with $LiAlH_4$, MeLi, and PhMgBr, respectively. The tetraol (**5**) was transformed to the tetramethyl derivative (**14**) and then to the corresponding *sec*-amine (**15**) by a sequence of methylation with MeI and NaH, and catalytic hydrogenolysis. The other D_2-symmetric 1,2-bis(1-pyrrolidino)ethane (**17**) was prepared from **15** via diamide (**16**) anologously with **9**. 2,5-Dimethoxymethyl-3,4-dimethoxy-N-(2-hydroxyethyl)-pyrrolidines (**19**-**21**) were prepared from **15** via the N-ethoxycarbonylmethyl derivative (**18**) according to the same procedures for the di-benzylidene acetals (**11**-**13**).

Reaction of aldehydes with dialkylzinc providing *sec*-alcohols does not take place without catalyst but accelerates in the presence of amines or β-aminoalcohols.[9] Excellent chiral inductions including asymmetric amplifications [10] by use of chiral β-aminoalcohols in this type of reaction have been reported.[9] As we had a series of C_2-symmetric chiral 2,3,4,5-tetrasubstituted pyrrolidines (**11**-**13**, **19**-**21**) which bear the β-aminoalcohol system and D_2-symmetric chiral 1,2-bis(1-pyrrolidino)ethanes (**9**) and (**17**) in hand, efficiencies of these amines as chiral catalyst ligand for the addition reaction of benzaldehyde and diethylzinc were investigated. The reaction was carried out in hexane using 1.0 equiv of benzaldehyde and 2.0 equiv of diethylzinc in the presence of 0.06 equiv of chiral pyrrolidines from 0 °C (initial temperature) to the room temperature for 5-60 h under monitoring the disappearance of benzaldehyde on tlc. The enantiomeric excess of the product 1-phenylpropanol (**22**) was determined by hplc analysis using chiral stationary phase (SUMIPAX-OA-4000) after derivation of the product to the corresponding 3,5-dinitrophenylurethane and the absolute configuration of the major enantiomer was assigned according to the correspondence of (*R*) to (+)-sign of the specific optical rotation of **22**.[10] The results are summarized in Table.

It should be worth noting that N-2-hydroxyethyl derivatives (**11**-**13**, **19**-**21**) exhibited higher catalytic efficiency in both chemical yield and chiral induction than the D_2-symmetric diamines (**9**, **17**) and the highest chiral induction of 82% ee was observed with the diphenylcarbinol derivative (**21**) among the pyrrolidines investigated. A dramatic change of enantioselectivity was observed between the bisbenzylidene acetal ligands (**11**-**13**) which gave favorably (*S*)-alcohol (**22**) and the methoxylated pyrrolidine ones (**19-21**) which afforded (*R*)-(**22**). The results suggest that the flexibility of the substituents at the 2- and 5-positions of pyrrolidine ligands is one of the important factors on the enantioselectivity.

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