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STEREOCONTROLLED CONVERGENT SYNTHESIS OF HYDROXYETHYLENE DIPEPTIDE ISOSTERES BY THE REACTION OF α-AMINO ALDEHYDE WITH ALKOXYTITANIUM HOMOENOLATES

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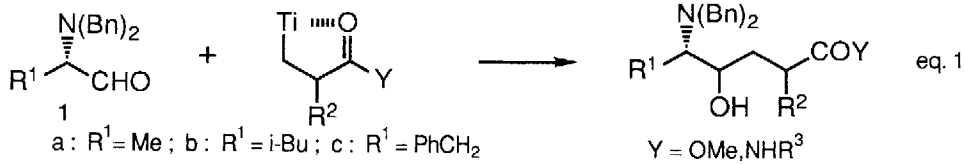
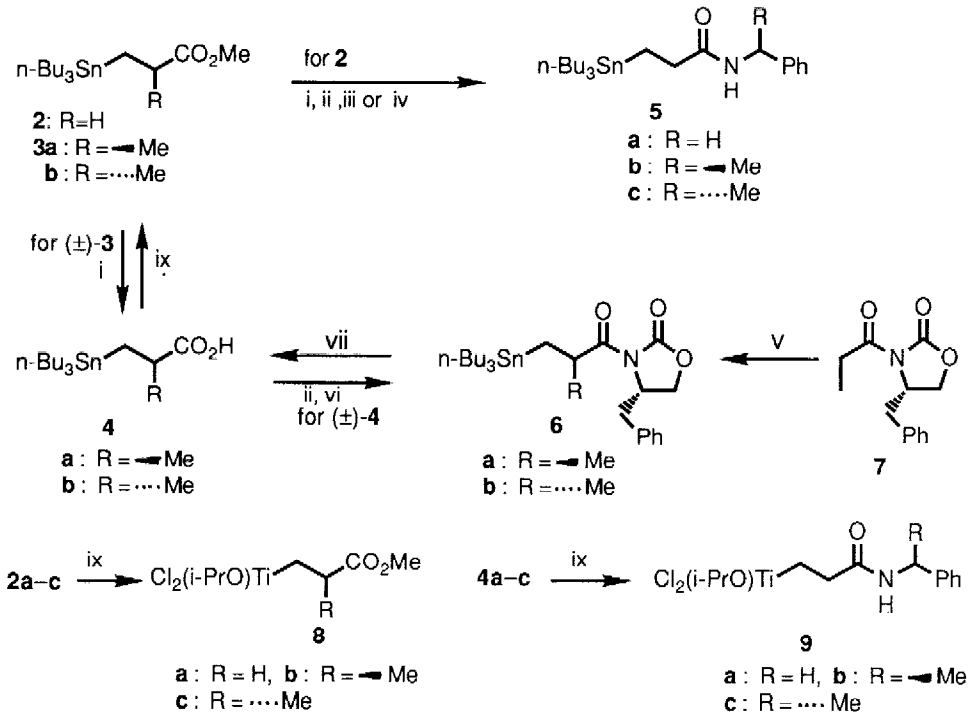
Summary: The reaction of (S)-α-dibenzylamino aldehydes with dichloroisopropoxytitanium ester homoenolates gave the corresponding γ-aminoalkyl γ-lactones with high erythro selectivity. The same reaction by the use of amide homoenolates also afforded the corresponding 2-amino alcohols with high erythro-selectivity.

The concept of replacing the scissile C-N unit of a peptide bond in enzyme substrates by suitable isosteric units such as hydroxymethylene and hydroxyethylene that could provide potential protease inhibitors has drawn a lot of attention in recent years in peptidomimetic chemisty.[1] Our own interest in this area promted us to explore stereocontrolled convergent sequences to such peptide mimic as hydroxyethylene dipeptide isostere[2] by condensation of titanium homoenolate,[3] with α-amino aldehydes (**1a-c**)[4] as shown in eq. 1.



