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Addition of Dilithiated Methyl-3-aminobutanoate to Aldehydes Proceeds with ul-1,2-Induction

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Abstract: Syntheses of 2-substituted 1-hydroxyethylene building blocks, useful as the central moiety of HIV-1 protease inhibitors, is described. Dilithiated N-protected-3-amino-4-phenylbutanoic methyl esters are reacted with aldehydes to give predominantly aldol products with l,u configuration. The diastereomeric ratio depends on the N-protecting group and on the experimental conditions. The configurations are assigned by ^{1}H-NMR of cyclic derivatives and are supported by X-ray structure.

Transition state mimics reflecting the C_2-symmetry of the HIV-1 protease homo-dimer (HIV-PR) have been shown to be highly potent and selective inhibitors of the enzyme[1]. However, recently, X-ray structure analysis of HIV-PR complexed with a C_2-symmetric dihydroxyethylene containing inhibitor made apparent, that this type of inhibitor does not exert symmetric contacts to the enzyme (Fig. 1.)[2].

As it was suggested by CAMD-studies, one of the hydroxyl groups should be replacable by carboxyl or hydroxymethyl substituents. The slight distortion of the symmetry in the central part of the inhibitor while preserving its peripheral C_2-symmetry might result in tighter binding to the active site. Therefore, we became interested in the synthesis of modified hydroxyethylene building blocks .

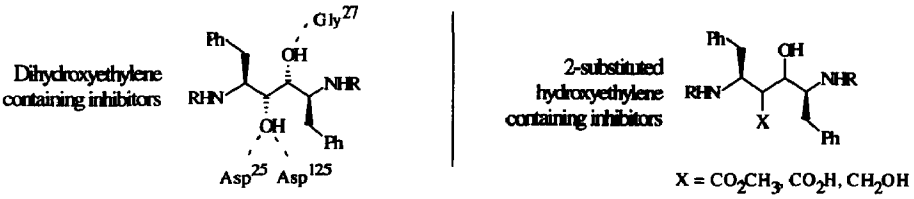
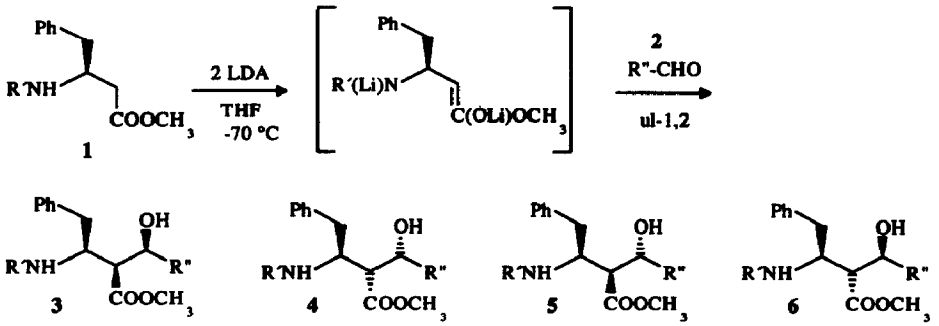


Fig. 1.

Carboxyl-hydroxy- or hydroxymethyl-hydroxy-ethylene derivatives with adequate stereochemistry should be readily available via aldol addition of protected phenylalaninal with enantiomerically pure N-protected methyl-3-amino-4-phenylbutanoate and subsequent saponification or reduction of the ester-functionality. It has been concluded from the alkylation of 3-aminobutanoates[3] that this reaction should take place with relative topicity lk-1.2[4], and the trigonal centers will combine with relative topicity lk. Furthermore, Reetz et. al [5] have demonstrated that N,N-dibenzyl protected phenylalaninal and Li-enolates combine without racemization.

When dilithiated **1a** (**1b**)[6] was reacted with benzaldehyde **2a** at -70 °C and the reaction mixture was allowed to reach room temperature within 12 h, only one single diastereomer **3a** (**3b**) was formed[7]. However, experimental conditions showed influence on the stereochemical result. This became evident by low temperature quenching of the reaction of **1b** with **2a**. **3b** remained the main product, but three additional diastereomers **4-6b** had formed. The diastereomeric ratio was determined according to the NMR spectra of the pre-purified product mixture. A separation of **3-6b** was not possible at this stage (see below).



Scheme 1[7]

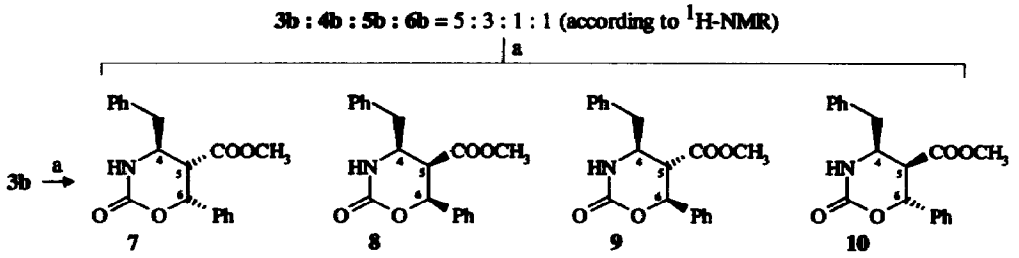
Table 1. Reaction conditions, yields and selectivities of the aldol addition.

