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Asymmetric Synthesis of Highly Substituted γ-Amino Acids from Allyltitanium Sulfoximines

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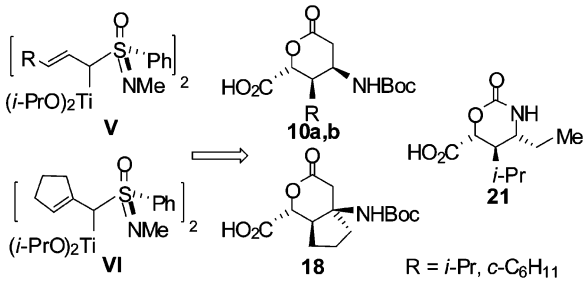
ABSTRACT



Asymmetric syntheses of the highly substituted protected γ-amino acids 10a, 10b, 18, and 21 have been developed starting from the allyltitanium sulfoximines V and VI, respectively, and furan-2-carbaldehyde.

The asymmetric synthesis of γ-amino acids,[1] and in particular that of α- and β-hydroxy-γ-amino acids,[2] is a topic of current interest. For example, γ-aminobutyric acid is an important neurotransmitter, and there is a strong quest for pharmacologically active analogues.[3] In addition, γ-amino acids are found in γ-lactams, and they are key components of natural and non-natural peptidomimetic protease inhibitors.[4] Finally, γ-amino acids can form peptides with stable secondary structures.[5] Besides the asymmetric synthesis of γ-amino acids, that of β-amino acids has gained much attention because of their natural occurrence as such or in β-lactams and the design of non-natural β-peptides.[6] We have therefore developed an interest in the asymmetric synthesis of α-hydroxy-γ-amino acids of types **I**−**IV** (Figure 1) which are analogues of not only γ-aminobutyric acid but also of β-aminopropionic acid and β-aminoadipic acid. α-Amino adipic acid, for example, has been shown to act as a *N*-methyl-D-aspartate receptor (NMDA) antagonist,[7a] and a β-aminoadipic acid derivative of type **I** is a constituent of

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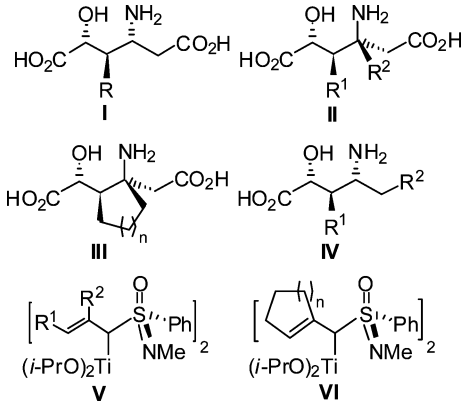
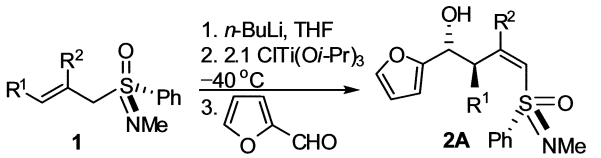


Figure 1. Substituted γ-amino acids and allyltitanium sulfoximines.

the microbial pseudopeptide AI-77-B, which has a strong and selective gastroprotective activity but suffers from a low oral activity.[7b] Thus, the synthesis of **I**−**III** could also contribute to both the development of medicinally useful analogues of AI-77-B and new NMDA receptor antagonists as potential drugs for Alzheimer's disease.[7c,d] We envisioned a synthesis of **I**−**IV** from allyltitanium sulfoximines of types **V** and **VI** and furan-2-carbaldehyde.[8] The starting allylic sulfoximines **1a**−**c** (Scheme 1) were prepared as described

Scheme 1. Synthesis of Furyl-Substituted Homoallylic Alcohols



a: R^1 = *i*-Pr, R^2 = H; **b**: R^1 = *c*-C_6H_{11}, R^2 = H; **c**: R^1 = R^2 = −$(CH_2)_3$-

2	R^1	R^2	dr[a] **A**:**B**:**C**	**2**:**1**[a]	**2A** (%)[b]	**1** (%)[b]
a	*i*-Pr	H	96:2:2	88:12	70	–[c]
b	*c*-C_6H_{11}	H	94:3:3	88:12	72	7
c	$-(CH_2)_3-$		95:5:–[d]	88:12	74	5

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction product. [b] Isolated yield. [c] Not determined. [d] Not detected.

