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CHIRAL SYNTHESIS OF STATINE

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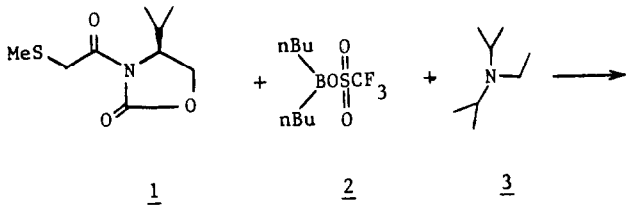
Abstract: Statine (8a) has been obtained in high enantiomeric purity as its N-Boc-ethyl ester (8b) in a chiral synthesis. The sequence involves the enantio- and erythro-selective aldol condensation of N-Boc-L-leucinal (5) with (S)-4-(1-methylethyl)-3-[(methylthio)acetyl]-2-oxazolidinone (1) via the boron enolate, followed by desulfurization and saponification in ethanol, according to the methodology of Evans.

Statine [S-(R*,R*)]-4-amino-3-hydroxy-6-methylheptanoic acid (3S,4S), (8a), key component in the pepstatin family of peptide-related inhibitors of aspartic proteinases, has potential utility in the synthesis of inhibitors of proteinases such as pepsin, cathepsin D, and renin, which are important in metabolic controls.[1,2] It has commanded significant attention in the recent search, through renin inhibition, for potential antihypertensive medicinal agents.[3]

Several syntheses of statine have been reported.[4,5] The most practical among them appear to be those based on the aldol condensation of an N-protected L-amino aldehyde (as the source of C3 and C4) with an acetic acid derivative (e.g., metalated, as the source of C1 and C2).[5] In the reported examples based on this approach, however, a derivative of statine with 3S,4S chirality, such as 8b, is generated as mixtures with its 3R,4S isomeric counterpart such as 9b, from which the proper isomer has to be separated by somewhat laborious column chromatography. We wish to report herein a chiral synthesis, whereby statine has been obtained, in high enantiomeric purity, as its N-Boc-ethyl ester (8b).



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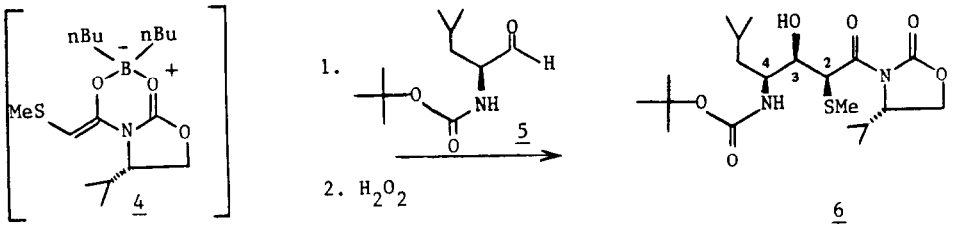

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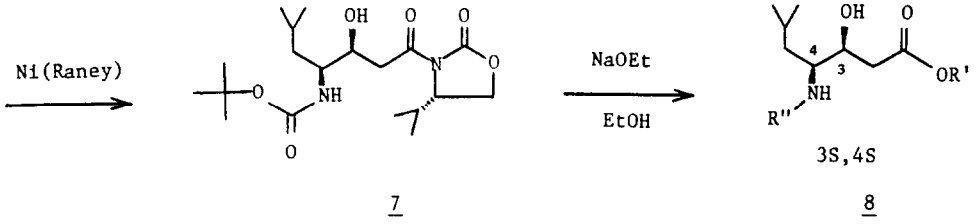

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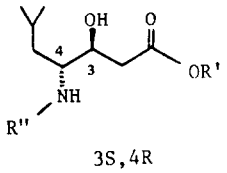


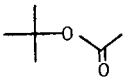
3S,4R

9

(a) R' = R" = H

(b) R' =-OEt

R" =



The synthesis utilized the boron enolate chiral aldol condensation methodology of Evans,[6] reported to be both highly enantio- as well as erythro-selective. Imide 1, containing the oxazolidinone chiral auxiliary which should induce the proper 3S chirality for the final product, was converted to the enolate (4) by treatment with di-n-butylboryl trifluoromethanesulfonate (2) in the presence of diisopropylethylamine (3) at 0°C.

Enolate 4 was then allowed to react, in situ, with N-Boc-L-leucinal (5).[7] After the oxidative decomposition of the boron complex, the product (6)[8a] was isolated by chromatography over a short silica gel column, which readily removed diasteriomers of 6 present in apparently minute quantities. Thus any 4R epimer of 6 derived from Boc-D-leucinal, which might have been present as a result of isomerization of 5,[5b,c,7] would be removed because of its substantially lower chromatographic mobility.[8b] Desulfurization of 6 thus prepared, containing some unreacted 5, by treatment with Raney nickel[9] in acetone at room temperature gave 7, which was then treated with sodium ethoxide in ethanol to give the desired product (8b). Analysis of the crude product by capillary gc, which could clearly differentiate the 3S,4S, or 3R,4R isomers, from the 3R,4S or 3S,4R isomers, showed a ratio of more than 99.9 to 0.1 in favor of the former.[8c] The product, isolated by chromatography over silica gel and identified by nmr comparison with an authentic sample, showed an optical rotation of -37.1° (c 1, methanol) (reported, -37.9°[5c]).[10] The overall yield of 8b was 24% based on 1.

The deprotection of N-Boc-statine ethyl ester (8b) to statine (8a) has been accomplished readily by saponification followed by mild hydrolysis with trifluoroacetic acid;[5c] compound 8b thus may serve as a useful intermediate in the synthetic incorporation of statine to form larger molecules of biological importance.[3]

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8. (a) Analysis by capillary gc (RSL310) showed the presence of 6 as the major product, the molar ratio of which, relative to unreacted 1, ranged from 3.1 to 2.0 in four runs. Three minor peaks showing peak area (retention time) ratios relative to the major product of 2.6% (1.14), 2.4% (1.18), and 2.8% (1.19) were identified by ms fragmentation patterns as diasteriomers of 6. These were removed from the crude product by chromatography over seven times its weight of silica gel. (b) reaction of Boc-D-leucinal with 1 gave about 3% of 6, if actually present, relative to the main product, i.e., the 4-epimer of 6; the latter epimer showed an Rf ratio of 0.65 in tlc (hexane:ethyl acetate, 2:1, silica gel), and a retention time ratio of 1.18 in gc, relative to 6, respectively. (c) The retention time of 9b, relative to 8b, was 1.11.

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10. The possible presence of more than mere trace of 3R,4R enantiomeric contaminant in the product 8b is negated by these data. Such 3R,4R enantiomer conceivably could have originated from: (a) racemization of 5 to N-Boc-"D"-leucinal, followed by coupling, in stereochemically disfavored manners,[6] with the boron enolate 4, yielding diasteriomers epimeric to 6 at C3 and 4 or C2, 3, and 4; (b) as a more unlikely alternative, sequential 3-keto formation in 6 and racemization at C4 during Raney nickel treatment (Kleiderer, E.C.; Kornfeld, E.C. J. Org. Chem., 1948, 13, 455), followed by totally stereospecific reduction of the ketone to the 3R alchol.

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