1	R´	2	R"	T[°C]	y[%]	m.p.[°C]	d.r.
1a	Boc	**2a**	Ph	-70→RT/ 12h	49	163-165	**3a**
1b	Cbz	**2a**	Ph	-70→RT/ 12h	32	121	**3b**
1b	Cbz	**2a**	Ph	-70/ 10 min	63		**3b:4b:5b:6b** = 47:30:11:11
1a	Boc	**2b**	(S)(Bn)$_2$NCHBn	-70→RT/ 12h	41		**3c:4c**= 77:23
1a	Boc	**2b**	(S)(Bn)$_2$NCHBn	-70/ 10 min	58-70		**3c:4c**= 59:41
1c[8]	Bz	**2b**	(S)(Bn)$_2$NCHBn	-70/ 30 min	69	110	**3d**

In order to synthesize the desired methoxycarbonyl-hydroxy-ethylene building block, Li-enolate of **1a** was treated with N,N-dibenzyl protected L-phenylalaninal **2b** at -70° C. After slow warming up of the reaction mixture within 12h and purifying of the addition products, ^{1}H-NMR spectroscopy revealed a diastereomeric mixture of **3c** : **4c** = 77 : 23. The isomers **3c** and **4c** could be separated chromatographically. When the reaction mixture was quenched at -70° C after 10 min, the diastereomeric ratio of the products was shifted in favour of **4c**, but formation of additional diastereomers was not indicated by the NMR spectra. Only a single isomer **3d** was formed when **2b** was reacted with benzoyl protected enolate of **1c**, reflecting protection-group dependency when the reaction is performed with chiral aldehydes.

In order to determine the stereochemistry of the products **3-6**, in a first step single diastereomer **3b** was converted to cyclic urethane **7**. The same reaction conditions were then applied to the pre-purified mixture of diastereomers **3b-6b**, isolated from condensation of **1b** with **2a** under kinetic control. The resulting mixture of urethanes **7-10** could be separated by column chromatography (*Scheme 2*).

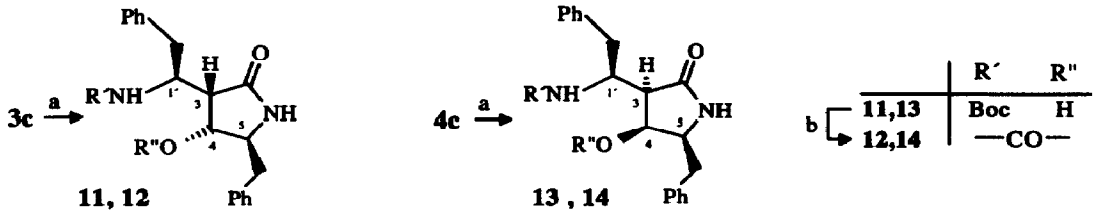
The configurations of stereo centers C(5) and C(6) created in the course of the reaction were assigned by ^{1}H-NMR spectroscopy relative to the known (S)-configuration of **1b**. Strong NOEs between H(6) and H(5) suggest relative cis-orientation of these protons in both derivatives **7** and **8**. H(6) and H(4) adopt a 1,3-diaxial conformation in **8** as it is suggested by the respective NOEs in **7** and **8**. This assignment was further confirmed by significant NOE between H(5) and H(4) in **8**. The stereochemical relations of the minor diastereomers **9**, **10** are supported by the measured coupling constants (Table 2), and further evidence is given by comparison with the already assigned isomers **7** and **8**. In conclusion, the major diastereomer **3b** from the reaction of **1b** with benzaldehyde **2a** has l,u-configuration.



Scheme 2: (a) i) 10% Pd/C, H_2, CH_2Cl_2, RT, 12h; ii) phosgene, pyridine, 0°C, 3h.

Table 2 . ^{1}H-NMR data ($CDCl_3$) of products **7 - 10**.

	δ [ppm]				J [Hz]		NOE[%]		
#	H_4	H_5	H_6	OCH_3	J_{H4-H5}	J_{H5-H6}	H_6-H_5	H_6-H_4	H_5-H_4
7	3.97	3.08	3.56	3.57	6.1	4.2	11	2	
8	4.14	3.06	5.50	3.52	4.6	3.0	8	6	8
9	4.17	2.85	5.31	3.40	10.4	10.3			
10	3.82	3.26	5.72	3.71	5.1	7.0			



Scheme 3: (a) Pd_{black}, H_2, CH_3OH, RT, 12h; (b) i) 6n HCl in dioxane, RT, 10 min; ii) phosgene, pyridine, 0°C, 3h.

