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AN EXPEDITIOUS SYNTHESIS OF (3*S*,4*S*)-STATINE AND (3*S*,4*S*)-CYCLOHEXYLSTATINE

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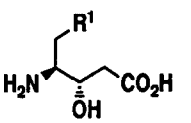
Abstract: The title synthesis could be accomplished by employing highly stereoselective aldol reaction of *O*-methyl-*O*-trimethylsilyl ketene acetal with the (*S*)-α-amido aldehyde (**2**) in the presence of titanium (IV) chloride as a key step.

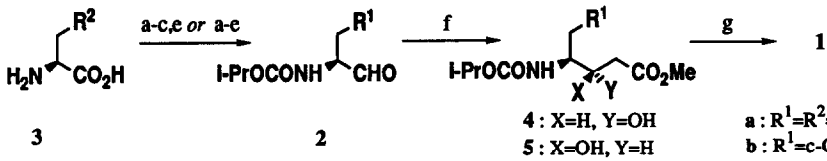
Renin is a highly specific aspartic protease which produces angiotensin I from angiotensinogen.[1] With an aim to develop a novel class of antihypertensive agents, studies on renin inhibitors constitute a current area of intense researches.[1] Since (3*S*,4*S*)-statine (**1a**) was found as a component of pepstatin, the natural peptide exhibiting inhibitory activity against renin,[2] a number of the synthetic peptide mimics bearing **1a** have so far been explored as renin inhibitors.[3] Recently, it was also reported that some peptide-like compounds which involve (3*S*,4*S*)-cyclohexylstatine (**1b**) in place of **1a**, show more promising profiles as antihypertensive agents.[3a, 4]



1a : $R^1 = Me_2CH$
1b : $R^1 = c\text{-}C_6H_{11}$

Due to the situations delineated above, numerous synthetic routes to **1** have hitherto been reported.[3-5] Although the aldol reaction of an enolate of acetic acid derivative with an (*S*)-α–amido aldehyde such as **2** obtainable from (*S*)-leucine [(*S*)-**3a**] or (*S*)-phenylalanine [(*S*)-**3b**], may constitute one of the simplest synthetic routes to **1**, it is well recognized that the addition reaction employing an achiral enolate results in no significant stereoselection[6] and the desired stereoselectivity can be realized only by using a precious chiral enolate.[7] In order to produce **1** more expeditiously, a novel synthetic method was sought which can effectively introduce an achiral acetic acid moiety into **2**. We have now found that the aldol reaction of *O*-methyl-*O*-trimethylsilyl ketene acetal with **2** undergoes in a highly stereoselective manner, giving rise to a mixture of the addition products (**4** and **5**) in which the former desired compound (**4**) is highly predominant (**4**:**5**>94:6). Acidic removal of the protective groups involving in **4** readily furnished **1**.

Thus, as shown in the scheme, (*S*)-**2a** could be readily prepared from (*S*)-**3a** in 4 steps. The reaction of (*S*)-**2a** with the ketene acetal proceeded in a highly stereoselective manner in the presence of $TiCl_4$ (1.5 equiv.) at -78°C, affording a mixture of the addition products (**4a**:**5a**=94:6)[8] in 89% yield.[9,10] Lewis acids other than $TiCl_4$ were also employed for the aldol reaction. These experiments always gave **4a** as a major product the same as described above. The combined yields and ratios of **4a** to **5a** are as follows: $BF_3{\cdot}Et_2O$ at -78°C [72%, 80:20]; ZnI_2 at 0°C [45%(55%)[11], 90:10]; Eu(fod)$_3$ at r.t. [48%(29%)[11], 93:7]. The stereochemistry of the major product could be rigorously determined as shown by the successful synthesis of **1a** from **4a** (*vide infra*). The preferential formation of **4a** may be rationalized by the so-called chelation controlled mechanism. This is quite interesting in view of the reported results that an α-alkoxy aldehyde is not susceptible to similar chelation controlled diastereofacial selection.[12] The major compound (**4a**) isolated in a pure state by column chromatography, was subjected to acidic hydrolysis, providing **1a** in 88% yield, mp 205°C (decomp.)



a) MeOH,$SOCl_2$ (a 100%,b 96%);b) i-PrOCOCl,K_2CO_3,CH_2Cl_2 (a 87%) or i-PrOCOCl,Et_3N,THF(b 91%);c) $NaBH_4$,LiCl,EtOH-THF(a 98%, b 100%);d) H_2 (4atom),Rh-Al_2O_3,MeOH,AcOH(100%);e) SO_3·Py,DMSO,Et_3N,PhMe(a 78%,b 79%);f) CH_2=C(OMe)(OTMS),$TiCl_4$,MS4A, CH_2Cl_2,-78°C[a 89%(4a/5a=94:6),b 95%(4b/5b=95:5)];g) 1) 6*M*HCl,AcOEt,100°C,2) Dowex AG 50W(H^+form) (a 88%,b 93%).

(recrystallized from H_2O-ethanol) and $[\alpha]_D^{20}$ -20.4° (c 0.502, H_2O) [lit.[13] mp 203°C (decomp.) and $[\alpha]_D^{16}$ -20° (c 0.64, H_2O)].

In completely the same manner, a mixture of **4b** and **5b** (**4b:5b**=95:5)[8] could be produced in 95% yield from (*S*)-**2b** prepared from (*S*)-**3b** in 5 steps. Acidic hydrolysis of **5b** separated in a pure state, similarly gave 93% yield of **1b**, mp 216°C (decomp.) (precipitated from 1*M* HCl by neutralizing with 1*M* NaOH) and $[\alpha]_D^{20}$ -25.3° (c 0.435, 1*M* HCl) [lit.[14] mp 231°C (decomp.) and $[\alpha]_D^{25}$ -26.2° (c 1.0, 1*M* HCl)].

Taking into account directness and operational simplicity, the explored overall process may serve as one of the most practical synthetic methods of **1a,b**.

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8. Determined by GLC analysis (5% Silar 10C chromosorb W, 190°C).
9. Detailed procedure for preparing **4a** and **5a** is as follows. A solution of $TiCl_4$ (0.065ml, 1*M* soln. in CH_2Cl_2) was added to a mixture of (*S*)-**4a** (8.7mg, 0.043mmol), molecular sieves 4A (4mg), and *O*-methyl-*O*-trimethylsilyl ketene acetal (19mg) in CH_2Cl_2 (0.8ml) at -78°C. After being stirred for 30 min at the same temperature,the mixture was quenched with $NaHCO_3$ solution and filtered through a pad of Celite. The Celite layer was washed with AcOEt, and the combined filtrates were dried and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane:AcOEt=4:1) to give a mixture of **5a** and **6a** (10.6mg, 89%) as a colorless oil. These diastereomers (**4a** and **5a**) could be separated in a pure state by column chromatography (SiO_2, hexane:AcOEt=10:1); **4a**:$[\alpha]_D^{20}$ -43.2° (c 1.07, $CHCl_3$) and **5a**: mp 63-65°C, $[\alpha]_D^{20}$ -29.8° (c 0.650, $CHCl_3$).
10. The relative configurations of **4a** and **5a** could be assigned by measuring the NMR spectra of the 1,3-oxazolidine derivatives prepared by treating **4a** and **5a** with 2,2-dimethoxypropane and *p*-TsOH in CH_2Cl_2.
11. Value in parenthesis represents recovery yield of **2a**.
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