Tetrahedron Letters,Vol.25,No.8,pp 857-860,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

ASYMMETRIC ALKYLATION OF CARBOXYAMIDES BY USING *trans*-2,5-DISUBSTITUTED PYRROLIDINES AS CHIRAL AUXILIARIES

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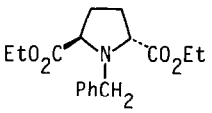
Summary: *trans*-2,5-Bis(methoxymethyl)- and *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidines proved to be excellent chiral auxiliaries for the asymmetric alkylation of the corresponding carboxyamide enolates giving good chemical yield and high stereoselectivity (invariably over 95% de), with remarkable flexibility to substrates and reaction conditions.

In the recent development of asymmetric synthesis,[1] the advantage of chiral auxiliaries having a C_2-axis of symmetry has been demonstrated by numerous examples. Five-membered ring structures built in the chiral auxiliaries or generated in intermediates to assume favourable conformations have also been the frequent choice. However, the combination of these two notions has rarely been examined.[2] Here, we describe the synthesis of chiral *trans*-2,5-bis-(methoxymethyl)- and *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidines having the above two features, and their highly successful application to asymmetric alkylation of the corresponding carboxyamide enolates.

Racemic *trans*-N-benzyl-2,5-bis(ethoxycarbonyl)pyrrolidine (*dl*-**1**) prepared according to Lowe et al.,[3] was saponified (NaOH, EtOH-H_2O) to the dicarboxylic acid (*dl*-**2**) which was then resolved through a salt with D-(-)-*threo*-(p-nitrophenyl)-2-amino-1,3-propanediol[4] to give (+)-**2**.[5,6] The (2*R*,5*R*) configuration of (+)-**2** was determined by catalytic debenzylation (H_2/5% Pd-C, H_2O) to (+)-pyrrolidine-2,5-dicarboxylic acid [**3**, mp 274°C, $[\alpha]_D^{25}$ +106°(c=1.02, H_2O)], the (-)-enantiomer of which has been known as a natural product and determined to have (2*S*,5*S*) configuration.[7] (+)-**2** was then reesterified ($SOCl_2$, MeOH), reduced ($LiAlH_4$, THF) to a (+)-diol (**4**), etherified (NaH and CH_3I or diisopropylethylamine and methoxymethyl chloride), and debenzylated to the (2*R*,5*R*)-(-)-dimethyl ether [**5**, an oil, $[\alpha]_D^{25}$ -13.5°(c=3.02, EtOH)] or to the (2*R*,5*R*)-(+)-diMOM ether [**6**, an oil, $[\alpha]_D^{24}$ +4.3°(c=4.00, EtOH)]. The (2*S*,5*S*)-(+)-**5** and the (2*S*,5*S*)-(-)-**6** were also prepared in a similar way. The N-acylation of these pyrrolidines to the corresponding amides was carried out by one of the conventional methods (acid anhydride, acid anhydride-dimethylaminopyridine-Et_3N, or acid chloride-Et_3N) in good yield.



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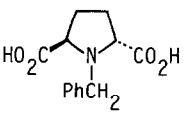

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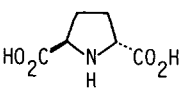

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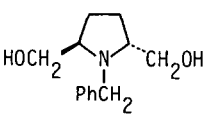

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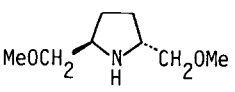

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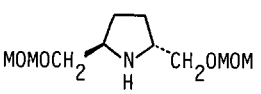

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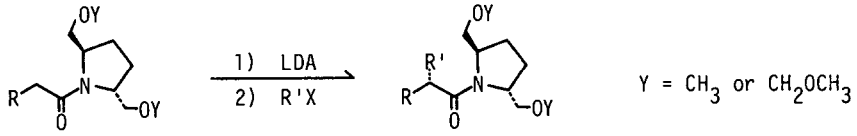
The amides (**7**, Y=CH_3) derived from optically active **5** were lithiated by LDA in THF at -78°C and then treated with alkyl halides. Reaction with a variety of combinations of substrates and alkyl halides proceeded smoothly with good chemical yields, and the purities of the alkylated products (**8**, Y=CH_3) were invariably over 95% de (CMR). Some examples are shown in Table 1. The compound (**8**) could be hydrolyzed without detectable racemization by treating it with BCl_3 in CH_2Cl_2 to cleave methyl ether and by subsequent refluxing in aqeous 1N-HCl.[8]