Titanium homoenolates were prepared in situ by direct tin-titanium exchange method by using 3-(tri-n-butylstannyl)propionic acid derivatives obtained as outlined in the following Scheme. Methyl acrylate and methyl methacrylate were led to **2** and (±)-**3** by treatment with $n\text{-}Bu_3SnH$ according to the method described by Goswami.[3a] Condensation of (±)-**4**, obtained by hydrolysis of (±)-**3**, with (S)-4-benzyloxazolidin-2-one gave a mixture of **6a,b**; this was separated by column chromatogaraphy on silica gel, **6a**: 42% yield, $[\alpha]_D$=+62.8° (c 1.1, $CHCl_3$), **6b**: 38% yield, $[\alpha]_D$=-7.68° (c 1.1, $CHCl_3$). Hydrolysis of each of **6a,b**, followed by esterification of **4a,b** with diazomethane afforded **3a**, $[\alpha]_D$=+17.0° (c 1.0, $CHCl_3$), and **3b**, $[\alpha]_D$=-16° (c 1.0 $CHCl_3$), respectively. Stereoselective synthesis of **6b** was also achieved by tri-n-butylstannylmethylation of **7** (i. $NaN(TMS)_2$, ii $n\text{-}Bu_3SnCH_2I$, -50°C, 10 h) by an application of Evans method[5] in a 1:9 ratio of **6a** and **6b**. The amides (**5a-c**) were obtained in about 75 % yield by treatment **2** with the corresponding amine in the presence of trimethylaluminum in CH_2Cl_2 or hydrolysis of **2**, followed by condensation with the corresponding amine by the usual way. Treatment of **2**, **3a,b** and **5a-c** with $TiCl_4$ (CH_2Cl_2, -20°C, 0.5 h)[3a] and further addition of 0.5 equiv. of $Ti(OPr^i)_4$ afforded the

corresponding dichloro-i-propoxytitanium homoenolates[3b] (**8a-c**, **9a-c**), respectively; these, generated in situ, were used for the following reaction.



Reagents and Conditions: i. NaOH/EtOH, ii. $(COCl)_2$/hexane, iii. $PhCH_2NH_2$/THF, iv. L- or D-α-phenethylamine/Me_3Al/CH_2Cl_2, v. $NaN(TMS)_2$, n-Bu_3SnCH_2I, –50°C vi. lithium amide of (S)-4-benzyloxazolidin-2-one, vii. LiOH/THF/H_2O, viii CH_2N_2 ix. $TiCl_4$, –20°C,CH_2Cl_2, 0.5h then 0.5 equiv. $Ti(i\text{-}PrO)_4$

Although the reaction of N-Cbz aminals with **8a** yielded the corresponding adducts in high yield, but resulted in low diastereoselectivity (erythro/threo=1-3). In contrast to this result, α-dibenzylamino aldehydes (**1a-c**) reacted with **8a-c** (-20°C, CH_2Cl_2, 12 h) to give the corresponding lactones (**10a-g**)[6] with high erythro-selectivity. Their yields and the ratio for erythro/threo were shown in the Table 1. In this reaction, the use of trichlorotitanium homoenolate did not give any desired product. The formation of **10d-g** with high erythro-selectivity shows that the alkyl substitutent at the α-position of ester group does not influence the erythro-selectivity. Stereostructure for **10d**, mp 86-88°C, was clearly established without ambiguity by the NOE study. The lactones (**10f,g**) were converted to the amides (**11a**; 75% yield), mp 94-95°C, $[\alpha]_D$ +39.8° (c 0.4, $CHCl_3$) and (**11b**; 80 % yield), an oil, $[\alpha]_D$ -17.5° (c 0.4, $CHCl_3$) by treatment with benzylamine in the presence of trimethylaluminum in CH_2Cl_2.

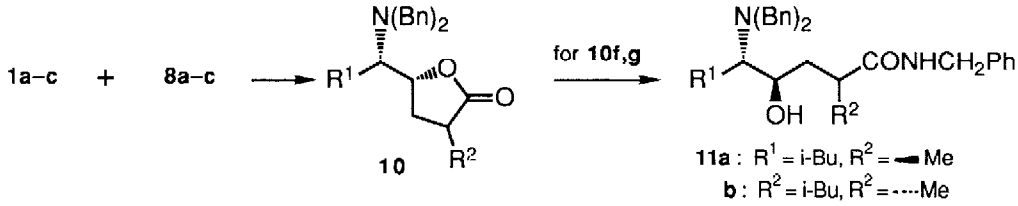


Table 1 Yield and Ratio for erythro/ threo of **10a-g**

10	R^1	R^2	Yield(%)	erythro/threo	$[\alpha]_D$ (deg . in $CHCl_3$)
a	Me	H	45	13 : 1	+24.0° (c 0.5)
b	i-Bu	H	65	10 : 1	−43.9° (c 0.5)
c	$PhCH_2$	H	60	12 : 1	+0.2° (c 1.0)
d	Me	Me	42	10 : 1	+19.8° (c 0.6)
e	Me	Me	39	10 : 1	+22.7° (c 0.6)
f	i-Bu	Me	53	10 : 1	−38.5° (c 0.6)
g	i-Bu	Me	54	10 : 1	−43.2° (c 0.6)

