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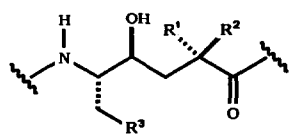
NEW DIASTEREOSELECTIVE SYNTHESIS OF NOVEL CHIRAL γ-(AMINOALKYL)-α-HYDROXY-γ-LACTONES AND THEIR APPLICATION FOR THE SYNTHESIS OF RENIN INHIBITORS

Rainer Metternich* and Werner Lüdi
Preclinical Research, SANDOZ Ltd., CH-4002 Basle, Switzerland

Summary: Using a new aldol approach, starting directly from the pyruvate enolate 7 and reacting it chelate controlled with the chiral α-aminoaldehyde 8, the aldol adduct 9 is obtained diastereoselectively and is converted subsequently by 1,3-induced asymmetric hydrogenation into the chiral title compound 11. This novel lactone is further used for the synthesis of potent renin inhibitors.

Dipeptide isosteres, i.e. dipeptides in which the amide-CONH linkage has been replaced by some approximately isosteric functional group e.g. ketomethylene[1] or hydroxyethylene[1,2a] resp. dihydroxyethylene[2b] group, have been used to prepare transition state analogues as enzyme inhibitors.

In the course of our work on renin inhibitors,[3] we were interested in compounds incorporating the 2-oxy-substituted hydroxyethylene dipeptide isostere 1:

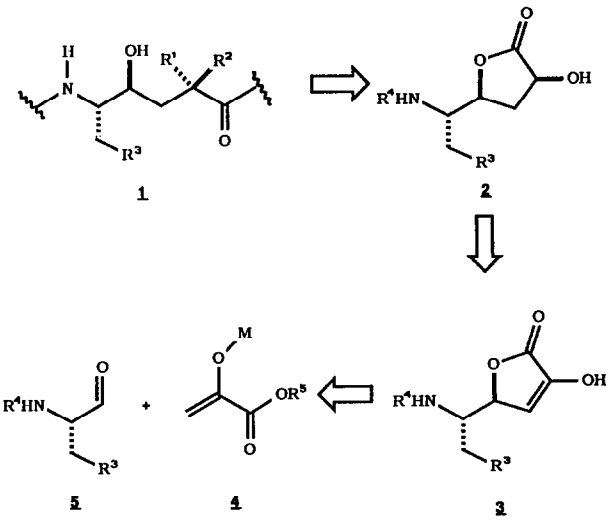


	R¹	R²	R³
1a	OR	H	cyclohexyl
1b	H	OR	cyclohexyl

Therefore we developed a new stereocontrolled synthesis of α-hydroxy-γ-lactones. Our synthetic strategy is shown in scheme 1. The required two new stereocentres should result by a sequence of chelate controlled[4] 1,2-induced asymmetric aldol addition of a pyruvate enolate 4 to a chiral α-aminoaldehyde 5 and 1,3-induced asymmetric hydrogenation of the resulting α-enol-γ-lactone 3.

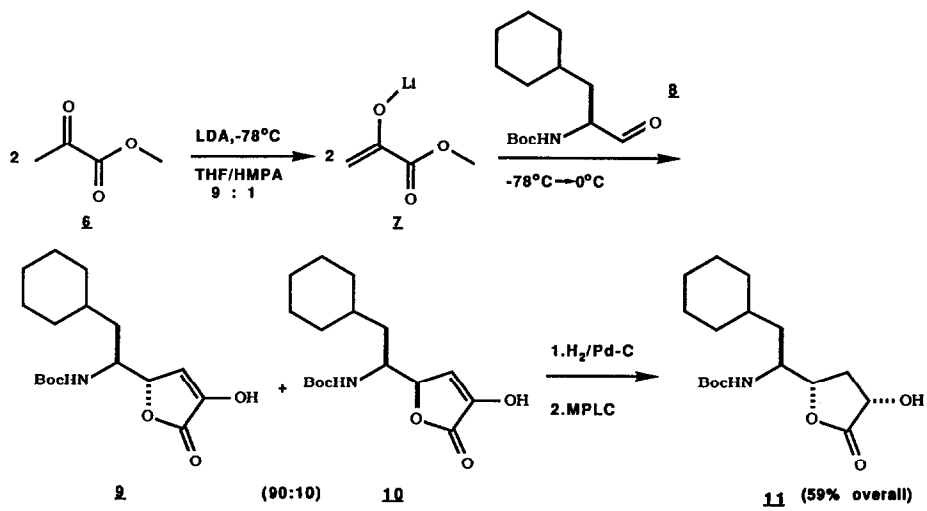
Previous syntheses of α-keto-γ-lactones resp. α-enol-γ-lactones[5] by condensation of α-keto acids or esters with aldehydes followed by lactonization[6,7] are often accompanied by side reactions.[7] Hence, synthons of pyruvate enolate are used to circumvent this problem.[8] Nevertheless, we felt that it should be worthwhile to examine the direct reaction of a lithiated methyl pyruvate with a N-lithiated chiral α-aminoaldehyde.

