Tetrahedron Letters,Vol.23,No.6,pp 619-622,1982 0040-4039/82/060619-04$03.00/0
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF THE DIHYDROXYISOLEUCINE CONSTITUENT OF THE AMANITA MUSHROOM TOXINS

Paul A. Bartlett*, Donna J. Tanzella, and James F. Barstow

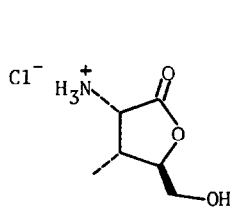
Department of Chemistry, University of California
Berkeley, California 94720

Ester-enolate Claisen rearrangement of cis-crotyl N-t-Boc-glycinate and iodolactonization of the N-phthaloyl derivative of the resulting unsaturated acid are used as the stereocontrolling steps in a synthesis of the title compound.

From the Green Death Cap Toadstool, *Amanita Phalloides*, Wieland and his coworkers have isolated and determined the structures of a number of toxic constituents: the phallotoxins and the amatoxins.[1] These cyclic peptides contain several unusual amino acid components, among them (2S,3R,4R)-γ,δ-dihydroxyisoleucine, which is isolated as the lactone hydrochloride 1 on hydrolysis of α- and β-amanitin.[2] The stereostructure of this compound was proven by a combination of chemical correlation[3] and X-ray crystallography.[4]

In the early stages of an investigation of the ester-enolate Claisen rearrangement[5] as a diastereoselective method for the construction of α-amino acid derivatives,[6] we applied this reaction to the synthesis of the diastereomeric γ,δ-dehydroisoleucines 3a and 3b. We present here the results of this initial study, and the subsequent elaboration of diastereomer 3b to lactone 1 (racemic) in a stereoselective manner. The only previously reported synthesis of 1 afforded the natural diastereomer as a minor component in a mixture of the four possible racemates.[7]

Trans-crotyl N-t-butoxycarbonylglycinate, 2a,[8] was synthesized by the dicyclohexylcarbodiimide/4-(dimethylamino)pyridine-induced coupling of the carboxylic acid with trans-crotyl alcohol.[9] Deprotonation of this material with two equivalents of lithium isopropylcyclohexylamide (THF, -75°C for 5 min), silylation (2 eq. Me_3SiCl), rearrangement (reflux for 1 hr), and desilylation (MeOH, room temp. overnight) afford a 60% yield of acid 3[8] as a 10:1 mixture of diastereomers. Catalytic hydrogenation (10% Pd/C), removal of the protecting group (10% HCl in MeOH, Δ, 1 hr), and comparison with authentic isoleucine by ^{13}C-NMR indicated that the major diastereomer has the allo configuration 3a. Making the reasonable assumption that Claisen rearrangement of the bis(silylated) intermediate involves the chair-like transition state,[10] it



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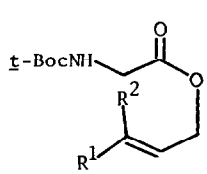

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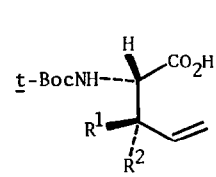

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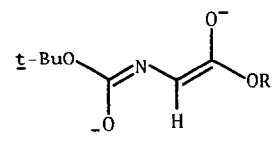

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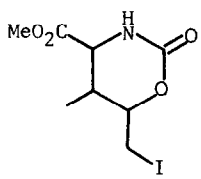
a: R^1 = Me, R^2 = H; b: R^1 = H, R^2 = Me

follows that the favored enolate has the enolate oxygen and deprotonated carbamate moieties in a cis relationship (see structure 4).

We anticipated that the desired diastereomer 3b would be favored on rearrangement of the cis-crotyl ester 2b.[8] Although this substrate could be prepared analogously using cis-crotyl alcohol, we found it experimentally easier to perform the esterification with 2-butyn-1-ol and semi-hydrogenate the acetylenic product[8] ($Pd/SrCO_3$, MeOH). Rearrangement of 2b by the sequence described above proceeds in 60% yield and 6:1 diastereoselectivity to give the expected isomer 3b (mp 119-121°C, from MeCN).[8] We studied the N-carbobenzoxy and -benzoyl analogs of 2a and 2b as well, but found that the stereoselectivity of their rearrangements is lower.