7 **8**

Table 1. Asymmetric Alkylation Using (2*R*,5*R*)-**5** in THF at -78°C

Entry	R in **7** (Y=CH_3)	R'X	Alkylated Amide(**8**, Y=CH_3)			
			Yield(%)	$[\alpha]_D^{25}$(EtOH)	% de[a]	Configur. at C(2')[b]
1	CH_3	C_2H_5I	87	+29.4°	> 95	*R*
2	CH_3[c]	C_2H_5I	78	-27.8°	> 95	*S*
3	C_2H_5	CH_3I	91	+81.7°	> 95	*S*
4	C_2H_5[c]	CH_3I	79	-79.4°	> 95	(*R*)
5	CH_3	C_4H_9I	81	+22.5°	> 95	(*R*)
6	C_4H_9	CH_3I	81	+70.0°	> 95	(*S*)
7	CH_3	$PhCH_2Br$	80	-47.3°	> 95	*R*
8	$PhCH_2$	CH_3I	76	+116.8°	> 95	*S*
9	$C_{16}H_{33}$	CH_3I	61	+46.8°	> 95	(*S*)
10	CH_3	CH_2=$CHCH_2Br$	81	+26.3°	> 95	(*R*)
11	CH_3[c]	CH_2=$CHCH_2Br$	73	-23.6°	> 95	(*S*)
12	CH_3	$PhCH_2OCH_2Cl$	74	+10.3°	> 95	(*R*)
13	CH_3	R"$OCH_2CH_2CH_2Br$[d]	78	+16.0°	> 95	(*R*)

a) Purities were determined by ^{13}CMR (JEOL JNM-FX90Q instrument; S/N ca. 40/1). No peaks of the other diastereomer were detected. b) Configurations were determined by optical rotations of the corresponding acids obtained by hydrolysis. Those in parentheses were tentative assignments from mechanistic analogy. c) (2*S*,5*S*)-Enantiomer of **5** was used. d) R"=t-$BuMe_2Si$.

Table 2. Stereoselectivity in Ethylation (EtI) of (2*R*,5*R*)-N-Propionyl-**5** with Different Bases and Solvents at -78°C

Bases	Solvent	% de[a] (CMR)
$LiN(i\text{-}Pr)_2$	Et_2O	> 95
$LiN(i\text{-}Pr)_2$	DME	> 95
$LiN(i\text{-}Pr)_2$	THF	> 95
$NaN(SiMe_3)_2$	THF	> 95
$KN(SiMe_3)_2$	THF	> 95

a) No peaks of the other diastereomer were detected

Table 3. Stereoselectivity in Ethylation (EtI) of (2*R*,5*R*)-N-Propionyl-**5** in THF at Different Temperatures

Temp.	Chem. Yield(%)	% de[a] (CMR)
-78°C	87	> 95
-40°C	79	> 95
0°C	76	> 95
20°C	75	> 95

a) No peaks of the other diastereomer were detected.

It has been recognized that the enantioselectivity of asymmetric alkylation is often very dependent on the reaction conditions and reactants, especially when the metal chelation plays an important role in the fixation of conformation at the crucial stage of the reaction. Therefore, we examined the effect of change in solvent, counterion, and temperature on the selectivity of the present alkylation. As can be seen in Table 2 and 3, the diastereomeric excess was not influenced by these factors as far as examined by CMR, giving invariably over 95% de. The more accurate solvent dependence will be shown by the data with MOM-derivatives below (Table 4, entry 3, 4, and 5).

Alkylation of the amides (**7**, Y=CH_2OCH_3) derived from **6** also proceeded successfully giving high diastereomeric excesses and chemical yields (Table 4). The hydrolysis of the alkylated amides could be easily effected without racemization by mere refluxing in aqueous 1N-HCl.[8] The reactants in the Table 4, except for the entry 7 and 8, were chosen in such combinations that both the (*R*)- and (*S*)-alkylcarboxylic acids could be prepared by using one enantiomer of **6**.[9]

Table 4. Asymmetric Alkylation Using (2*S*,5*S*)-**6** at -78°C

Entry	R in **7** (Y=CH_2OCH_3)	R'X	Solvent	Alkylated Amide (**8**, Y=CH_2OCH_3)		
				Yield(%)	Prod. Ratio	Configur.
1	CH_3	C_2H_5I	THF	79	100:1[a]	*S*
2	C_2H_5	CH_3I	THF	77	100:1[a]	*R*
3	CH_3	$PhCH_2Br$	THF	87	65:1[a,b]	*S*
4	CH_3	$PhCH_2Br$	DME	43[c]	100:1[b]	*S*
5	CH_3	$PhCH_2Br$	Et_2O(-20°C)	81	200:1[a,b]	*S*
6	$PhCH_2$	CH_3I	THF	83	90:1[a,b]	*R*
7	CH_3	C_4H_9I	THF	79	> 100:1[a]	*R*[d]
8	C_4H_9	CH_3I	THF	70	> 100:1[a]	*R*
9	CH_3	$C_8H_{17}Br$	THF(-20°C)	75	> 100:1[a]	*S*
10	C_8H_{17}	CH_3I	THF	73	> 100:1[a]	*R*

a) Determined from intensities of relevant PMR signals. b) Determined after HPLC separation. c) As the reaction was slow, it was interrupted after 8 h. d) (2*R*,5*R*)-**6** was used.