previously by the addition−elimination−isomerization route[8a,9] from (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (≥98% ee)[10] and 3-methylbutanal, cyclohexylacetaldehyde, and cyclopentanone, respectively. Lithiation of **1a**−**c** in THF followed by the titanation of the lithiated allylic sulfoximines with 1 equiv of ClTi(O*i*Pr)$_3$ furnished the corresponding allyltitanium complexes **V** and **VI**[8a] which reacted with furan-2-carbaldehyde in the presence of 1.1 equiv of ClTi(O*i*-Pr)$_3$ with high regio- and diastereoselectivities and afforded the homoallylic alcohols **2aA**−**2cA**, respectively. Alcohols **2aA**−**2cA** were obtained diastereopure in good yields by washing the crude reaction products with Et_2O or Et_2O/pentane. HPLC of the washings allowed the isolation of the minor diastereomers **2aB**, **2aC**, and **2cB**.[11] We had previously observed that in reactions of complexes **V** and **VI** with unsaturated aldehydes only the transfer of the first allylsulfoximine moiety, which is much faster than that of the second one, occurs with high diastereoselectivity.[8a,c] We now found that both high conversion and diastereoselectivity can be achieved in the reaction of complexes **V** and **VI** derived from **1a**−**c** with furan-2-carbaldehyde.[12a] It is important to use an additional 1.1 equiv of ClTi(O*i*Pr)$_3$ and only 1.1 equiv of the aldehyde, a solution of which has to be slowly added to the solution of **V** and **VI** at −40 °C.[12b]

Conversion of the homoallylic alcohols **2aA**−**2cA** into γ-amino acids of types **I**−**IV** required, besides the oxidation of the furan ring and the substitution of the sulfoximine group by a carboxy group, a stereoselective amination of the double bond. We had previously developed an asymmetric synthesis of β-amino acids from homoallylic alcohols of type **2** using an intramolecular carbamate amination and chloride substitution of the sulfoximine group.[13] Thus treatment of **2aA** and **2bA** with trichloroacetyl isocyanate and the subsequent hydrolysis of the trichloroacetyl group with $(NH_4)_2CO_3$ in MeOH gave carbamates **3a** and **3b**, respectively, as *E*/*Z*-mixtures (Scheme 2). The crude carbamates **3a** and **3b** were directly subjected to the treatment with LiN(H)*t*-Bu in THF, which gave the oxazinones **4a** and **4b**, respectively, both as single diastereoisomers (^{1}H NMR) in good yields. The configuration of **4a** was determined by X-ray crystal structure analysis. Independent experiments with the pure *E*- and *Z*-configured carbamates, (*E*)-**3a**, (*Z*)-**3a**, (*E*)-**3b**, and (*Z*)-**3b**, showed that both the *E*- and *Z*-isomers undergo a highly diastereoselective cyclization with formation of oxazinones **4a** and **4b**, respectively.

Having achieved an efficient amination, we replaced the sulfoximine group of **4a** and **4b** with a carboxy group. Treatment of sulfoximines **4a** and **4b** with $ClCO_2CH(Cl)$-

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(11) **2cB** has the S_S,*S*,*S*-configuration according to X-ray crystal structure analysis. The NMR data suggest that **2aB**−**2cB** have the same configuration. The configurations of **2aC** and **2bC** have not been determined.

(12) (a) This protocol was also successfully used for the reaction of **1a** with crotonaldehyde: Lejkowski, M.; Gais, H.-J.; Banerjee, P.; Vermeeren, C. *J. Am. Chem. Soc.* **2006**, *128*, 15378. (b) The intermediate monoallyltitanium sulfoximines, which are formed in the reaction of **V** and **VI** with the aldehyde, most likely feature a coordination of both sulfoximine groups to the Ti atom. It is assumed that these intermediates are activated by ClTi(O*i*Pr)$_3$ through coordination to one of the sulfoximine groups, thereby creating a free coordination site at the Ti atom for the aldehyde.