In the course of extension of this work, we were interested in a direct synthesis of this type of amides, which would be considered as tripeptide isostere. The reaction of **1a-c** with **9a-c** under the same conditions as above gave the corresponding amino alcohols (**12a-d**) with high erythro-selectivity as in a synthesis of **10**. Their yields and the ratio for erythro/threo were listed in the Table 2. The optical purity for **12** was determined as > 95% by analysis of ^{1}H-NMR (400 MHz, $CDCl_3$) spectra of both (+)- and (-)-α-methoxy-α-trifluoromethylphenylacetate[7] of **12b**. Conversion of **12a,b** to the threo-isomers (**13a,b**) was easily performed by Swern oxidation[8] (Me_2SO, $(COCl)_2$), followed by reduction of the resulting ketone with $NaBH_4$ in > 10:1 threo-selectivity. Both **12a** and **13a** were converted to the corresponding N-benzyl-4,5-cis- (**14a**) and 4,5-trans-oxazolidin-2-ones (**14b**) by reductive debenzylation with Pd black/HCOOH in methanol, followed by carbonylation with carbonyldiimidazole in CH_2Cl_2. Comparison of ^{1}H-NMR spectra of **14a** and **14b** and NOE study strongly supported the relative configuration of **12** to be erythro and **13** to be threo.[9]

Finally, application of this method was focussed on a diastereoselective synthesis of 2-amino alcohols (**17a-c**), which would be useful derivatives for preparation of potentially inhibitory active compounds to the endothelin converting enzyme.[10] Condensation of **15** with **8a-c**, followed by ring opening of the resulting lactone (**16a-c**) with n-butylamine in the presence of trimethylaluminum to give **17a** in 28 % yield from **15**, $[\alpha]_D$=+20.3° (c 0.5, $CHCl_3$), **17b** in 25 % yield, $[\alpha]_D$=+40.9° (c 0.6, MeOH), **17c** in 23 % yield, $[\alpha]_D$=+44.6° (c 0.5, MeOH), respectively.

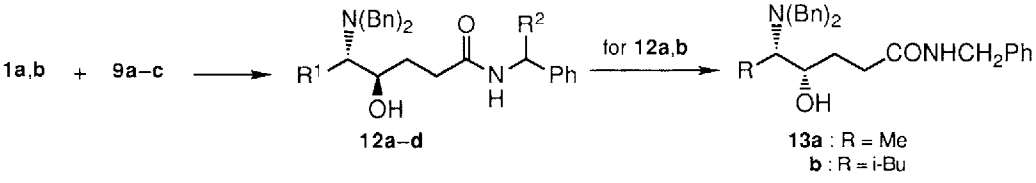
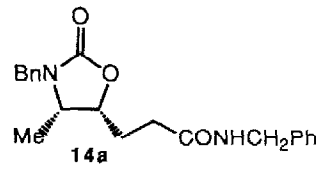
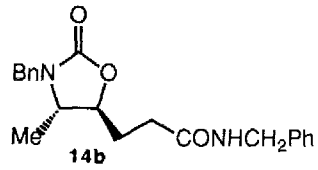


Table 2 Yield and Ratio for erythro/threo of **12a-d**

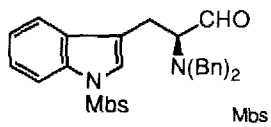
12	R^1	R^2	Yield(%)	erythro/threo
a	Me	H	60	10 : 1
b	i-Bu	H	55	10 : 1
c	i-Bu	▬ Me	58	10 : 1
d	i-Bu	···· Me	63	11 : 1



14a

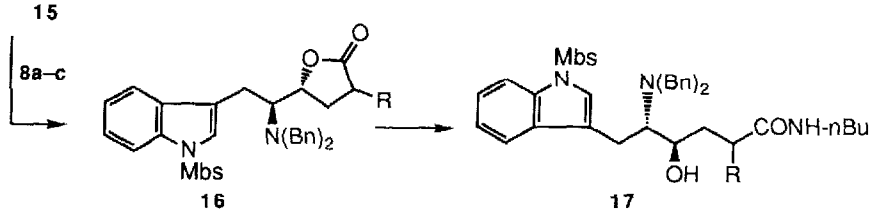


14b



15

Mbs = p-methoxybenzenesulfonyl



16 **17**

a: R = H, **b**: R = ···· Me, **c**: R = ▬ Me

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