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A STEREOSELECTIVE SYNTHESIS OF (3S,4S) STATINE AND RELATED COMPOUNDS

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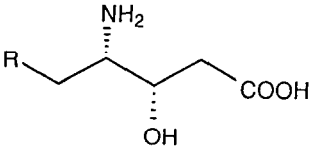
Abstract: (3S,4S)Statine and (3S,4S)AHPPA were synthesized efficiently using a highly stereoselective iodocyclocarbamation of the chiral Z-olefins 6a and 6b derived from the correspondent α-aminoacids.

The 1,2-aminohydroxy system has gained particular interest due to his presence in natural products[1] or in peptidomimetic chemistry as target of pharmacological researches.[2] In this context, the (3S,4S)4-amino-3-hydroxy-6-methyl heptanoic acid (statine) 1a, and the (3S,4S)4-amino-3-hydroxy-5-phenyl pentanoic acid (AHPPA) 1b are the key constituents of microbially produced aspartic peptidase inhibitors, pepstatin[3] and related peptides.[4]



1a R = i-Pr (3S,4S)Statine
1b R = Ph (3S,4S)AHPPA

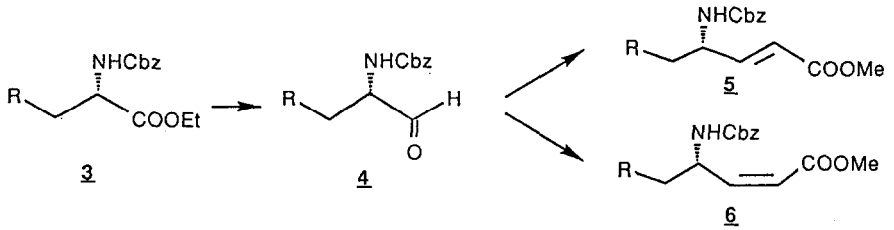
Since it has been shown that only the natural (3S,4S) isomer exhibits inhibitory activity,[5] several syntheses[6] of statine and related compounds have been reported, most of them leading to a mixture of the two diastereoisomers (3S,4S) and (3R,4S), but their stereoselective synthesis is the subject of interest.[7]

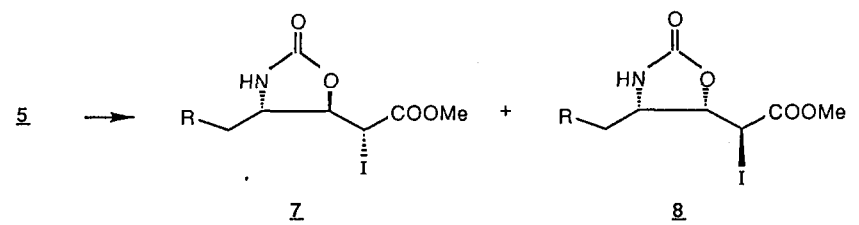
We wish to report[8] here our synthesis to these compounds based on the highly stereoselective iodocyclocarbamation[9] of suitable mono-protected N-Cbz allylamines, 5 and 6, in order to introduce the desired 3S hydroxy group.

The required allylamines 5 and 6 have been prepared by conventional methods via conversion of the N-benzyloxycarbonyl α-aminoacid ethyl esters 3a and 3b in the α-amino aldehydes 4a and 4b[10] (DIBAH, toluene, -78°C) followed by conversion into the known E-γ--amino-α,β-unsaturated esters 5a and 5b[11] [$(MeO)_2POCH_2COOMe$/NaH, THF, 0°C, E/Z 15:1] in 75% yield[12] (Scheme). The Z isomers 6a and 6b, instead, were prepared by treatment of the above α-amino aldehydes with the Still's reagent[13] [$(CF_3CH_2O)_2POCH_2COOMe$/$(Me_3Si)_2NK$,

18-crown-6·MeCN, THF, -78°C; Z/E ratio 25/1] in 75% yield.

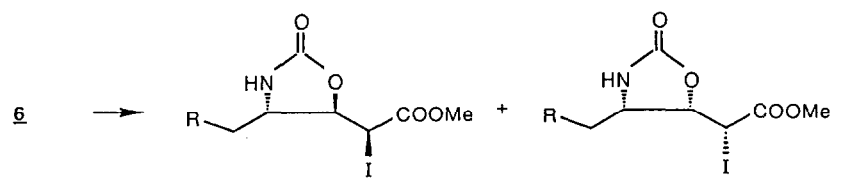
When the pure E-olefins were treated with I (3 eq) in MeCN at room temperature, a mixture of diastereoisomers 7 and 8 was obtained in ~80/20 ratio[12] in favour of the (2R,3R,4S) stereoisomer.





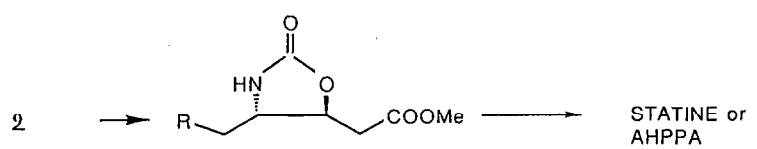
7a : 83
7b : 81

8a : 17
8b : 19



9a : 98,0
9b : 97,5

10a : 2,0
10b : 2,5



a : R = i Pr. b : R = Ph.

