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# A NOVEL METHOD FOR THE PREPARATION OF PEPTIDYL α-KETO ESTERS

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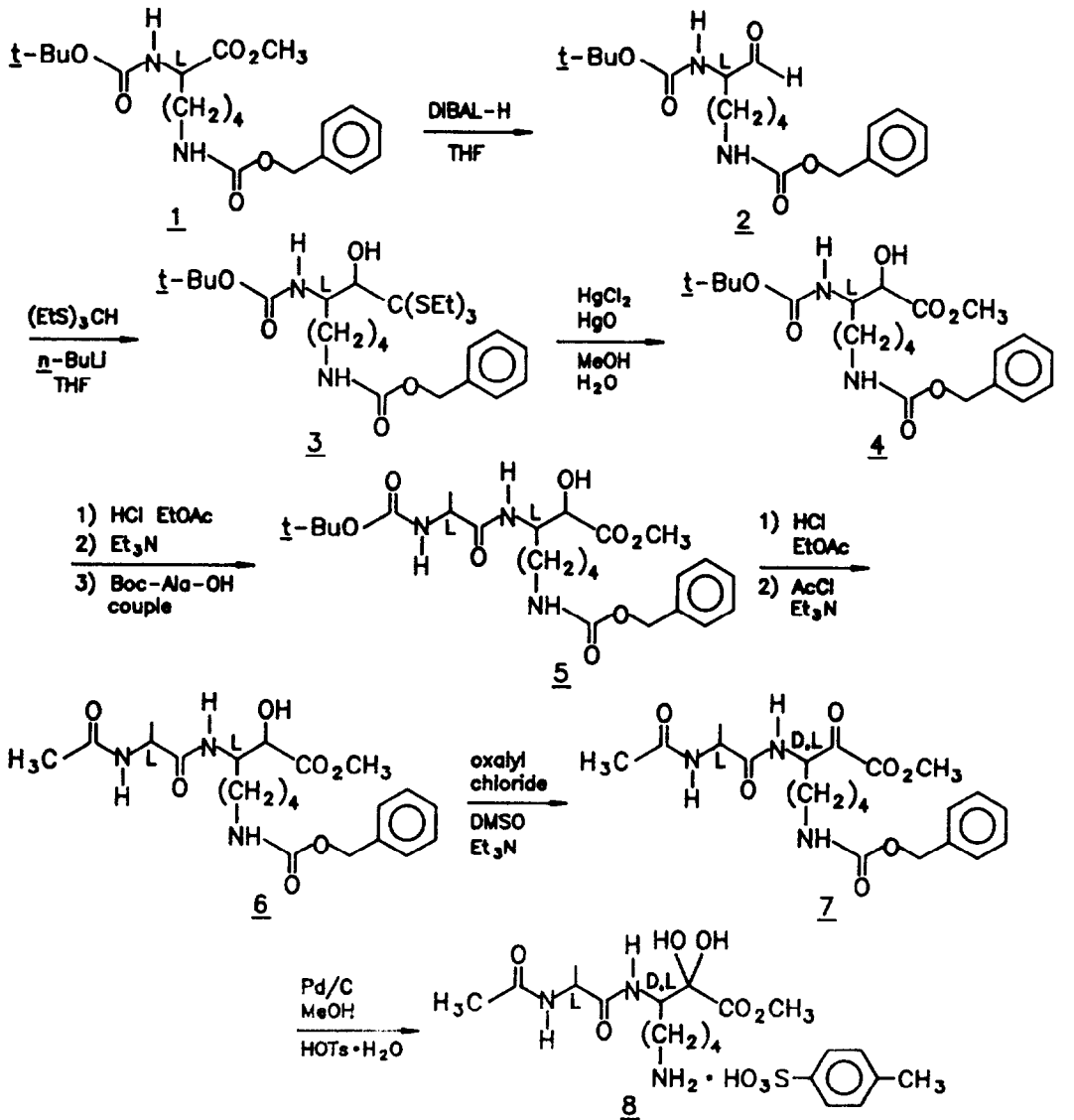
Abstract: A new method for the synthesis of peptidyl α-keto esters is described, which is particularly useful for the construction of proteinase inhibitors with a lysine side chain.

Peptidyl α-keto esters are potent, competitive inhibitors of proteinases.[1-5] The selectivity of peptidyl proteinase inhibitors often is primarily determined by the nature of the residue in the $P_1$ position. For example, inhibitors of trypsin[6] and trypsin-like enzymes of the complement[7] and blood coagulation[8] systems require basic amino acid residues at the $P_1$ position. Although many methods are available for the preparation of α-keto esters, no synthesis incorporating a basic residue in the $P_1$ position has yet appeared. In this report, we describe the synthesis of a differentially N-protected α-hydroxy-β-aminopropanoate bearing a lysine side chain (4) and its transformation to peptidyl α-keto 8, which is a potent trypsin inhibitor. We feel that 4 is a generally useful building block for the construction of peptidyl α-keto ester proteinase inhibitors which incorporate a lysine residue at the $P_1$ position.