For the stereocontrolled functionalization of the double bond in 3b, we planned to use the iodolactonization process which we developed previously.[11] The preferred conditions for maximal stereoselectivity: iodine in acetonitrile in the absence of base, result in cleavage of the t-Boc protecting group by hydrogen iodide generated during the course of the reaction. The alternative, non-acidic procedure for thermodynamically controlled iodolactonization: cyclization of the methyl ester (formed with MeI/K_2CO_3/18-crown-6, 73% yield),[8] was in its turn foiled by competitive cyclization of the carbamate and formation of the cyclic urethane 5[9] as the major identifiable product. After investigating a series of N-protecting groups, we found that replacement of the t-Boc moiety with the phthaloyl group (1) TFA at 21°C; 2) Nefkens' reagent,[12] 70% yield) affords a derivative 6 which is iodolactonized smoothly to give the anticipated product 7[8] in 82% yield (mp 154-155°C, from CH_2Cl_2/pet. ether).[13] In the crude reaction product, less than 5% of the β,γ-cis isomer is present.



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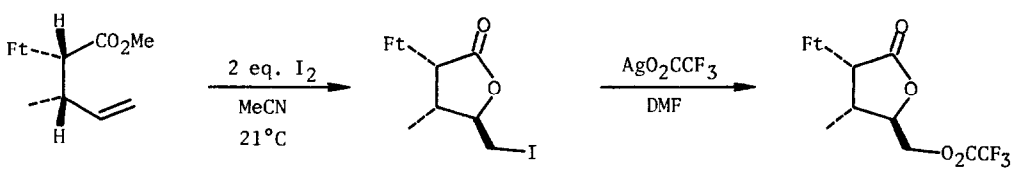
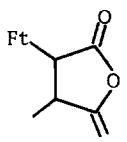


6 7 8

(Ft = *phthalimido*)

We encountered difficulties in displacing the iodide as well: reaction of 7 with potassium acetate under a variety of conditions gives only the γ-methylene lactone elimination product 9.[14] On the other hand, treatment with silver acetate in acetic acid at 120°C results in simultaneous epimerization of the amino substituent, affording the thermodynamically more stable trans,trans isomer 10 (mp 130-133°C, from $CHCl_3$/pet. ether)[8] in 50% yield. This proved to be simply the result of acid-catalysis, and was avoided by using the more soluble trifluoroacetate salt in DMF at room temperature. Under these conditions trifluoroacetate 8 is formed without significant epimerization.[15] Without purification of this labile material, 8 was hydrolyzed with 20% HCl at 110°C for 24 hr, affording racemic α-amino lactone hydrochloride 1 in 80% yield from iodolactone 7. The hydrolysis step is unfortunately also accompanied by about 10% epimerization of the amino group (probably prior to complete cleavage of the phthaloyl moiety); however, recrystallization (MeOH/ether) affords the pure diastereomer, mp 209.5-211°C.[15]

That our synthetic material had the same relative stereochemistry as the naturally-derived isomer was evident from the ^{1}H-NMR spectrum. The mixture of four diastereomeric racemates synthesized by Georgi and Wieland shows doublets due to the β-methyl groups at δ 1.08, ~1.13, 1.25, and ~1.33 ppm in 20% DCl.[7] The doublet at δ 1.25 arises from the natural diastereomer, and corresponds to that observed for our synthetic racemate. The 2-epi diastereomer 11, which appears as a side product in the hydrolysis of 8 or is obtained directly by cleavage of 10, is responsible for the methyl doublet at δ 1.33 ppm.



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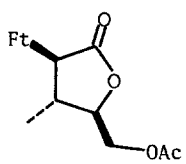

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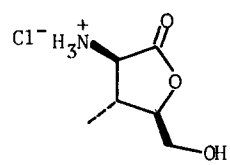

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Acknowledgment. Support by the National Institutes of Health (grant no. CA-16616) is gratefully acknowledged.

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(Received in USA 5 October 1981)