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ASYMMETRIC SYNTHESIS OF α-ALKYL α-AMINO ACIDS BY ALKYLATION OF A CHIRAL AMIDINE ESTER

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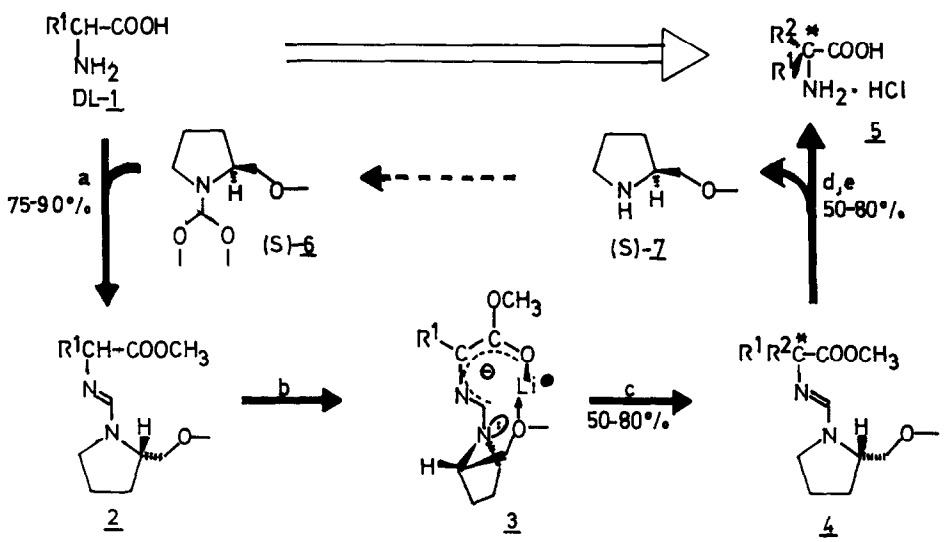
Summary : A short and convenient asymmetric synthesis of α-alkyl α-amino acids is described, using (S)(-)-1-dimethoxymethyl-2-methoxymethyl pyrrolidine (6) as chiral auxiliary reagent.

Many α-substituted α-amino acids have been shown to be specific inhibitors for the enzyme using the parent α-amino acid as substrate[1]. As a consequence of the high stereoselectivity displayed by the enzymes for their substrates, the inhibitory property is usually found to reside only with one enantiomer, and an efficient asymmetric synthesis of α-substituted α-amino acids would obviously be of interest.

We here wish to report a diastereoselective[2] asymmetric synthesis of α-alkyl α-amino acids 5 from the parent DL-α-amino acid 1[3]. This is achieved via derivatization of 1 into the chiral amidine ester 2[4] which can be deprotonated to form 3. Regiospecific and diastereoselective alkylation[2] of 3 yields 4 which after deprotection gives the α-alkyl α-amino acid 5 (scheme 1).

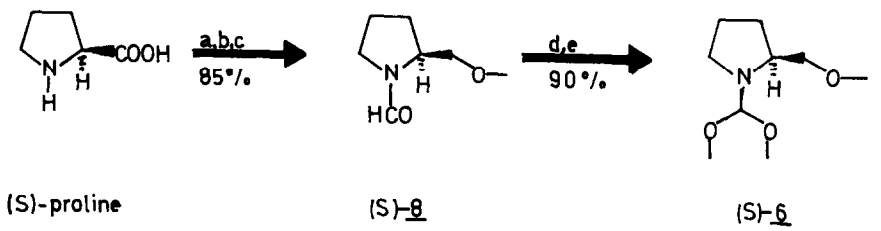
Scheme 1 :



a = 110°C, 3 h ; b = $LiN(i\text{-}C_3H_7)_2$, THF, -78°C, 30 min ; c = R^2X, -78°C → 25°C, 14 h ; d = CH_3OH/H_2O, 25°C, 14 h ; e = 3 N HCl aq., reflux, 60 h.