Scheme I details our synthesis of Ac-Ala-D,L-Lys-$CO_2CH_3 \cdot H_2O \cdot$HOTs (8). α-Boc-ε-Cbz-Lys-OMe (1) was treated with diisobutylaluminum hydride using the general procedure of Rich et al.,[9] to provide a 70% yield of aldehyde 2, mp 77-81°C (lit.[10] mp 78-80°C); $[\alpha]_D^{amb}$ = +29.2° (C=1.1, $CH_2Cl_2$) [lit.[10] $[\alpha]_D^{20}$ = +24.9° (C=1, $CH_2Cl_2$)]. Lithiated tris(ethylthio)methane was employed as an acyloxy anion equivalent[11] to give adduct 3 from 2 in 64% yield. Hydrolytic conversion of trithioorthoformic ester 3 with $HgCl_2/HgO$ in $CH_3OH$[12] and water afforded 70% of 4 as an 85:15 mixture (by hplc) of diastereomers. α-Hydroxy esters 4 were treated with HCl/EtOAc and neutralized with $Et_3N$ to remove the Boc protecting group, and then coupled with Boc-Ala-OH using the isobutyl chloroformate anhydride coupling procedure to give α-hydroxy esters 5 in quantitative yield, again as an 85:15 ratio of diastereomers. Exchange of the Boc group for acetyl was accomplished in 93% yield to give 6 by treatment with HCl/EtOAc followed by acetylation with acetyl chloride and triethylamine, and the diastereomers (85:15 ratio) were oxidized using the Swern procedure[13,14] to give an 80% yield of Ac-Ala-ε-Cbz-D,L-Lys-$CO_2CH_3$ (7).[20] Removal of the Cbz protecting group was best accomplished by catalytic hydrogenolysis with Pd/C in MeOH in the presence of p-toluenesulfonic acid monohydrate (HOTs$\cdot H_2O$) to give hydrated α-keto ester 8.


t-BuO
CO2CH3
(CH2)4
NH
DIBAL-H
THF
1
2
(EtS)3CH
n-BuLi
THF
C(SEt)3
OH
3
HgCl2
HgO
MeOH
H2O
CO2CH3
4
1) HCl EtOAc
2) Et3N
3) Boc-Ala-OH
couple
5
1) HCl
EtOAc
2) AcCl
Et3N
H3C
6
oxalyl
chloride
DMSO
Et3N
D,L
7
Pd/C
MeOH
HOTs·H2O
HO
NH2 · HO3S
CH3
8

SCHEME I

The key step in the synthesis of Scheme I is the addition of lithiated tris(ethylthio)methane to the differentially protected diamino aldehyde 2. Thus, to a stirred solution of tris(ethylthio)methane (7.45 mL, 40.0 mmol) in dry THF (120 mL) under an inert atmosphere at -78°C was added n-BuLi (16.5 mL, 38.0 mmol of a 2.3 M solution in hexane). After 20 min a cold (-78°C) solution of 2 (3.64 g, 10.0 mmol) in THF (15 mL) was added. After 2.5 h the mixture was partitioned between $CH_2Cl_2$ and aqueous $NH_4Cl$ and the organic layer was dried (brine, $MgSO_4$) and concentrated. Flash chromatography on silica gel (EtOAc:hexane::2:3) gave 3[21] (3.59 g, 64%) as a colorless, viscous oil.

In summary, the readily accessible, differentially protected diamino aldehyde 2 was homologated to 3 by treatment with lithiated tris(ethylthio)methane. Orthothioformate 3 is a key intermediate for the preparation of peptidyl α-keto esters containing lysine side chains, as demonstrated by the preparation of 8. Inhibitory constants for 8 and related compounds for trypsin and other proteinases will be reported elsewhere.

## REFERENCES AND NOTES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14. The Swern oxidation of peptidyl substrates in this case and others caused epimerization at the center α to the ketone.[15] Another shortcoming of the Swern oxidation with these substrates which we have observed is the formation of α,β-unsaturated ketones. These products of over-oxidation may arise from initially formed α-chloro ketones which dehydrohalogenate to produce the enones, since Kende et al.[16] and Smith et al.[17] have both recently isolated α-chloro carbonyl compounds from Swern oxidations of the corresponding alcohols. The Dess-Martin periodinane reagent has been effectively used for oxidizing α-hydroxy esters to α-keto esters[18] and trifluoromethyl carbinols to trifluoromethyl ketones[19] without side product formation, and it was shown to produce Cbz-Val-Phe-$CF_3$ from the corresponding trifluoromethyl carbinol without epimerization.[5] However, this reagent is no longer commercially available.
15. Epimerization of the center alpha to the ketone in 7 occurred during the Swern oxidation, as evidenced by multiplicities observed in the $^1H$ NMR and $^{13}C$ NMR spectra. The ratio of diastereomers was ca 1:1 (see ref. 20).
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20. For 7: $^1H$ NMR ($CDCl_3$, TMS): δ 3.88, 3.86 (2s, 3H, $CO_2CH_3$), 1.97, 1.94 (2s, 3H, $CH_3CO$), 1.34, 1.24 (2s, 3H, alanine $CH_3$); $^{13}C$ NMR ($CDCl_3$) 191.78, 191.72 (ketone C=O), 173.00, 172.92 (amide C=O), 170.59, 170.51 (amide C=O), 160.81 (ester C=O), 156.77, 156.64 (carbamate C=O); ms (CI/$CH_4$) 436 ($M^+$+1), 464 ($M^+$ + 29), 476 ($M^+$ + 41).
21. For 3: $^1H$ NMR ($CDCl_3$, TMS): δ 7.30 (s, 5H, Ar), 4.70-5.36 (m, 4H, $OCH_2$ and both NH groups), 3.39-4.28 (m, 3H, NCHCHO and OH), 3.02-3.39 (m, 2H, $NCH_2$), 2.79 (q, 6H, $SCH_2$ groups), 0.88-1.89 [m, 24H, $NCH_2(CH_2)_3$, with t-Bu s at 1.42 and $S(CH_2CH_3)_3$ t at 1.22]. Orthothioformate 3 was immediately converted to methyl ester 4.

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