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A NOVEL SHORT AND EFFICIENT ASYMMETRIC SYNTHESIS OF STATINE ANALOGUES

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Abstract The statine analogues 1a-c have been obtained in high optical purity via addition of the chiral acetate enolate 4 to the α-aminoaldehydes 5a-c, followed by transesterification.

The unusual β-hydroxy-γ-amino acid statine (1d) is the essential component of pepstatine, which shows inhibitory activity against some proteolytic enzymes such as pepsin, cathepsin D and the blood pressure regulating enzyme renin.[1] The inhibitory activity of pepstatine is believed to be due to the close resemblance between the statine moiety and the tetrahedral transition state of the proteolytic hydrolysis of a peptide bond.[2] Incorporation of statine or its side chain analogues into synthetic peptides has led to potent renin inhibitors[3a-c], which are of particular interest as therapeutic agents in the treatment of hypertension.[4]

Several syntheses of statine derivates have been reported,[5a-f] most of them leading to a mixture of the (3S,4S)- and (3R,4S)-diastereomers 1 and 2, which have to be separated by laborious chromatographic methods. Since it has been shown that only the (3S,4S)-diastereomer exhibits potent inhibitory activity[2] the stereoselective synthesis of (3S,4S)-statine derivatives is a challenging problem. Very recently, a few stereoselective syntheses have been published, but all of them are multistep syntheses involving at least one low-yield reaction step.[6a-e] We now wish to report a simple two step synthesis leading to the optically pure statine analogue derivatives 1a-c.

The known strategy used for the synthesis involves the addition of an acetate enolate to N-protected α-aminoaldehydes. Since the addition of the achiral enolate of ethyl acetate to chiral α-aminoaldehydes does not show any significant diastereoselection[7,5d], a successful way to tackle this stereochemical problem should be the use of a potent chiral acetate enolate. In order to achieve the desired (3S,4S)-stereochemistry the chiral enolate should attack the aldehyde preferentially from the si-side.

Based on our work with the chiral α-unsubstituted acetate enolate 4, which adds in a predictable and highly stereoselective manner to achiral aldehydes and chiral alkoxyaldehydes[8,9], we investigated the addition of the (S)-configurated enolate 4 to the α-aminoaldehydes 5a-c.[10,11]

Enolate 4 was prepared as described previously by reaction of (S)-2-acetoxy-1,1,2-triphenylethanol (3; 10 mmol) with lithium diisopropylamide (22 mmol) in THF.[8] The aldehyde (5a-c; 8 mmol) was added at -78 °C and after stirring for two hours the reaction was quenched with aqueous ammonium chloride followed by extraction with methylene chloride. HPLC analysis showed the predominant formation of one major compound along with 9 - 10 % of the minor diastereomer and excess acetate 3 (see table).[12,13] Transmetallation of the lithium enolate 4 with $MgBr_2$ did not lead to any improvement of the diastereoselectivity. The diastereomers 6/7 were separated by HPLC and fully characterized by NMR, mass spectra and elemental analysis.