As chiral auxiliary reagent we use (S)(-)-1-dimethoxymethyl-2-methoxymethyl pyrrolidine (6), easily synthesized in large quantities from (S)-proline in 77 % overall yield (scheme 2). [A solution of (S)-8[5] and FSO_3CH_3 (1.1 equiv) in CH_2Cl_2 (2 ml/mMol) is stirred at 25°C overnight, concentrated, and washed with ether (3 x 2 ml/mMol) to yield an orange-brown oil. Addition of CH_3ONa/CH_3OH (4 equiv, 1 ml/mMol), stirring for 30 min and removal of the solvents on a rotatory evaporator (water bath 30°C) give a white residue. (S)-6 is isolated from this residue by extraction with ether and fractional distillation : colourless oil, bp 48°C/0.05 mm. ^{1}H-nmr (CCl_4) : δ = 4.50 (s, O-CH-O) ; 3.17 and 3.20 (2s, O-CH_3) $[\alpha]_D^{20}$ = -33° (c = 2.08, benzene) ; stable for several months in the refrigerator, sensitive to traces of acids].

Scheme 2 :



a = $LiAlH_4$, THF ; b = HCO_2CH_3 ; c = NaH, CH_3I, THF ; d = FSO_3CH_3, CH_2Cl_2
e = CH_3ONa, CH_3OH

Heating a mixture of DL-1 and 6 (3 equiv) under N_2 [3 h, 110°C (oil-bath temp.)] yields 2 (R^1 = CH_3, 75 % ; R^1 = i-C_3H_7, 90 % ; R^1 = $C_6H_5CH_2$, 75 %)[6] which proved to be distillable colourless oils. Deprotonation of 2 to form 3 is accomplished by addition of a THF solution of 2 (1 ml/mMol) to lithium diisopropylamide [1 to 2 equiv, prepared in situ from diisopropylamine and n-BuLi in THF/hexane (4:1, 2 ml/mMol)] at -78°C. After 1 h, 1.1 equiv of R^2X are added to the pale yellow solution ; the dry-ice cooling bath is removed and the reaction mixture is stirred overnight at 25°C. Aqueous work-up gives 4[6] as an oil. Deprotection to the α-alkylated amino acid 5 is achieved by treatment with CH_3OH/H_2O (1:1, 100 ml/g) and then with 3 N HCl aq. (100 ml/g). The reported direct hydrolysis of dimethylformamidine methylester derivatives of α-amino acids with HCl[4] gave lower yields. Product 5[6] is isolated from the aqueous hydrolysis-medium by ion-exchange chromatography (Dowex 1 X 8, 50-100 mesh, $OH^{\ominus}$).

The results of various alkylations are summarized in Table 1.

Table 1 :

DL-1	R^2X	% 4 a)	% 5 a)	$[\alpha]_D^{20}$ b)	% ee c)
alanine	CHF_2-Cl d)	40	54	- 1.0 e)	
"	C_2H_5-I	75	76	0 f)	
"	n-C_4H_9-I	73	79	- 0.1 f)g)	(R) [3a]
"	$C_6H_5CH_2$-Br	60	68	+ 3.4	51 (R) [7]
"	3.4$(CH_3O)_2C_6H_3$-CH_2-Br	80	31	+ 1.3	30 (R) [3a]
isovaline	CH_3-I	50	50	+ 4.6	
phenylalanine	CH_3-I	68	78	- 1.0	15 (S) [7]
"	C_2H_5-I	79	53	- 3.0	

a) isolated, analytically pure compound ; b) measured in water, c = 2 ; c) by comparison with literature values ; d) experimental details for alkylations with CHF_2Cl see ref. 1a ; e) c = 1 in water ; f) the use of the bromides instead of the iodides as electrophile did not alter the chemical or optical yields ; g) $[\alpha]_{436}^{20}$ -0.4 ; $[\alpha]_{365}^{20}$ -1.0.

The stereoselectivity of the reaction was determined by measurement of the specific rotation of isolated 5. As one expects, the degree of asymmetric induction in the alkylation step appears to depend on the size of the electrophile R^2 and the interchange of R^1 and R^2 in the reaction sequence changes the configuration at the α carbon atom in 5. These results seem to indicate that the α-alkyl α-amino acids 5 formed in our experiments are configuratively interrelated. They can be rationalized by re-face (bottom side) alkylation of the anion 3 in the configuration given in Scheme 1. However, as neither the configuration of the anion nor the influence of the reaction conditions on the degree of asymmetric induction were investigated[8] all mechanistic interpretations of our observations are speculations at this stage.

The results described here suggest that the reaction sequence outlined in Scheme 1 is a general approach to the asymmetric synthesis of α-substituted α-amino acids from the readily available α-amino acids affording good chemical yields with appreciable enantiomeric purity. No attempts were made to optimize the reaction sequence. The applicability of the chiral auxiliary reagent 6 to other asymmetric syntheses is under investigation.

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