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First Stereocontrolled Synthesis of (*S*)-Cleonin and Related Cyclopropyl-Substituted Amino Acids†

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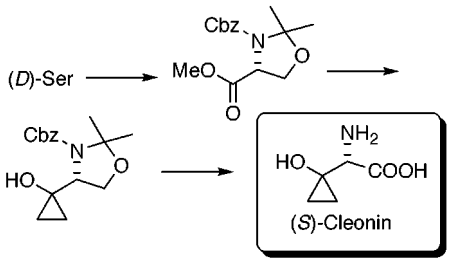
ABSTRACT



Enantiomerically pure (*S*)-cleonin, a key component of the antitumor antibiotic cleomycin, was prepared starting from (*R*)-serine. The Kulinkovich cyclopropanation of the methyl ester of *N*-Cbz serine acetonide gave the hydroxycyclopropyl moiety. The amino alcohol region was further oxidized to amino acid. The Kulinkovich cyclopropanation allowed also the preparation of other non-natural substituted cyclopropylglycines.

Amino acids are one of the most important classes of compounds in the pool of chiral molecules and have been the source for the preparation of natural products and complex biologically active compounds.[1] In addition to the 20 DNA coded amino acids, hundreds of additional "exotic" amino acids have been isolated from natural sources, mainly as components of peptides and pseudopeptides. Many of these products possess interesting pharmacological activities or can be used as analogues of the coded amino acids.[2] When inserted into peptide sequences, they can enhance biological properties, for example, the stability to endopeptidases of the modified peptide.

Cyclopropyl-substituted amino acids are quite regularly found in plants and microorganisms. Most of them are formally derived from proteinogenic amino acids. Among naturally occurring cyclopropane-derived amino acids, cyclopropylglycines are the largest family.[3] Some of them show antibacterial properties as, for example, 2-(1-hydroxycyclopropyl)-acetic acid, cleonin, which is a fragment of the macrocyclic antitumor antibiotic cleomycin.[4] Although this class of products shows promising therapeutic properties, very few syntheses have been described,[5] and to our knowledge no synthesis of enantiomerically pure cleonin has been reported in the literature.

Following our interest in the synthesis of atypical amino acids,[6] we envisaged that the Kulinkovich ester to cyclo-

† Dedicated to the memory of Guido Sodano, Professor of Organc Chemistry at the University of Salerno, deceased June 7, 2001.

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(2) Barret, G. C.; Elmore, D. T. *Amino Acids and Peptides*; Cambridge, University Press U.K.: Cambridge, 1998.

(3) Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867 and references therein.

(4) Umezawa, H.; Muraoka, Y.; Fujii, A.; Naganawa, H.; Takita, T. *J. Antibiot.* **1980**, *33*, 1079.

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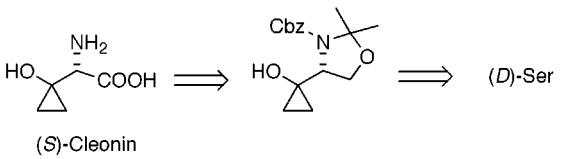
Scheme 1



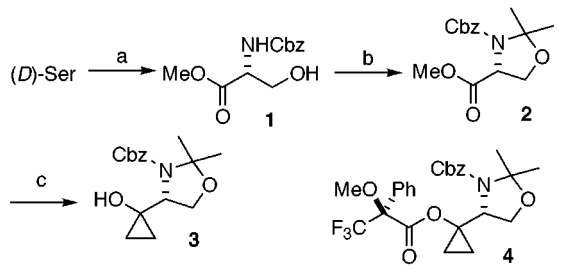
propanol conversion[7] applied to (*R*)-serine would not only represent a straightforward approach to enantiomerically pure cleonine but also give the opportunity for the preparation of related new non-natural substituted cyclopropylglycines.

The desired hydroxycyclopropyl amino acid should be obtained from a hydroxycyclopropyl oxazolidine, which can be obtained by Kulinkovich reaction with EtMgBr and the oxazolidine carboxylate derived from serine.