Starting from BOC-L-cyclohexylalaninal[9] 8 and the pyruvate enolate 7, the corresponding α-keto-γ-lactone (which exists exclusively in the enol form[5] 9) was formed diastereo-



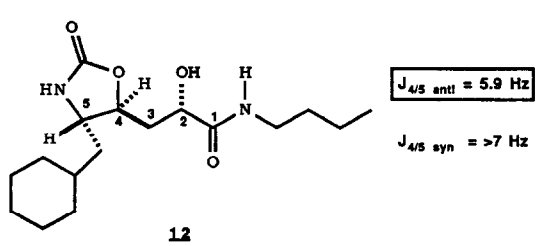
SCHEME 1

selectively (9:10=90:10) and was converted subsequently into the chiral α-hydroxy-γ-lactone 11 which was obtained as a white crystalline compound in 59% overall yield.



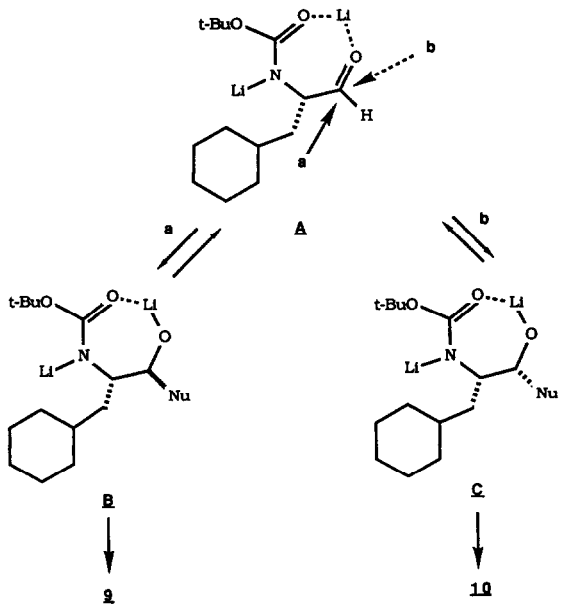
SCHEME 2

Conversion of 11 to the corresponding oxazolidinone 12 (1. $BuNH_2$, R.T.; 2. NaH, THF) permitted assignment of the relative configuration between C-4 and C-5 by ^{1}H-NMR arguments:[10,11]



