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STEREOSELECTIVE SYNTHESIS OF STATIN ANALOGUES.

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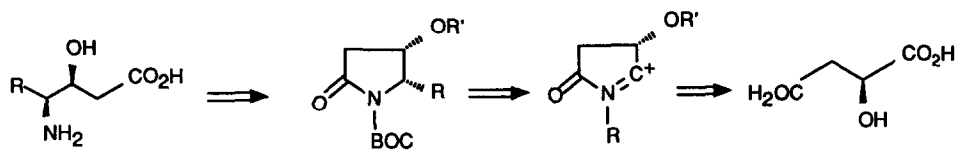
Abstract. *Statin analogues can be synthesized stereoselectively (diastereomeric ratios up to 4:1) starting from malic acid. The key step involves an unprecedented* cis*-selective allylation of an* α*-alkoxy N-acyliminium ion.*

The peptide pepstatin is a strong competitive inhibitor of aspartyl proteases.[1] Its biological activity is largely due to the presence of the unusual γ-aminoacid statin **1**, wich is believed to behave as a transition state analogue of the scissile dipeptide unit of the natural substrates. Peptides containing the statin analogues **2-4**, where the iPr group has been replaced by a more lipophilic residue, were found to be even more active than pepstatin itself in inhibiting human renin, the aspartyl protease which cleaves angiotensinogen to begin the cascade of the renin-angiotensin system.[2]

Scheme 1.

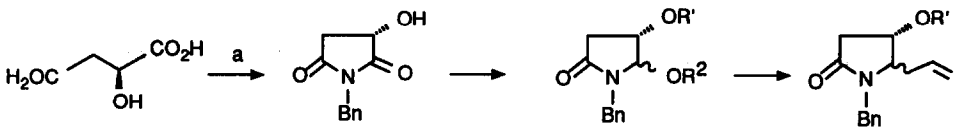


1 R=iPr **3** R=cyclohexyl **5** **6** (S)-Malic acid

2 R=Ph **4** R= 

Due to the crucial role of renin in regulating blood pressure, in recent years a great deal of efforts has been devoted to designing practical syntheses of statin and its analogues.[3] Almost all the published methods, however, are based on the use of natural aminoacids as starting materials, and on their elongation with some sort of acetate equivalent. Such an approach poses severe limitations to the number and type of R residues that can actually be introduced. We reasoned that *cis*-selective alkylation of an acyliminium ion **6** (Scheme 1) to give lactam **5** (a known intermediate *en route* to statin[3f-h,3q]) would allow a lot more of flexibility in the choice of R residues. The precursor to **6**, in turn, ought to be accessible in enantiomerically pure form from the inexpensive (S)-malic acid.[4] However, *cis*-selective intermolecular alkylation of cyclic acyliminium ions like **6** are unprecedented in the literature.[5,6] We therefore set about to find the best conditions for *cis* selectivity by using (±)-malic acid as starting material and trimethyl allylsilane as a model alkylating agent.

Scheme 2.



7

8a[b,c] R'=Ac R^2=Et
8b[c,d,c] R'=Ac R^2=Ac
9a[b,e] R'=Bn R^2=Et
9b[e,d,c] R'=Bn R^2=Ac

10 R'=Ac
11 R'=Bn

a. $PhCH_2NH_2$ in refluxing xylene (70%). b. $NaBH_4$, EtOH, 0°C, 10 min, followed by 1N H_2SO_4 in EtOH. c. AcCl, Py, CH_2Cl_2, 1h, RT. d. $NaBH_4$, MeOH, followed by sat. $NaHCO_3$. e. $PhCH_2Br$, Ag_2O, Et_2O.

Imide **7** (Scheme 2) was obtained in 70% yield from malic acid by a modification of the known procedure.[7] Lactams **8a-b** and **9a-b** were synthesized from **7** by alcohol protection / regioselective reduction[8] sequences, as shown in Scheme 2.[9] In all cases a mixture of two stereoisomers was obtained upon treatment with $NaBH_4$. Products arising from reduction of the less electrophilic carbonyl group were not detected.

Acid catalyzed allylsilane addition to acetates **8a** and **8b** gave rise to amide **10**[9] with moderate *trans* selectivity[10] (Table 1, Entries 1-3).

Table 1. Addition of trimethylallylsilane to **8** and **9**.[a]

Entry	Subst.	Lewis acid[b]	Conditions	Prod.	*trans/cis*[c]	Conv.(%)[d]
1	**8a**	Me_3SiOTf	24h, RT	**10**	3:1	80 (73)
2	**8b**	Me_3SiOTf	3h,-20°C	**10**	2.5:1	90 (81)
3	**8b**	BF_3Et_2O	3h,-20°C	**10**	2:1	90
4	**9a**	Me_3SiOTf	3h, RT	**11**	1:1	99 (93)
5	**9a**	$SnCl_4$	3h, RT	=	=	=
6	**9b**	$SnCl_4$	12h, RT	**11**	1:2	99
7	**9b**	$MgBr_2$	12h, RT	**11**	1:1.4	93 (89)
8	**9b**	$MgBr_2$	18h, RT	**11**	1:1.7[e]	99

a. Unless otherwise stated, all reactions were performed in dry CH_2Cl_2, adding the Lewis acid to a solution of the substrate and 4 eq. of allylsilane in the presence of 4Å molecular sieves. b. Me_3SiOTf: 0.25 eq.; BF_3Et_2O: 1 eq.; $SnCl_4$ and $MgBr_2$: 2.5 eq. c. As determined by ^1H NMR and/or GLC. d. As determined by NMR of the crude reaction mixtures. Isolated yields are in brackets. e. Reaction performed in toluene.