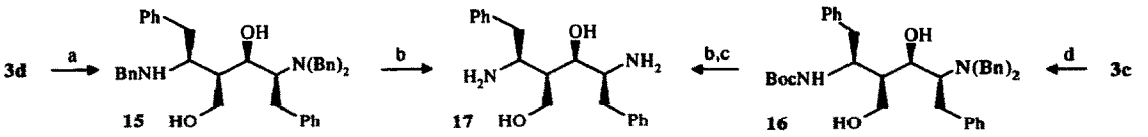
Table 3. ^{1}H-NMR data and m.p. of products **11-14**.

	δ (ppm)					J [Hz]				NOE[%]			m.p.[°C]
#	$NH_{1'}$	$H_{1'}$	H_3	H_4	H_5	$J_{NH-H1'}$	$J_{H1'-H3}$	J_{H3-H4}	J_{H4-H5}	H_3-H_4	H_3-$H_{1'}$	H_3-H_5	
11[a]	6.38	4.07	2.27	4.28	3.57	8.9	5.7	5.7	<4.0	4.2	1.8	0	175-178
12[b]	5.75	3.99	2.40	4.65	4.01	3.7	2.5	6.3	0				186
13[b]	5.38	4.22	2.57	4.29	3.71	9.8	0	4.3	5.4	10	4	5	193-195
14[b]	5.69[c]	3.89	2.76	4.81	3.89	0	3.2	5.4	4.0				210-211

[a] DMSO-d_6; [b] $CDCl_3$; [c] NH can be either at $C_{1'}$ or C_5.

Determination of the stereochemical outcome of the attack of chiral aldehyde **2b** to dilithiated **1a** was performed with the aid of derivatives **11-14**, obtained by transformation of the separated reaction products (**3c,4c**) to pyrrolidones (**11, 13**), followed by additional ring-closure to bicyclic **12** and **14** (*Scheme 3*). Comparison of both - NOEs between H(3)-H(5) in **11, 13** and coupling constants between H(4)-H(5) in derivatives **12, 14** - assigns the absolute configuration of the created stereocenters in **3c** and **4c** relative to the known S-configuration of the initial aldehyde **2b**. The assigned configurations are in agreement with X-ray structure analysis of **13**[9]. As in the former case (**3b**), the main diastereomer **3c** turned out to have l,u-configuration.

In a final experiment, the single diastereomer **3d** generated by the reaction of **1c** with **2b** was converted to 1,4-diaminoalcohol **17**, which was shown to be identical with the product obtained from isomer **3c**. Compound **17** represents a first example of the desired hydroxymethyl-hydroxyethylene derivatives.



Scheme 4: (a) LAH, THF, 0°C→RT, 3h, 60°C, 16h; (b) Pd_{black}, H_2, CH_3OH, RT, 12h; (c) 6n HCl in dioxane, RT, 10 min; (d) LAH, THF, -30°C→RT, 12h.

From the assigned configurations of **3b-d** we conclude that the addition of benzaldehyde **2a** and other aldehydes (e.g. **2b**) to the dilithiated enolate of **1a-c** takes place with ul-1,2 induction, and that the two trigonal centers of aldehyde and enolate combine with relative topicity lk. Thus, dilithiated (S)-enolate of protected 3-aminobutanoates are attacked by aldehydes from the Re-face. Asymmetric induction is higher for benzoyl-protection (**1c**) as compared to Boc- (**1a**) or Cbz-(**1b**) protection, and diastereoselectivity depends on experimental conditions. The results described here are contradictory to the already reported alkylation of dilithiated 3-aminobutanoates, which resulted in lk-1,2-induction[3].

Incorporation of hydroxymethyl-hydroxyethylene substructure as the central moiety of a new type of protease inhibitors and the consequence of stereochemistry on antiviral activity will be described in a forthcoming publication.

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7. Typical Procedure: Methyl-N-protected-4-phenyl-3-aminobutanoate (12 mmol) is deprotonated by 2.0 equiv. LDA in 50 ml THF at -70 °C. After 1 h a precooled solution of 24 mmol aldehyde in 30 ml THF is rapidly added via cannula. The reaction mixture is quenched by addition of 17 ml of a 1.5M solution of acetic acid in THF. Ethyl acetate and 5% aqueous HCl are added and the organic layer is washed with saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the products are isolated by chromatography on silica gel and recrystallized from ethyl acetate/n-hexane. All products gave satisfactory elemental analyses and/or mass spectra. All spectra were compatible with the structures shown in the schemes.
8. **1c** was prepared out of **1a** by deprotection and subsequent benzoylation.
9. Weber, H.P.; Ettmayer, P.; Hübner, M.; Gstach, H. *Acta. Cryst. in preparation*.

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