12

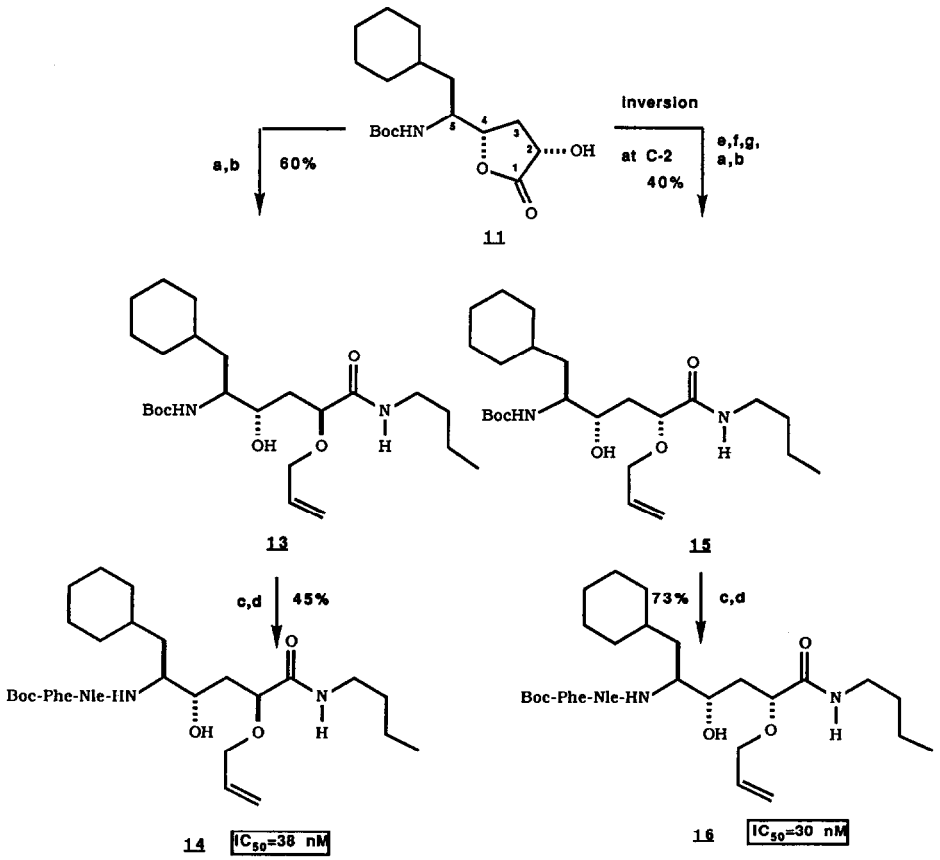
The observed diastereoselectivity is not consistent with the Felkin model[12] for asymmetric induction. However, with regard to the fact that the enolate 7 adds to the chelated aldehyde species A, this result is consistent with the cyclic Cram model[4] in which the incoming nucleophile adds from the less hindered side of the chelate (kinetically favoured pathway a). One might also propose equilibration of the two chelated species B and C via a retroreaction to species A.[13] The trans isomer B is then thermodynamically favoured over the more hindered cis isomer C (scheme 3):



SCHEME 3

Typical aldol-hydrogenation procedure

To a solution of 63 mmol of LDA in THF/hexane (1.5 mol^{-1}) at -78°C is added a solution of 60 mmol of methyl pyruvate in 120 ml of THF/HMPA (9:1) over a 1 h period. After additional 15 min at -78°C, a solution of 20 mmol of BOC-L-cyclohexylalaninal 8 in toluene (0.88 mol^{-1}) is added. The reaction mixture is warmed up to 0°C overnight and is quenched by the addition of 0.67 mol^{-1} aqueous tartaric acid. The aqueous layer is extracted several times with diethyl ether, the combined organic layers are washed with brine, dried over sodium sulfate, filtered and concentrated. - Pure α-enol-γ-lactone 9 is obtained by recrystallization from CH_2Cl_2/hexane; mp 178°C, $[\alpha]_D^{25°C}$ = - 22.4° (c=0.92, CH_2Cl_2). The crude α-enol-γ-lactone 9 is dissolved in ethyl acetate (0.1 mol^{-1}) and is hydrogenated (H_2/1 atm) overnight in the presence of 5 g of 10% Pd/C. The reaction mixture is filtered over celite and concentrated in vacuo. After chromatography (MPLC, hexane/ethyl acetate (1:1)), the α-hydroxy-γ-lactone 11 is obtained in diastereomerically pure form (> 99%, 360 MHz ^{1}HNMR); mp 143-144°C, $[\alpha]_D^{25°C}$ = - 2.25° (c=0.4, CH_2Cl_2). The application of the new lactone 11 for the synthesis of dipeptide isosteres[14] e.g. 13 and 15 and potent renin inhibitors[15] 14 and 16 is shown in scheme 4.



SCHEME 4 (a) CH_2=CH-CH_2Br, Ag_2O, Et_2O; (b) n-$BuNH_2$, R.T.; (c) TFA, CH_2Cl_2 (1:2), R.T.; (d) Boc-Phe-Nle-OH, HOBT, EDCI, THF/DMF (1:1), 0°C-R.T.; (e) MsCl, Pyr., R.T.; (f) MeCOONa, HMPT, THF; (g) K_2CO_3, MeOH, R.T.

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14. Satisfactory combustion analyses and spectral data (NMR, MS) were obtained for all new compounds reported herein.
15. IC_{50}-values in scheme **4** are related to human renin.

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