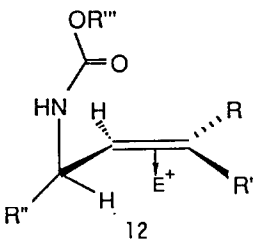
On the other hand, when the Z-allyl amines 6a and 6b were treated under the same conditions, the desired cyclic trans-carbamates 9a and 9b were obtained in 85% yield (9/10 ratio ~98/2).[11,16]

The trans stereochemistry of the oxazolidin-2-ones 7 and 9 has been confirmed by conversion into the known 11a and 11b[4b] (n-Bu_3SnH, toluene, reflux, 85%) which show a ^1H-NMR coupling constant J_{3-4} of 5.0 Hz in agreement with the reported value.[4b]

The synthesis was completed by alkaline hydrolysis of 11a and 11b to give the desired products 1a[17] and 1b[17] in 45% and 47% overall yield, respectively.

The high stereoselection observed in the cyclocarbamation of allylic carbamates 5 and 6 can be rationalized on the basis of consideration of the transition state which can be visualized in Figure.

Preferential reaction of the conformer 12 is consistent with the allylic hydrogen in the same plane of the double bond. This conformation results particularly favourable in the case of Z-allyl amines 6a and 6b.[18]



12

R = H
R' = COOMe
R" = CH_2-$CHMe_2$
R" = CH_2Ph

Further studies are in progress in our laboratory to explore other synthetic applications.

Acknowledgement - We thank Prof. G. Cardillo for the helpful discussions during the course of this work.

References and notes

1. For a review see: Wagner, I.; Musso H. Angew. Chem. Int. Ed. (1983) 22, 816.
2. See for example: Boger, J.; Lohr, N.; Ulm, E.; Poe, M.; Blaine, E.; Fanelli, G.; Lin, T.; Payne, L.; Schorn, T.; La Mont, B.; Vassil, T.; Stabilito,I.; Veber, D.; Rich, D.H.; Bopari, A. Nature (1983) 81, 303; Hanson, G.; Baran, J.; Lindberg, T.; Walsh, G.; Papaioannou, S.; Babler, M. Biochem. Biophys. Res. Comm. (1985) 132, 155.
3. Umezawa, H., Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. J. Antibiot. (1970) 23, 259.
4. a) Isolation of AHPPA: Omura, S.; Imamura, N.; Kawakita, N.; Mori, Y.; Yamazaki, Y.; Masuma, R.; Takahashi, Y.; Tanaka, H.; Huang, L.; Woodruff, H. J. Antibiot. (1986) 39, 1079.
b) Synthesis of AHPPA: Rich, D.H.; Sun, E. J. Med. Chem. (1980) 23, 27.
5. Rich, D.H. J. Med. Chem. (1985) 28, 263.
6. For example: a) Rittle, K.; Homnick, C; Ponticello, G.; Evans, B. J. Org. Chem. (1982)

47, 1981; b) Danishefsky, S.; Kobayashi, S.; Kerwin, J. J. Org. Chem. (1982), 47, 3016; c) Sakaitani, M.; Ohfune, Y. Tetrahedron Lett. (1987) 28, 3987; d) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. Tetrahedron Lett. (1988) 29, 6327 and references therein.

7. a) Yamagisawa, H.; Kanazaki, T.; Nishi, T.; Chem. Lett. (1989) 687; b) Vara Prasad, J.; Rich, D. Tetrahedron Lett. (1990) 31, 1803; c) Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. Tetrahedron Lett. (1990) 31, 217.
8. Misiti, D.; Zappia, G. in "Progress and Prospects in Organic Synthesis", Lausanne and Champery, Switzerland, 27-9/1-10-89, P105
9. Pauls, H.; Fraser Reid, B. J. Am. Chem. Soc. (1980) 102, 3956; Overmann, L.; Mc Cready, R. Tetrahedron Lett. (1982) 23, 4887; Parker, R.; O'Fee, R. J. Am. Chem. Soc. (1983) 105, 654; Kobayashi, S.; Isobe, T.; Ohno, M. Tetrahedron Lett. (£ç') 25, 5079; Kamiyama, K.; Urano, Y.; Kobayashi, S.; Ohno, M. Tetrahedron Lett. (1987) 28, 3123; Cardillo, G.; Orena, M. Pure and Appl. Chemistry (1988) 60, 1617.
10. Luly, J.; Dellaria, J.; Pattner, J.; Soderquist, J.; Yi, N. J. Org. Chem. (1987) 52, 1487;
11. Moriwake, T.; Hamano, S.; Miki, K.; Saito, S.; Torii, S. Chem. Letters (1986) 815
12. All new compounds exhibited satisfactory 'H NMR, IR and elemental analysis; diastereoisomeric ratios, when indicated, were performed on a Waters HPLC apparatus (Column: Bondapack C-18, eluent: for 7 and 8, H_2O/MeCN 50/50 v/v; for 9 and 10, H_2O/MeOH 50/50 v/v).
13. Still, W.C.; Gennari, C. Tetrahedron Lett. (1983) 24, 4405
14. Kogen, H.; Nishi, T. J. Chem. Soc. Chem. Comm. (1987), 311.
15. Bartlett, P.A.; Meyerson, J. J. Am. Chem. Soc. (1978) 100, 3950
16. The stereochemistry for 10a and 10b was assigned on the basis of consideration of the transition state, but they were not isolated.
17. For 1a $[\alpha]_D$ = -21.1° (c = 0.5, H_2O); mp 209-210°C [Lit[7a] $[\alpha]_D^{16}$ = -20° (c = 0.64, H_2O); mp 203°C].
For 1b $[\alpha]_D$ = -24.2° (c = 0.5, H_2O); mp 194-195°C (H_2O/EtOH) [Lit $[\alpha]_D^{16}$ = -24° (c = 0.44, H_2O); mp 193°C (H_2O/EtOH)].
18. Chamberlin, A.R.; Mulholland, K.L.; Kahn, S.; Hehre, W.J. J. Am. Chem. Soc. (1987) 109, 672

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