

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

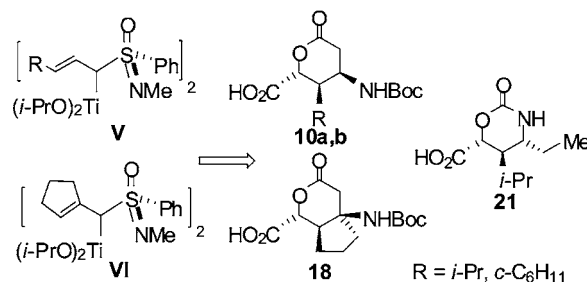
Franz Köhler, Hans-Joachim Gais,* and Gerhard Raabe

Institut für Organische Chemie der Rheinisch–Westfälischen Technischen Hochschule (RWTH) Aachen, Landoltweg 1, D-52056 Aachen, Germany

gais@rwth-aachen.de

Received December 20, 2006

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

(1) (a) Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, 9, 1127. (b) Zhenliang, C.; Zhiyong, C.; Yaozhong, J.; Wenhao, H. *Tetrahedron* **2005**, 61, 1579. (c) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, 18, 2701. (d) Takigawa, Y.; Ito, H.; Omodera, K.; Koura, M.; Kai, Y.; Yoshida, E.; Taguchi, T. *Synthesis* **2005**, 2046. (e) Moutevelis-Minakakis, P.; Sinanoglou, C.; Loukas, V.; Kokotos, G. *Synthesis* **2005**, 933. (f) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, 18, 3–99.

(2) (a) Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Lett.* **2001**, 3, 3753. (b) Sun, I.-C.; Chen, C.-H.; Kashiwada, Y.; Wu, J.-H.; Wang, H.-K.; Lee, K.-H. *J. Med. Chem.* **2002**, 45, 4271. (c) Yuste, F.; Díaz, A.; Ortiz, B.; Sanchez-Obregón, R.; Walls, F.; Ruano, J. L. G. *Tetrahedron: Asymmetry* **2003**, 14, 549. (d) Kondekar, N. B.; Kandula, S. R. V.; Kumar, P. *Tetrahedron Lett.* **2004**, 45, 5477. (e) Kambourakis, S.; Rozzel, J. D. *Tetrahedron* **2004**, 60, 663. (f) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, 70, 4569. (g) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Punzi, P. *Org. Lett.* **2006**, 8, 4803.

(3) (a) Galeazzi, R.; Mobbili, G.; Orena, M. *Curr. Org. Chem.* **2004**, 8, 1799. (b) Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, 19, 149.

(4) (a) Shiraki, R.; Tadano, K. *Rev. Heteroatom Chem.* **1999**, 20, 283. (b) Bang, J. K.; Naka, H.; Teruya, K.; Aimoto, S.; Konno, H.; Nosaka, K.; Tatsumi, T.; Akaji, K. *J. Org. Chem.* **2005**, 70, 10596. (c) Tamamura, H.; Araki, T.; Ueda, S.; Wang, Z.; Oishi, S.; Esaka, A.; Trent, J. O.; Nakashima, H.; Yamamoto, N.; Peiper, S. C.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, 48, 3280.

(5) Vasudev, P. G.; Shamala, N.; Ananda, K.; Balaram, P. *Angew. Chem., Int. Ed.* **2005**, 44, 4972.

(6) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, 58, 7991. (b) Lelais, G.; Seebach, D. *Biopolymers* **2004**, 76, 206. (c) *Enantioselective Synthesis of β -Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: Hoboken, NJ, 2005.

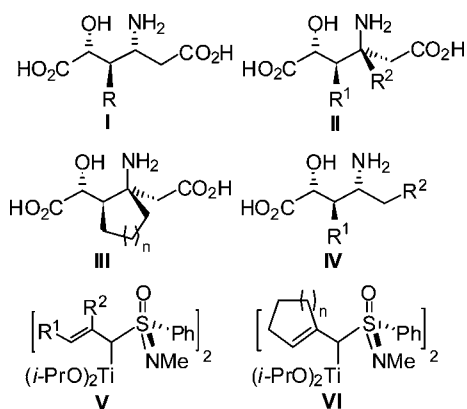
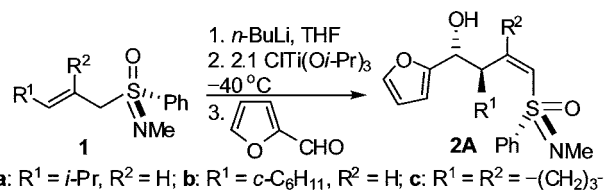


Figure 1. Substituted γ -amino acids and allyltitanium sulfoximines.