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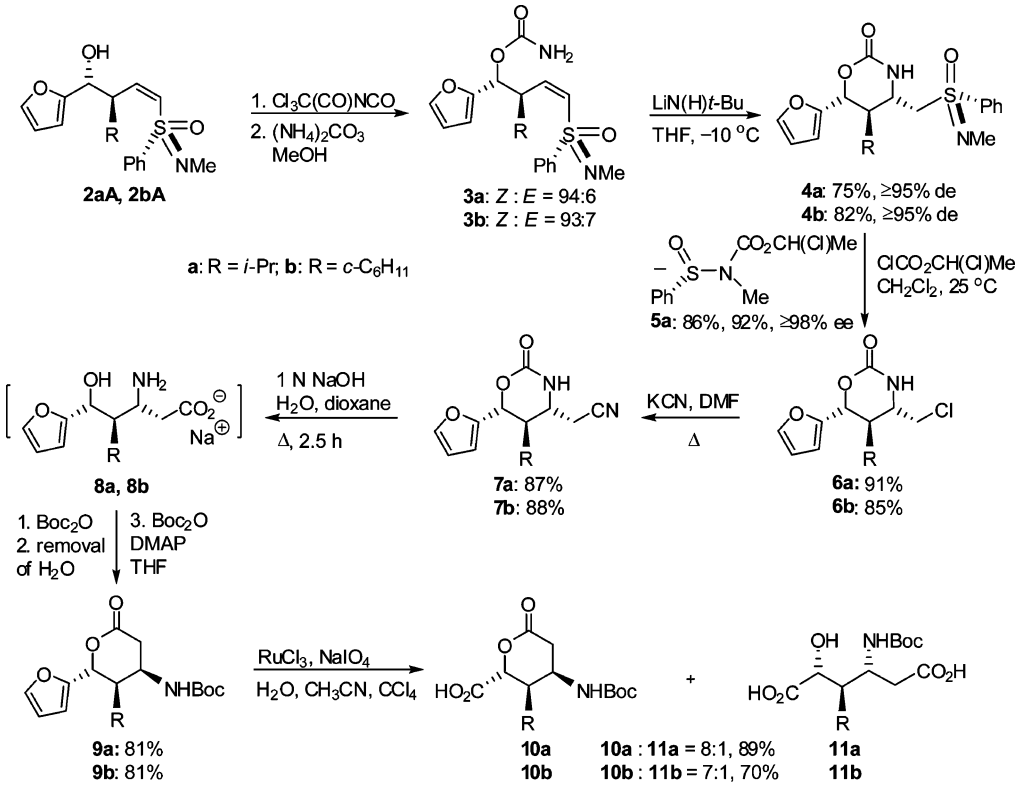
Scheme 2. Asymmetric Synthesis of Substituted Acyclic γ-Amino Acids



Me in CH_2Cl_2 at ambient temperatures furnished, besides sulfinamide **5a**, chlorides **6a** and **6b**, respectively, in high yields. Acylation of the sulfoximine group of **4a** and **4b** at the N atom generates the corresponding *N*-acyl aminosulfoxonium salts which undergo a facile substitution by the Cl^- ion because of the high nucleofugacity of the aminosulfoxonium group.[13,14] The conversion of sulfinamide **5a** (≥98% ee with regard to the S atom) to the starting (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine of ≥98% ee has already been described.[14a]

Reaction of chlorides **6a** and **6b** with KCN at elevated temperatures afforded nitriles **7a** and **7b**, respectively, in good yields. Nitriles **7a** and **7b** were submitted to a treatment with 1 N aqueous NaOH in dioxane at reflux, whereby the cyano and carbamate groups were hydrolyzed. The thus obtained β-amino acids **8a** and **8b** were not isolated but directly treated in basic aqueous solution with an excess of Boc_2O in order to protect not only the amino but also, through lactonization, the hydroxy and carboxy group.[15] This led to the formation of mixtures of lactones **9a** and **9b** and the corresponding Boc-protected β-amino acids. In order to convert the hydroxy acids into the lactones, the mixture of both were treated with Boc_2O following the removal of the water. Thereby the diastereomerically pure lactones **9a** and **9b** could be prepared starting from nitriles **7a** and **7b**, respectively, in a two-pot sequence without purification of **8a** and **8b** in high yields. Finally, an oxidative degradation of the furan ring was required. Therefore, the furan derivatives **9a** and **9b** were treated with $RuCl_3$ and $NaIO_4$,[16] which gave the γ-amino acids **10a** and **10b**, respectively, in good yields. According to NMR and LC/MS analysis, lactones **10a** and **10b** contained small amounts of the corresponding hydroxy acids **11a** (11%) and **11b** (13%), respectively.

The same route was successfully applied to the synthesis of the cyclic γ-amino acid **18** (Scheme 3). Carbamate **12** was obtained from the homoallylic alcohol **2cA** as a single *Z*-isomer in high yield.