Therefore, we started from (*R*)-serine as a relatively inexpensive starting material and decided to employ Cbz protection for the amino group.[8] Thus, methyl serine was prepared from (*R*)-serine by reaction with $SOCl_2$ in MeOH. The so formed hydrochloride was reacted with Cbz-Cl under basic conditions to give **1** in good overall yield (81%). Finally the oxazolidine **2** was formed by reacting **1** with 2,2-dimethoxypropane in acetone and in the presence of $BF_3 \cdot OEt_2$ (95% yield). Kulinkovich cyclopropanation was carried out with 2.5 equiv of EtMgBr (freshly prepared) in the presence of 0.5 equiv of Ti(O*i*-Pr)$_4$ in Et_2O. Compound **2** was completely converted, and cyclopropanol **3** was isolated in 64% yield after column chromatography on silica gel.

The ^{1}H NMR spectrum of the cyclopropyloxazolidine **3** showed two sets of signals at δ 0.8−0.6 indicating the formation of the cyclopropyl group. The ^{1}H NMR spectrum was complicated by the existence of two conformers slowly interconverting on the NMR time scale.[9] The presence of the OH group was confirmed by the strong IR band at 3330−3100 cm^{-1}. The ^{13}C NMR spectrum, showing nine clean singlets below 100 ppm, confirmed the proposed structure.[10]

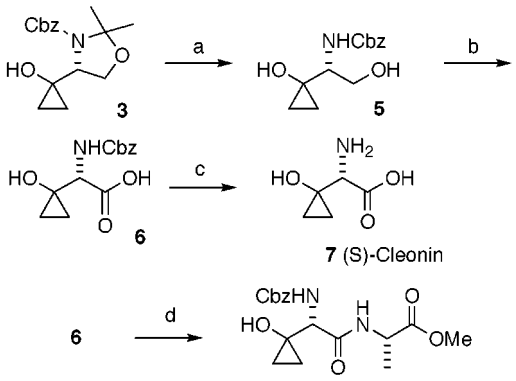
Scheme 2[a]



[a] (a) MeOH, $SOCl_2$, rt, 6 h, followed by Cbz-Cl, $NaHCO_3$, H_2O, rt, 3 h, 81%; (b) 2,2′-dimethoxypropane, BF_3OEt_2, 95%; (c) EtMgCl, Ti(O*i*-Pr)$_4$, Et_2O, 12 h, rt, 64%.

Having successfully synthesized the cyclopropyl-isoxazoline **3**, the next step was to selectively deprotect the OH and carry out the oxidation. Oxazolidine ring opening was accomplished with PPTS in MeOH, and the alcohol **5** was oxidized to the acid with PDC (6 equiv) in DMF. Product **6** was purified by extraction with EtOAc and chromatography on silica gel. Chromium residues were separated from the product by passing a solution of **6** in MeOH through a short pad of silica gel and sodium sulfite. Compound **6** was transformed into dipeptide **8** which resulted, according to NMR and HPLC analysis, as a single diastereoisomer. Finally, the Cbz group was removed by microwave-induced tranfer hydrogenation with $HCOONH_4$ in *i*-PrOH and in the presence of Pd/C[11] to give enantiomerically pure (*S*)-cleonin **7**.[12]

Scheme 3[a]



[a] (a) PPTS, MeOH, 12 h, rt, 83%; (b) PDC, DMF, 12 h, rt, 75%; (c) $HCOONH_4$, *i*-PrOH, Pd/C, microwaves, 5 min, 85%; (c) H-Ala-OMe, DMTMM, DIPEA, THF, rt, 6 h, 86%.

Once the procedure to settle the cyclopropyl on the serine structure and to transform the product into (*S*)-cleonin was successfully concluded, we envisaged that the modified Kulinkovich procedure based on the ligand exchange of the intermediate titanacyclopropane with a terminal olefin[13] would allow a convenient access to substituted cyclopropylglycines.