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



2	R^1	R^2	dr ^a A:B:C	2:1^a	2A (%)^b	1 (%)^b
a	<i>i</i> -Pr	H	96:2:2	88:12	70	— ^c
b	<i>c</i> -C ₆ H ₁₁	H	94:3:3	88:12	72	7
c	—(CH ₂) ₃ —		95:5:— ^d	88:12	74	5

^a Determined by ¹H 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 ($\geq 98\%$ ee)¹⁰ and

3-methylbutanal, cyclohexylacetaldehyde, and cyclopentanone, respectively. Lithiation of **1a–c** in THF followed by the titration of the lithiated allylic sulfoximines with 1 equiv of C(Ti)(Oi-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 C(Ti)(Oi-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 Et₂O or Et₂O/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 C(Ti)(Oi-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 (NH₄)₂CO₃ 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 (¹H 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 ClCO₂CH(Cl)-

(9) Gais, H.-J.; Müller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453.

(10) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

(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.

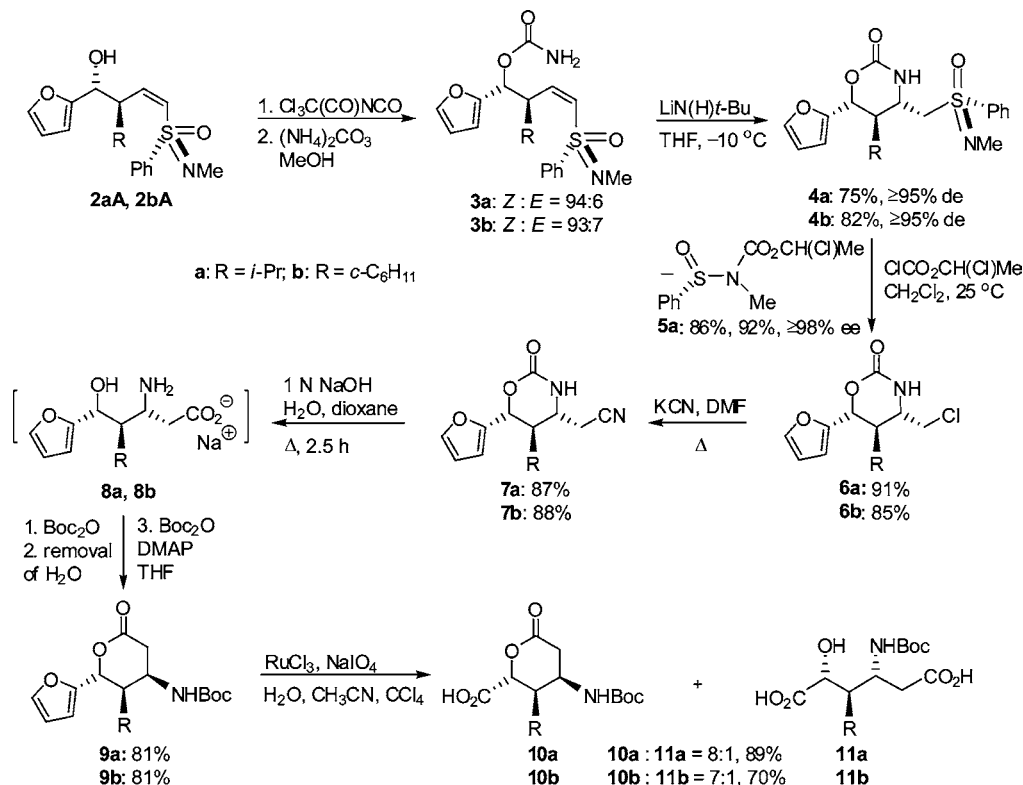
(12) (a) This protocol was also successfully used for the reaction of **1a** with crotonaldehyde: Lejkowski, M.; Gais, H.-J.; Banerjee, P.; Vermeeren, C. *J. Am. Chem. Soc.* **2006**, *128*, 15378. (b) The intermediate monoallyltitanium sulfoximines, which are formed in the reaction of **V** and **VI** 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 C(Ti)(Oi-Pr)₃ through coordination to one of the sulfoximine groups, thereby creating a free coordination site at the Ti atom for the aldehyde.

(13) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500.

(7) (a) Wong, H. F.; Kemp, J. A. *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401. (b) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, 821. (c) Pallas, M.; Carmins, A. *Curr. Pharm. Des.* **2006**, *12*, 4389. (d) Golde, T. E. *J. Neurochem.* **2006**, *99*, 689.

(8) (a) Gais, H.-J.; Hainz, R.; Müller, H.; Bruns, P. R.; Giesen, N.; Raabe, G.; Runsink, J.; Nienstedt, S.; Decker, J.; Schleusner, M.; Hachtel, J.; Loo, R.; Woo, C.-W.; Das, P. *Eur. J. Org. Chem.* **2000**, 3973. (b) Schleusner, M.; Gais, H.-J.; Koep, S.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 7789. (c) Reddy, L. R.; Gais, H.-J.; Woo, C.-W.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 10427. (d) Koep, S.; Gais, H.-J.; Raabe, G. *J. Am. Chem. Soc.* **2003**, *125*, 13243.

