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Synthesis of Statine and Its Analogues

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Statine, (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid, and its analogues were prepared from 5,6-anhydro-3-deoxy-1,2-O-isopropylidene-D-glucofuranose. The key step is the stereospecific reaction of the epoxy sugar with the Grignard reagent.

The unusual γ-amino acid statine 1 is a component of the general aspartyl protease inhibitor pepstatin[1] and plays an important role in binding with enzyme as a transition state or tetrahedral intermediate analogue of the scissile dipeptide unit of a substrate.[2] The inhibitor of renin, the aspartyl protease which cleaves angiotensinogen to begin the cascade of the renin-angiotensin-aldosterone pressor system, has been expected to be an antihypertensive agent. Since the renin inhibitor having the statine unit had been shown to have a potent inhibitory activity,[3] many statine analogues have been reported. For example, replacement of the isopropyl group in 1 by the cyclohexyl[4] or 1,3-dithiolan-2-yl[5] groups enhances the inhibitory activity and the inhibitors possessing homostatine, monomethylene extended statine, and its analogues[6,7] have potent activity. Several stereospecific syntheses of 1 and its analogues have been demonstrated[8] but there has been only one[9] which employed sugar as a starting material where Grignard reaction of the pentodialdofuranose derivative with isopropylmagnesium bromide was the key step.

In this paper we describe the stereospecific synthesis of 1 and its

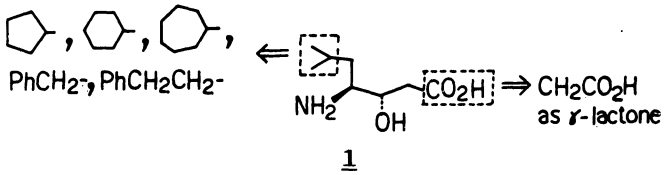

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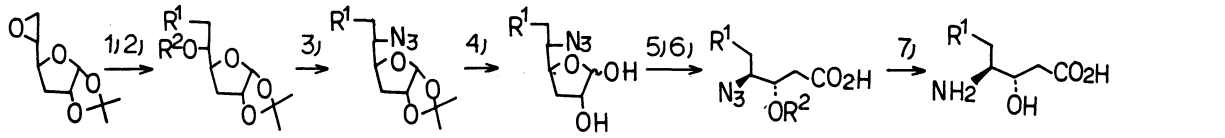
Fig. 1.

analogues shown in Figure 1 based upon Grignard reaction of the epoxy sugar **2**[10] derived from 1,2,5,6-di-O-isopropylidene-D-glucofuranose.

The synthesis of **1** and the analogues **9b-f** modified at the isopropyl moiety of **1** is shown in Scheme 1. The epoxy sugar **2** was allowed to react with the Grignard reagents R^1MgBr in the presence of cuprous iodide to give the alcohols **3a-f**. Mesylation of **3a-f** followed by treatment with sodium azide gave the azido sugars **5a-f**. In the case of the phenethyl derivative (R^1=Ph), demethylsulfonyloxylation occurred and the 5,6-dehydosugar was obtained with the azido sugar in a ratio of 1:1. Removal of the isopropylidene group of **5a-f** with aqueous acetic acid gave **6a-f** of which oxidation with sodium periodate in the presence of a catalytic amount of potassium permanganate followed by hydrolysis with sodium hydroxide afforded the hydroxy acids **8a-f**. These compounds **8a-f** are useful for synthesis of renin inhibitors because the amino group of **1** and its analogues is protected as the azide group. Catalytic hydrogenation of **8a-f** by palladium on carbon gave **1** and its analogues **9b-f**.[11]



2 **3a-f**; R^1=**a-f**, R^2=H; **4a-f**; R^1=**a-f**, R2=SO_2Me **5a-f**; 6**a-f**; R^1=**a-f** **7a-f**; R^1=**a-f**, R^2=CHO **8a-f**; R^1=**a-f**, R^2=H **1**; R^1=**a**: **9b-f**; R^1=**b-f**

a, $CH(CH_3)_2$; **b**,  ; **c**,  ; **d**,  ; **e**, CH_2Ph; **f**, CH_2CH_2Ph.

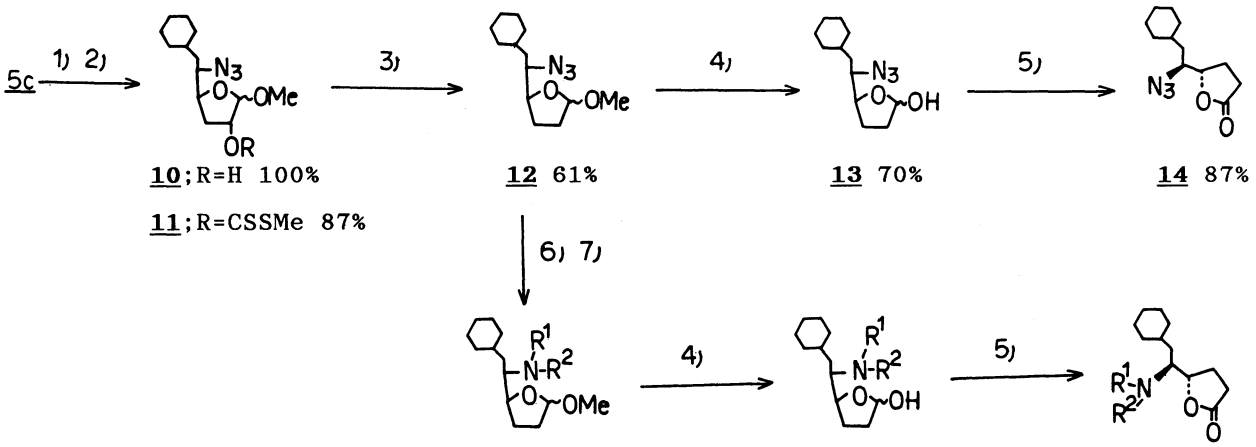
Yields (%):

