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1,4-Additions to γ-Aminoalkyl-Substituted α-Methylene γ-Butyrolactones: Synthesis of Highly Functionalized Amino Acid Derivatives

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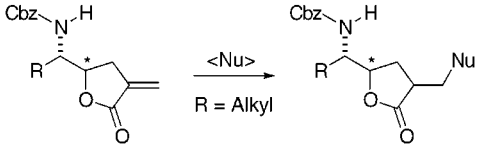
ABSTRACT



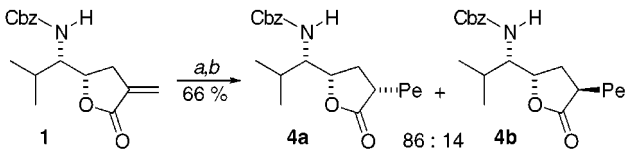
Addition of *C*- and *O*-nucleophiles to α-amino acid derived α-methylene γ-butyrolactones led to the corresponding Michael adducts. Addition of cuprates or cyanide, respectively, could be achieved with excellent selectivities. Addition of malonate anion or methanolate could be performed with good yields, but with rather poor selectivities. Hydrogenation led to methyl-substituted lactones, and ozonolysis yielded the corresponding α,β-dicarbonyls. The configuration of the products could be established by X-ray crystallographic analyses and NOE experiments.

α-Methylene γ-butyrolactones are important due to their various biological activities including antibiotical, fungicidal, anthelmintical, and antitumoral properties. Additionally, some of them are potent antiplatelet agents, antifeedants, or antagonists against opioid receptors.[1] In addition, they have been used for the preparation of HIV-1 protease and renin inhibitors.[2] Recently, we utilized a protocol developed by Schmidt et al.[3] for the diastereoselective preparation of α-amino acid derived γ-aminoalkyl-substituted α-methylene γ-butyrolactones **1**−**3**.[4] Inspection of several X-ray crystallographic analyses of these compounds showed that one side of the five-membered ring (and consequently of the exo-methylene moiety) should be effectively blocked by the aminoalkyl substituent. This seems to be favorable for further diastereoselective transformations of the double bond.

Herein, we wish to present our first results on conjugate additions of *C*- and *O*-nucleophiles to α-amino acid derived α-methylene γ-butyrolactones.

Addition of higher order cuprates[5] prepared from butyllithium and copper(I) cyanide to the valine-derived lactone **1** led to the corresponding adducts with poor selectivity and yield.[6,7] Nevertheless, both selectivity and yield could be significantly improved by addition of trimethylsilyl chloride (TMSCl) to the reaction mixture (Scheme 1).[8,9] The thus

Scheme 1



[a] 2 *n*BuLi, CuCN, TMSCl, Et_2O, −78 °C, 3 h. [b] 1 N HCl, rt, 0.5 h.

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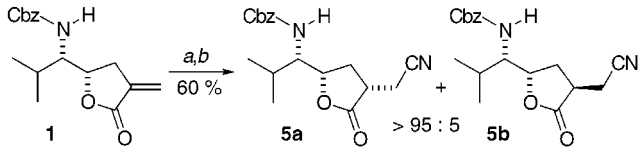
intermediately formed silyl enol ether was cleaved by hydrochloric acid with simultaneous formation of the new stereogenic center. Obviously, attack of the proton occurs preferentially from the less hindered face of the silyl enol ether leading to the *cis*-substituted lactone **4a**.

Addition of cyanide using acetone cyanohydrin and a catalytic amount of potassium cyanide led to the Michael adducts **5a**,**b** with a poor selectivity not exceeding 3:2.[10] Obviously, the enolate intermediate is either inter- or intramolecularly protonated by the reagent and/or by the carbamate-NH, respectively. Consequently, the use of TMSCN instead of acetone cyanohydrin (again leading intermediately to a silyl enol ether which is not cleaved before addition of hydrochloric acid) improved the selectivity significantly. No second isomer was observed in the spectra of crude product, when valine-derived lactone **1** was used as substrate (Scheme 2).[11] Therefore we estimate the selectivity to be better than 95:5.

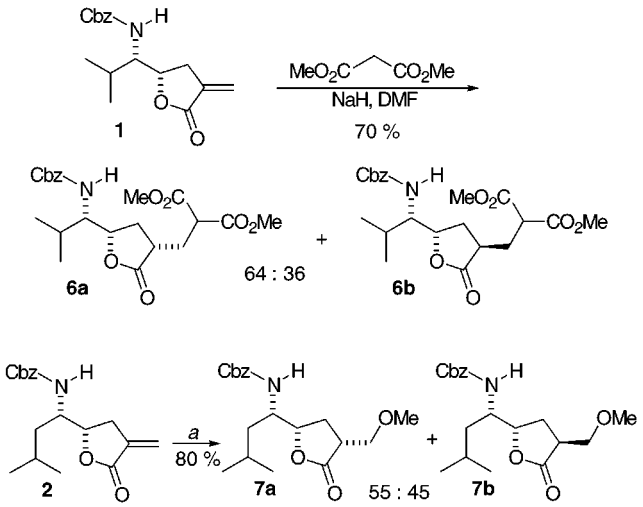
Scheme 2



[a] 2.2 TMSCN, 2 Et_3Al, THF, 60 °C, 24 h. [b] 1 N HCl, rt, 0.5 h.