The cyclization of **12** under the conditions described above occurred with high diastereoselectivity and afforded the bicyclic oxazinone **13** in high yield. Chloride **14** was obtained together with the enantiopure sulfinamide **5a** upon treatment of sulfoximine **13** with $ClCO_2CH(Cl)Me$ in good yield. The reaction of **14** with KCN gave nitrile **15** in almost quantitative yield. The complete hydrolysis of **15** turned out to be more difficult than that of **7a** and **7b**. It could be accomplished, however, upon treatment of the nitrile with aqueous CsOH in dioxane at reflux, which afforded the β-amino acid **16** in good yield. Protection and lactonization of **16** upon treatment with Boc_2O under nonaqueous conditions in MeCN[17] proceeded readily despite the steric hindrance of the amino group and gave lactone **17** in 60% overall yield based on **15**. Oxi-

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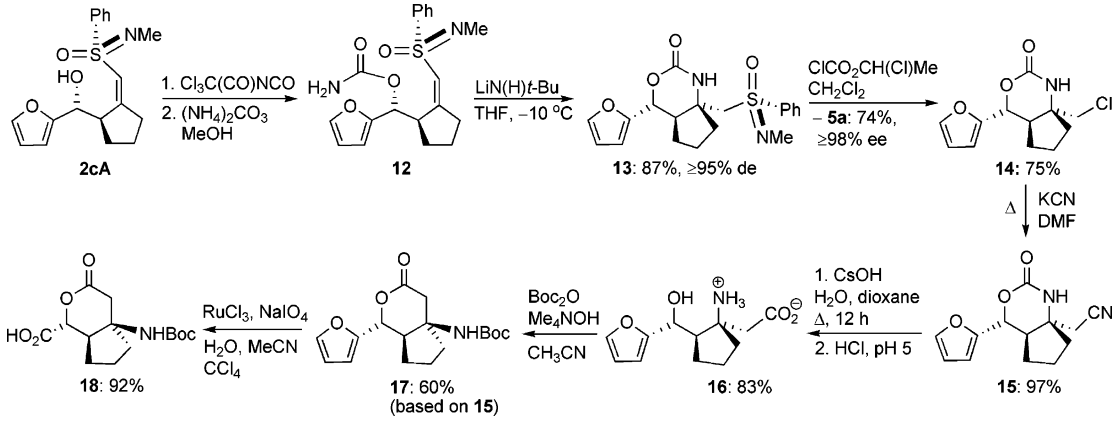
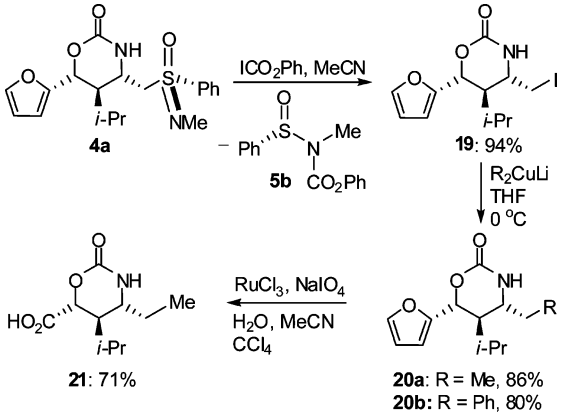
Scheme 3. Asymmetric Synthesis of a Substituted Cyclic γ-Amino Acid



dation of the furan derivative **17** with $RuCl_3$ and $NaIO_4$ furnished the pure bicyclic γ-amino acid **18** in high yield.

Finally, the synthesis of γ-amino acids of type **IV** was probed. Although chlorides **6a** and **6b** could serve as starting material, β-amido iodides of type **19** (Scheme 4) should be

Scheme 4. Synthesis of an Acyclic α-Hydroxy-γ-Amino Acid



synthetically more versatile building blocks for the synthesis of not only **IV** but also for 1,3-amino alcohols[13,18] because of their potential conversion to the corresponding alkylzinc iodides[19] and ready cross-coupling reaction with cuprates.[20] Thus, it was of interest to see whether iodide **19** can also be directly synthesized from sulfoximine **4a** by the haloformate method. The required ICO_2Ph was prepared by treatment of $ClCO_2Ph$ with NaI in MeCN at 70 °C.[21] The reaction of sulfoximine **4a** with ICO_2Ph in MeCN for 2 h at 25 °C gave, besides sulfinamide **5b** (≥98%), iodide **19** in high yield. Iodide **19** readily reacted with Me_2CuLi and Ph_2CuLi and afforded the 1,3-amino alcohols **20a** and **20b**, respectively, in good yields. The subsequent oxidative degradation of the furan ring of **20a** furnished the protected γ-amino acid **21** in good yield.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2cA**, **17**, and **18**; copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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