Mechanistically, the exclusive formation of (*Z*)-enolate by kinetic abstraction of one specific proton by LDA is quite obvious from the experiment carried out by Evans et al. on a prolinol amide.[10] The configurations of the alkylated carboxylic acids indicated that the approach of alkyl halides also exclusively directed to one enantiotopic face of the (*Z*)-enolate [*si*-face at (2*R*,5*R*)-compounds, for example] by C_2-symmetrically placed substituents. This is also supported by CPK model examination. It is not clear to what extent the chelation of an oxygen atom on a substituent to lithium ion contributes to the stereoselectivity, but the results shown in Table 2 seem to indicate that the effect must be small, if any.[11]

The experimental procedure is exemplified below.

Propionic anhydride (830 mg), (-)-**6** (700 mg), 4-dimethylaminopyridine (40 mg), and Et_3N (1.07 ml) in CH_2Cl_2 (10 ml) were stirred for 12 h. The usual work-up and purification by silica gel column gave N-propionyl-**6** (an oil, 834 mg, 95%).

The above amide (38.1 mg) dissolved in THF (200 μl) was added slowly to a solution of LDA (0.64N, 234 μl, 1.1 eq) in THF at -78°C and the mixture was stirred for 1 h at -20°C and then cooled again to -78°C. Benzyl bromide (28.4 mg, 1.2 eq) was added and the mixture was stirred for 6 h. Aqueous phosphoric acid (5%, 100 μl) was then added and the mixture was stirred for 30

min at the same temperature and then warmed to rt. Extraction (CH_2Cl_2), drying, concentration, and TLC (silica gel) gave N-(2-benzylpropionyl)-**6** [an oil, 44.4 mg, $[\alpha]_D^{23}$ +51.3°(c=1.00, EtOH)].

N-(2-benzylpropionyl)-**6** (44.1 mg) was refluxed in 1N-HCl (0.7 ml) for 3 h. The mixture was neutralized with sat. aqueous $NaHCO_3$ and then brought to pH 1 with 2N-HCl. Extraction (CH_2Cl_2), drying, concentration, and purification (silica gel column) gave 2-benzylpropionic acid [17.8 mg, 90%, $[\alpha]_D^{26}$ +21.0°(c=0.87, EtOH); lit,[12] $[\alpha]_D$ +25.4°(neat)].

Further application of the chiral auxiliaries to other enantioselective reactions and the facile recovery of the auxiliaries after the reaction, are under investigation.

References and Notes

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4) The compound and the corresponding L-body were generously gifted by Dr. Issei Iwai of Sankyo Co. Ltd. to whom the authors are very grateful.

5) The resolving agent (21.2 g, 0.1 mol) and *dl*-**2** (24.9 g, 0.1 mol) were dissolved in hot ethanol (1700 ml) and the solution was cooled to room temperature and stirred for 12 h. The salt separated (18.9 g, 41%, ca. 90% de from specific rotation) was once recrystallized from hot methanol (280 ml) to give practically pure salt [10.0 g, 22%, mp 192-196°C, $[\alpha]_D^{24}$ +31.5° (c=2.00, MeOH)]. The salt was treated with aqueous 2N-NaOH (21.7 ml) and the resolving agent was removed by filtration. The filtrate was acidified with aqueous 5N-HCl (8.7 ml) to pH 3 to give the (+)-**2** acid (4.32 g). The overall yield from *dl*-**2** was 17% without counting less pure fractions. The optical purity of the sample was determined to be >98% ee by PMR examination of the corresponding dimethyl ester ($SOCl_2$, MeOH) in C_6D_6 under the presence of a shift reagent, Eu(tfc)$_3$. The other enantiomer was not detected. The (+)-**2** acid (recrystallized once from water): mp 239°C, $[\alpha]_D^{25}$ +93°(c=1.00, H_2O).

6) At first we resolved *dl*-**5** through its acidic salt with D-(+)-dibenzoyltartaric acid giving (2*R*,5*R*)-(-)-**5**. But the procedure described in reference 5) was soon found to be much efficient. A study for a more practical resolution is under way.

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10) D.A.Evans and J.M.Takacs, Tetrahedron Lett., 4233(1980).

11) For comparison, *dl-trans*-2,5-dimethylpyrrolidine was prepared (reference 2) and its N-acyl derivatives were alkylated in a similar manner, giving a little but distinctly small de's as 88% for methylation of the butanoyl amide and 95% for ethylation of the propionyl amide. However it is not clear whether the difference is due to the chelation effect or to the difference of bulkiness between the substituents.

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(Received in Japan 26 November 1983)