(6) Demarcus, M.; Ganadu, M. L.; Mura, G. M.; Porcheddu, A.; Quaranta, L.; Reginato, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 697. Ciapetti, P.; Mann, A.; Shoenfelder, A.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3843. D'Aniello, F.; Mann, A.; Shoenfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447 and references therein.

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(8) Extensive investigations of de Meijere and co-workers. showed that cyclopropylcarbinols are more stable to hydrogenolysis conditions (Pd/C) than to acidic mediums; see: de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, *3105*, 5.

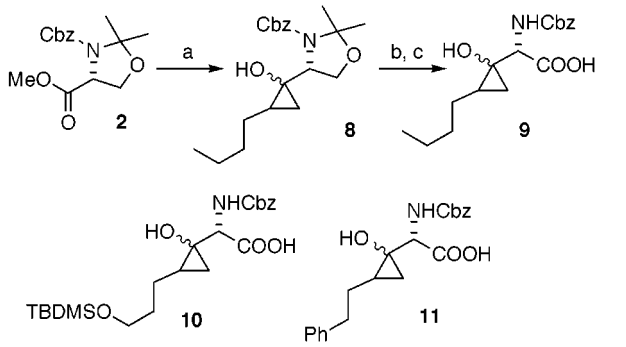
(9) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979.

(10) The enantiomeric integrity of compound **3** was confirmed by the ^{19}F NMR spectrum of the (*S*)-MTPA **4** ester, which showed a single signal at δ 7.02 (ext TFA).

(11) Daga, M. C.; Taddei, M.; Varchi, G. *Tetrahedron Lett.* **2001**, *42*, 5191.

(12) The enantiomeric integrity of cleonin was established by the ^{19}F NMR spectrum of the (*S*)-MTPA amide, which showed a single signal at δ 9.74 (ext TFA).

Scheme 4[a]



[a] (a) Cyclohexyl-MgBr, ClTi(O*i*-Pr)$_3$, 1-hexene, THF/Et$_2$O, rt, 6 h, 65%; (b) PPTS, MeOH, 12 h, rt, 80% (c) PDC, DMF, 12 h, rt, 75%.

Thus, a mixture of the ester **2** and 1-hexene in THF was treated with different Grignard reagents (EtMgBr, *c*-C_6H_{11}-MgBr, *i*-PrMgBr in Et$_2$O) in the presence of Ti(O*i*-Pr)$_4$ or ClTi(O*i*-Pr)$_3$. Slow addition of commercially available *c*-C_6H_{11}MgBr in Et$_2$O to a solution of the ester **2** (1 equiv), 1-hexene (1.1 equiv) and ClTi(O*i*-Pr)$_3$ gave the best results.

The hydroxycyclopropyl oxazolidine **9** was obtained, after column chromatography on silica gel, in 65% yield as a mixture of diastereoisomers in approximatively 1:0.7:0.2 ratio.[14] Compound **9** was further treated just as compound **3** to accomplish the transformation into the *N*-Cbz amino acid **10**. Analogously compounds **11** and **12** were prepared using *O*-TBDMS-1-penten-5-ol and 4-phenyl-1-butene, repectively, as the alkenes. Although we did not explore the full potential of this reaction, its extension to several other alkenes as described by Cha[15] should be possible, giving access to several substituted cyclopropylglycines.

In summary, we have reported the first example of the application of the Kulinkovich reaction to the preparation of substituted cyclopropylglycines and the first synthesis of enantiomerically pure (*S*)-cleonin, an amino acid constituent of the antitumor antibiotic cleomycin.

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of compounds **3**−**7** and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The ratio was determined by integration of the signals corresponding to the benzyl CH_2 at δ 5.10, 5.16, and 5.24, respectively. For an analogous behavior of α-oxy carboxylic esters, see: Cho, S. Y.; Cha, J. K. *Org. Lett.* **2000**, *2*, 1337.

(15) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.