Similar reasons as described above might be responsible for the low selectivities obtained, when malonate anion or methanolate[12] was added to the valine- or leucine-derived lactones **1** and **2**. The carbamate-NH protons as well as the α-proton of the malonate are acidic enough for a nonselective protonation of the intermediate enolates (Scheme 3).

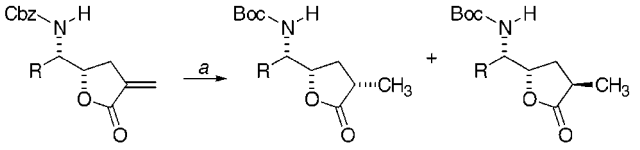
Scheme 3



[a] MeONa, MeOH, rt, 3 h.

Hydrogenolysis of methylene lactones **1** and **2** led to methyl-substituted butyrolactones **8** and **9**, respectively, with selectivities better than 10:1. With the conditions used herein (Pd/C, H_2, MeOH), the Cbz group was cleaved,[13] but the unprotected amine was reprotected in situ as the Boc derivative by adding Boc_2O to the reaction mixture (Scheme 4).[14]

Scheme 4



[a] Pd/C, H_2, Boc_2O, MeOH, rt, 19 h.

Ozonolysis[15] of the exocyclic double bond in the *tert*-leucine-derived lactone **3** yielded a dicarbonyl, which actually exists, at least in $CDCl_3$, as its enol tautomer **10** (Scheme 5).[15a] The enol was isolated essentially pure in 99% yield. Further chromatographic purification of the crude product led to decomposition of the substrate. Nevertheless, purification could be achieved by recrystallization. This and analoguous substrates should in the future enable a facile substitution in the β-position of our lactones and therefore give access to further classes of compounds.

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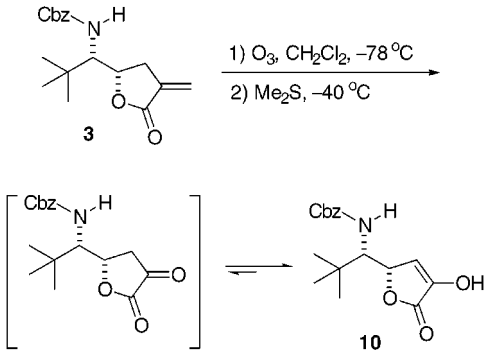
Scheme 5



The configuration of the methanolate adducts **7a** and **7b** and the hydrogenated product **8** could be unambiguously proved by X-ray crystallographic analyses (one example is given in Figure 1), showing the *cis*-configuration of the major products **7a** and **8**.

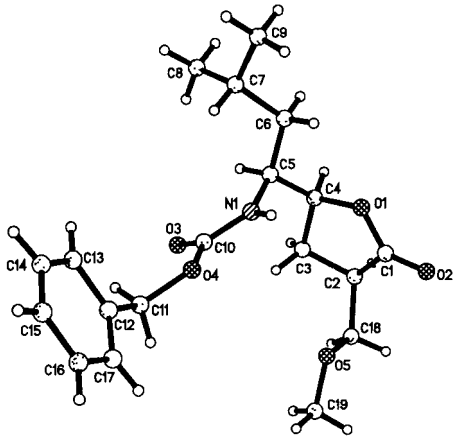


Figure 1. Major isomer of the methanolate adduct **7a** (X-ray).

The configuration of all other isomers presented herein could be established by thorough NMR spectroscopic investigations including NOE experiments.

We have presented a variety of nucleophilic additions to amino acid derived α-methylene lactones wich led to a plethora of amino acid derivatives bearing several functionalities and stereogenic centers on a minimum of space, therefore being useful intermediates in organic synthesis. The thus accessible substance classes are schematically depicted in Figure 2. Utilization of double protection at the amino functions might lead to improved selectivities. Work in this direction is ongoing in our laboratories.

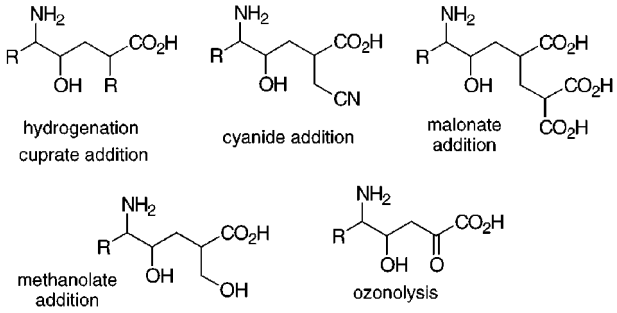


Figure 2.

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Supporting Information Available: Full characterization for compounds **4**−**10**. X-ray data for compounds **7a**, **7b**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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