3a 83, **b** 84, **c** 88, **d** 80, **e** 93, **f** 93; **4a** 82, **b** 98, **c** 90, **d** 90, **e** 100, **f** 82; **5a** 82, **b** 88, **c** 97, **d** 91, **e** 79, **f** 100; **6a** 80, **b** 91, **c** 92, **d** 92, **e** 79, **f** 82; **7a** 89, **b** 98, **c** 95, **d** 89, **e** 99, **f** 96; **8a** 95, **b** 99, **c** 92, **d** 82, **e** 100, **f** 100; **1** 85; **9b** 74, **c** 88, **d** 92, **e** 83, **f** 81.

Reagents and reaction conditions. 1) R^1MgBr (1.8 mol equiv.), CuI (0.5 mol equiv.) in THF; -20--15 ℃, 1 h → -10-0 ℃, 0.5 h → 0-10 ℃, 0.5 h. 2) $MeSO_2Cl$ (1.25 mol equiv.), Et_3N (3.5 mol equiv.) in CH_2Cl_2; 5 ℃, 2 h. 3) NaN_3 (4.5 mol equiv.) in DMF; 80 ℃, 40 h. 4) H_2O-AcOH (1:1, v/v); 100 ℃, 1 h. 5) $NaIO_4$ (5 mol equiv.), $KMnO_4$ (0.07 mol equiv.) in H_2O-t-BuOH (3:2, v/v); r.t., 2 h. 6) 1 mol dm^{-3} NaOH (1.1 mol equiv.), r.t., 1.5 h. 7) H_2 (760 Torr), 5 % Pd on C (10 wt. %) in AcOH; 40 ℃, 2.5 h.

Scheme 1.

Synthesis of the homostatine analogues is shown in Scheme 2. Methanolysis of **5c** in the presence of sulfuric acid gave the methyl furanoside **10** as a mixture of α and β anomers in a ratio of 1:11. Deoxygenation of **10** was carried out by Barton's procedure[12] via the dithiocarbonates **11** to give **12**. Hydrolysis of **12** in aqueous acetic acid followed by oxidation with pyridinium chlorochromate in the presence of a molecular sieve 3A[13] gave the azido-γ-lactone **14**[14] which is a key intermediate of the renin inhibitor having the homostatine unit. Catalytic hydrogenation of **12** by palladium on carbon gave the amine **15** of which the amino group was protected by phthaloyl or benzyloxycarbonyl groups to afford **16a,b**. Conversion of **16a,b** to the γ-lactones **18a,b**[14] was achieved by the same procedure described in the preparation of **14** from **12**. The lactones **18a,b** are precursors of the hydroxymethylene isostere[15] of cyclohexylalanylvaline.[7]



Phth = Phthaloyl; Z = Benzyloxycarbonyl

Reagents and reaction conditions. 1) concd. H_2SO_4 (1 mol equiv.) in MeOH; r.t., 2 h. 2) i) 55% NaH (1.3 mol equiv.), CS_2 (1.5 mol equiv.), imidazole (0.05 mol equiv.) in THF; 5 ℃, 1 h. ii) MeI (1.5 mol equiv.); 5 ℃, 1 h. 3) n-Bu_3SnH (1.25 mol equiv.), AIBN (0.05 mol equiv.) in toluene; 100 ℃, 15 min. 4) H_2O-AcOH (1:1, v/v), 100 ℃, 2 h. 5) PCC (1.4 mol equiv.), powdewed molecular sieve 3A in CH_2Cl_2, r.t., 2 h. 6) H_2 (760 Torr), 5 % Pd/C (10 wt. %) in EtOH; r.t., 12 h. 7) Ethoxycarbonylphthalimide (1.5 mol equiv.), $NaHCO_3$ (4 mol equiv.) in H_2O-DMF (1:2, v/v); 70 ℃, 2 h or N-(benzyloxycarbonyl-oxy)succinimide (1.1 mol equiv.), Et_3N (1.1 mol equiv.) in CH_2Cl_2; r.t., 16 h.

Scheme 2.

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11) Melting points and $[\alpha]_D$ measured at a 1% solution in 1 mol dm^{-3} HCl at 25 ℃ : **1**, 211 ℃ (dec), -27.7 ° ; **9b**, 228 ℃, -23.8 ° ; **9c**, 230-231 ℃ (dec), -26.2 ° ; **9d**, 209-211 ℃ (dec), -21.5 ° ; **9e**, 200-202 ℃, -11.4 ° ; **9f**, 221-222 ℃, -15.0 ° .

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