This observation can be explained by the known ability of acetoxy groups to bridge to adjacent cationic centers,[11] thus favoring trans addition. This interpretation is also supported by the fact that no selectivity is observed upon Me_3SiOTf catalyzed addition of allylsilane to benzylether **9a** (Table 1, Entry 4, cf. Entry 1). Prevalent formation of the *cis* isomer was eventually obtained by switching to different Lewis acids. Choice of the proper combination of leaving group and Lewis acid is crucial : for instance $SnCl_4$ cannot promote the allylation of 5-ethoxy lactam **9a** (Table 1, Entry 5), but gives 99% conversion to **11**[9] and 2:1 *cis* selectivity[12] with the 5-acetoxy derivative **9b** and allylsilane (Table 1, Entry 6).

Table 2. Addition of tributylallyltin to **9b**.[a]

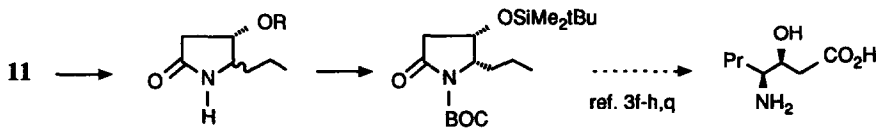
Entry	Lewis acid	Conditions	**11** *trans/cis*[b]	Solvent	Yields(%)[c]
1	$SnCl_4$	18h, RT	=	CH_2Cl_2	=
2	$MgBr_2$	3h, RT	1:2	CH_2Cl_2	88
3	$MgBr_2$	18h, RT	1:4	Toluene	85

a. The reactions were performed by adding 2.5 eq. of the indicated Lewis acid to a solution of **9b** and 3 eq. of tin reagent in the indicated solvent at 0°C. The resulting mixture was kept at RT for the indicated time, before quenching with phosphate buffer. b. As determined by GLC on the crude reaction mixtures. c. Isolated yields.

The nature of the nucleophile was also found to be influential: tributylallyltin proved to be superior to trimethylallylsilane in the $MgBr_2$ catalyzed addition to **9b** (cfr. Table 1, Entry 7 and Table 2, Entry 2). Finally, the best *cis* selectivity was achieved by promoting the allyltin reaction with $MgBr_2$ in a toluene solution (Table 2, Entry 3). This reaction, albeit slowed down by the low solubility of the intermediates in such medium, gave rise to **11** in 85% yield and 4:1 *cis*:*trans* ratio.

From **11**, lactam **14** was obtained through ordinary functional group manipulations (Scheme 3).

Scheme 3.



12 R=H
13 R=Me_2tBuSi

14

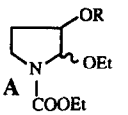
Double bond reduction of a 3:1 *cis*-**11**:*trans*-**11** mixture (H_2, Pd-C, 95%) followed by removal of the benzyl groups (Na, liq.NH_3, THF, -78°C, 70%) gave rise to alcohol **12**.[9] The corresponding silylethers *cis*-**13** and *trans*-**13** could be easily separated by flash chromatography (20/80 hexane/AcOEt). From pure *cis*-**13** the Boc derivative **14**[9] was isolated in 85% yield upon treatment with Boc_2O (cat. DMAP, TEA, CH_2Cl_2, RT, 1h),[13] thus completing the formal synthesis of the *syn* amino alcohol.[3f-h,3q]

In summary, we have proved that statin analogues can be prepared with stereoselectivity up to 4:1 by acid catalyzed allylation of the malic acid derived 5-acetoxy lactam **9b**. Further work is in progress to expand the scope of the method to more lipophilic R residues as well as to understand the reasons of the observed *cis* selectivity.

Aknowledgments. Financial support by Luso - Farmaco d'Italia is gratefully aknowledged.

References and Notes.

1. Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J.Antiobiot.* **1970**, *23*, 259.
2. Boger, J.; Payne, L.S.; Perlow, D.S.; Lohr, N.S.; Poe, M.; Blaine, E.H.; Ulm, E.H.; Schorn, T.W.; LaMont, B.I.; Lin, T.Y.; Rich, D.H.; Veber, D.F. *J.Med.Chem.* **1985**, *28*, 1779; Sham, H.L.; Stein, H.; Cohen, J. *J.Chem:Soc.Chem.Commun.* **1987**, 683.
3. a. Maibaum, J.; Rich, D.H. *J.Org.Chem.* **1988**, *53*, 869. b. Schuda, P.F.; Greenlee, W.J.; Chakravarty, P.K.; Eskola, P. *J.Org.Chem.* **1988**, *53*, 873. c. Raddotz, P.; Radunz, H-E.; Schneider, G.; Schwartz, H. *Angew.Chem.Int.Ed.Engl.* **1988**, *27*, 426. d. Nishi, T.; Kitemura, M.; Noyori, R. *Tetrahedron Lett.* **1988**, 6327. e. Reetz, M.T.; Drewes, M.W.; Matthews, B.R.; Lennick, K. *J.Chem.Soc.Chem.Commun.* **1989**, 1474. f. Katsuki, T.; Yamaguchi, M.*Bull.Chem.Soc.Jap.* **1976**, *49*, 3287. g. Jouin, P.; Castro, B.; Nisato, D. *J.Chem.Soc.Perkin Trans.I* **1987**, 1177.h. Klutchko, S.; O'Brien, P.; Hodges, J.C. *Synth.Comm.* **1989**, 2573. i. Rich, D.H.; Sun, E.T.; Boparai, A.S. *J.Org.Chem.* **1978**, *43*, 3624.l. Rittle, E.K.; Homnick, C.F.; Ponticello, G.; Evans, B.E. *J.Org.Chem* **1982**, *47*, 3016. m. Woo, P.W.K. *Tetrahedron Lett.* **1975**, 2973. n. Devant, R.M.; Radunz, H-E: *Tetrahedron Lett.* **1988**, 2307. o. Reetz, M.T.; Diewes, M.W.; Schmitz, A. *Angew.Chem.Int.Ed.Engl.* **1987**, *26*, 1141. p. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem.Letters* **1987**, 1531. q. Andrew, R.G.; Conrow, R.E.; Elliott, J.D.; Johnson, W.S.; Ramezani, S. *Tetrahedron Lett.* **1987**, 6535. r. Danishefsky, S.; Kobayashi S.;Kerwin, J.F.Jr *J.Org.Chem.* **1982**, *47*, 1981. s. Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J.Org.Chem.* **1988**, *53*, 3865. s. VaraPrasad, J.V.N.; Rich, D.H. *Tetrahedron Lett.* **1990**, 1803.
4. Chamberlin, A.R.; Chung, J.Y. *J.Am.Chem.Soc.* **1983**, *105*,3653.
5. *Trans*-selective (65:35) allylation of carbamate **A** (R=Ac) has been reported: Kraus, G.A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, 3841.



6. While this work was well in progress a report on *cis*-selective alkylation of **A** (R=TBDMS) appeared in the literature: Thaning, M.; Winstrand, L-G. *J.Org.Chem.* **1990**, *55*, 1406.
7. Malic acid and benzylamine were refluxed for 5h in xylene. 4A molecular sieves between the condenser and the flask were used to trap the water formed in the process, see: Masayuki, S.; Yoshikazu, J.; Seiju, K. *Chem.Pharm.Bull.* **1984**, 1303; Bowers Nemia, M.M.; Lee, J.; Jouillé, M. *Synth.Comm.* **1983**, *13*, 1117.
8. Hubert, J.C.; Wijnberg, J.B.P.A.; Speckamp, W.N. *Tetrahedron* **1975**, *31*, 1437; Wijnberg, J.B.P.A.; Schoemaker, H.E.; Speckamp, W.N. *Tetrahedron* **1978**, *34*, 179. The original procedure for $NaBH_4$reduction of imides calls for controlling the pH of the medium by slow addition of 2N HCl. In accordance with Chamberlin we found that such procedure is superfluous with the substrates at hand, as long as the reactions followed by "basic workup" are performed in MeOH, see *ref.4*.
9. New compounds had spectral data consistent with the assigned structures.
10. The product stereochemistry was determined by NMR spectroscopy. The observed vicinal coupling constants $J_{4,5}$ were: *major*, 0 Hz; *minor*, 6 Hz. These values are typical of, respectively, *trans* and *cis* 4,5 disubstituted pentalactams, see *ref.3g* and references therein. Moreover, in a NOESY experiment the minor reaction product showed a cross peak correlating H_4 and H_5, thus proving their *cis* relationship.
11. Capon, B. *Q.Rev.Chem.Soc.* **1964**, *18*, 45. Note, however, that anchimeric participation by a 3-acyl group does not appear to take place in the acid catalyzed reaction of allylsilane with sugar acetals: Kozikowski, A.P.; Sorgi, K.L. *Tetrahedron Lett.* **1982**, 2281; Lewis, M.D.; Cha, J.K.; Kishi, Y. *J.Am.Chem.Soc.* **1982**, *104*, 4976.
12. The stereochemistry of *cis*- and *trans*-**11** was assigned by chemical correlation to **10**.
13. Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J.Org.Chem.* **1983**, *48*, 2424.

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