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



Me in CH₂Cl₂ at ambient temperatures furnished, besides sulfonamide **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 sulfonamide **5a** ($\geq 98\%$ ee with regard to the S atom) to the starting (*S*)-(+)-*N,S*-dimethyl-*S*-phenylsulfoximine of $\geq 98\%$ 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 Boc₂O 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 Boc₂O 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 RuCl₃ and NaIO₄,¹⁶ 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.

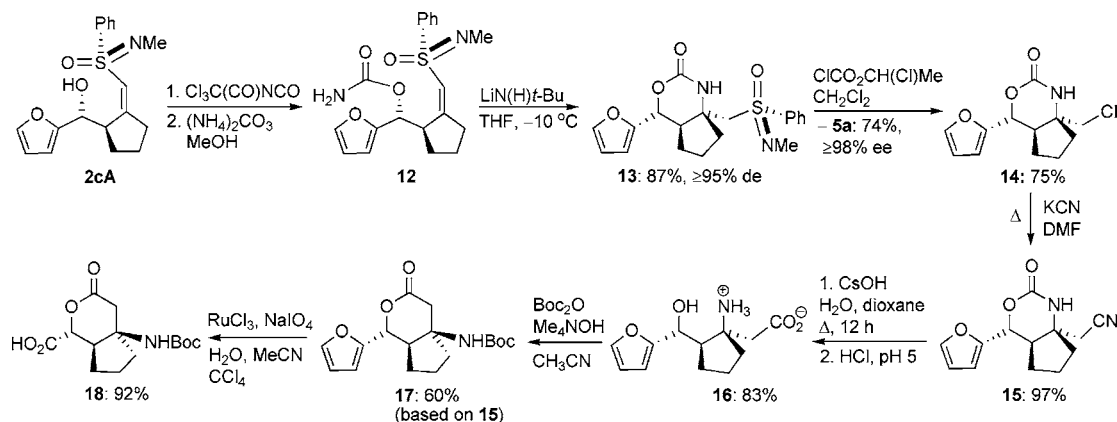
The same route was successfully applied to the synthesis of the cyclic γ -amino acid **18** (Scheme 3). Carbamate **12** was obtained from the homoallylic alcohol **2cA** as a single *Z*-isomer in high yield.

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 sulfonamide **5a** upon treatment of sulfoximine **13** with ClCO₂CH(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 Boc₂O under nonaqueous conditions in MeCN¹⁷ proceeded readily despite the steric hindrance of the amino group and gave lactone **17** in 60% overall yield based on **15**. Oxi-

(14) (a) Gais, H.-J.; Babu, G. S.; Günter, M.; Das, P. *Eur. J. Org. Chem.* **2004**, 1464. (b) Tiwari, S. K.; Gais, H.-J.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, 128, 7360.

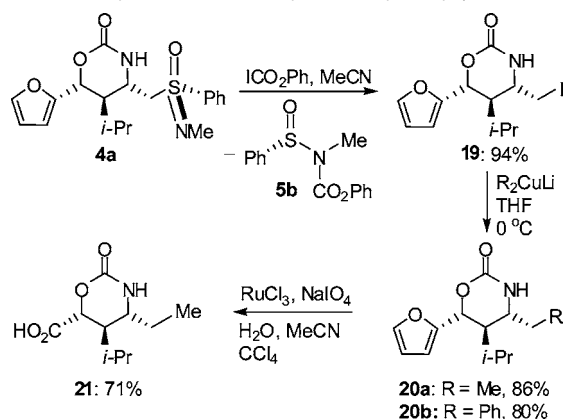
(15) Baldwin, J. E.; Flinn, A. *Tetrahedron Lett.* **1987**, 28, 3605.

(16) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, 46, 3936. (b) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, 48, 2346.

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

ation 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

iodides¹⁹ 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 $CICO_2Ph$ with NaI in $MeCN$ at $70\text{ }^\circ C$.²¹ The reaction of sulfoximine **4a** with ICO_2Ph in $MeCN$ for 2 h at $25\text{ }^\circ C$ gave, besides sulfinamide **5b** ($\geq 98\%$), 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.

Acknowledgment. Financial support of this work by the Gruenenthal Company, Aachen, and the Deutsche Forschungsgemeinschaft (SFB 380 and GK 440) is gratefully acknowledged.

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>.

OL063082Q

(17) Cativiela, C.; López, P.; Lasa, M. *Eur. J. Org. Chem.* **2004**, 3898.

(18) (a) Enders, D.; Moser, M.; Geibel, G.; Laufer, M. C. *Synthesis* **2004**, 2040. (b) Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, 70, 8148.

(19) Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F. W.; Grabowska, U.; Rae, A.; Tozer, M. J. *Org. Biomol. Chem.* **2005**, 3, 4117.

(20) Adrien, A.; Gais, H.-J. Unpublished results.

(21) Hoffmann, H. M. R.; Iranshahi, L. *J. Org. Chem.* **1984**, 49, 1174.