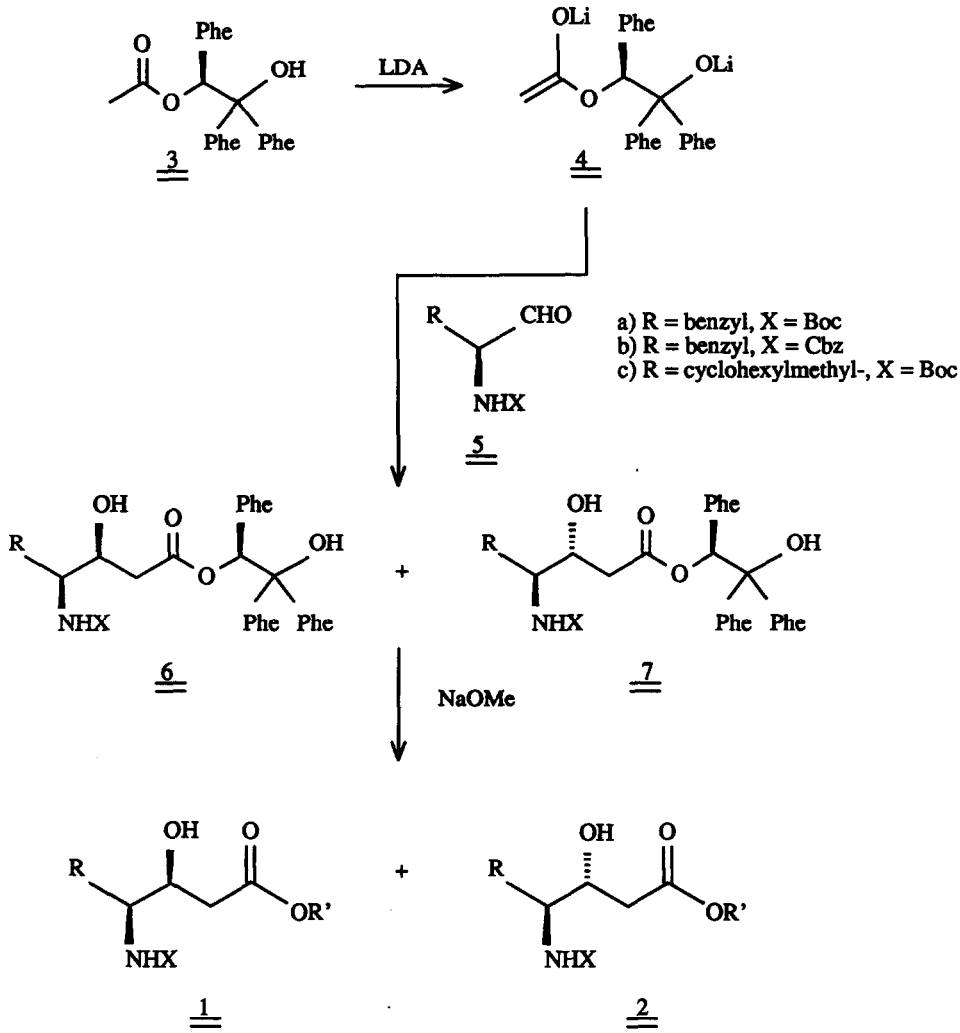
Table:

Aldehyde	Yield [%][a]	mp. [°C]	$[\alpha]_D^{20}$ [°] [b]	Isomer ratio
		1		6 : 7
5a	61	98.5	-34.5	90 : 10
5b	53	99.5	-45.5	91 : 9
5c	49	68	-36.0	91 : 9

[a]overall yield based on aldehyde, [b] C=1 in methanol

Removal of the chiral auxiliary was achieved by transesterification of the above obtained crude reaction product with sodium methoxide in dioxan/methanol at 0 °C. After flash chromatography the methyl esters 1a-c were obtained optically pure in 49 - 61 % overall yield (see table). The thus obtained statine derivatives were compared with authentic samples by HPLC and NMR.[14]

Since (S)-2-acetoxy-1,1,2-triphenylethanol (3) is a readily available reagent the addition of 4 to α-aminoaldehydes may serve as a useful method for the synthesis of statine analogues in optically pure form even on a larger preparative scale.



a) R = benzyl, X = Boc, R' = Me
b) R = benzyl, X = Cbz, R'= Me
c) R = cyclohexylmethyl-, X = Boc, R'= Me
d) R = isopropyl, X = R' = H

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11. In order to avoid possible racemization, the aldehydes 5a-c were freshly prepared and stored refrigerated. The enantiomeric purity of the aldehydes was determined by HPLC analysis of the Mosher's esters of the corresponding amino alcohols, which were obtained from the aldehydes by reduction with sodium borohydride. In each case, the optical purity was at least 96 % ee.
12. The HPCL analysis of the diastereomers 6/7 was performed on a Gilson HPLC apparatus (Column: Merck Si60 silica gel; flow rate: 1 ml/min). The following retention time ratios were observed. 6a/7a: 1.19, eluent: methylene chloride/ethyl acetate 90:10; 6b/7b: 1.17, eluent: methylene chloride/ethyl acetate 93:7; 6c/7c: 1.33, eluent: hexane/ethyl acetate 80:20.
13. No significant amount of (4R)-diastereomers could be detected by HPLC. This clearly indicates that under the applied reaction conditions no racemization of the aminoaldehydes occurs. This fact was proven by independent control experiments. Addition of the (R)-configurated acetate R-3 to the α-amino-aldehydes leads in a 4:1 ratio to a mixture of diastereomers with predominant formation of the anti-diastereomer. The chromatographic behavior of this pair of diastereomers is identical with that of the diastereomers which would be obtained by addition of the (S)-configurated acetate to the (R)-configurated aminoaldehydes. Since these diastereomers could not be detected by HPLC analysis in the crude reaction mixture 6/7, racemization of the aminoaldehyde can be excluded.
14. Unequivocal confirmation of the correct (3S,4S)-stereochemistry was also achieved by preparation of the cyclic carbamate, which shows a ^{1}H-NMR coupling constant $J_{3,4}$ of 5.0 Hz.

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