clohexylcarbamate, 64294-84-4; 1-cyclopropylvinyl *N*-phenylcarbamate, 64294-85-5; 1-*tert*-butylvinyl *N*-cyclohexenylcarbamate, 64294-86-6; pinacolone trimethylsilyl enol ether, 17510-46-2; 1-cyclopropyl-1-trimethylsilyloxyethylene, 42161-96-6.

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(17) However, the methodology to be developed should complement and not parallel chemistry with VOC-Cl because the derivatives (**1**, R′ = Me) are so different in reactivity vs. VOC amides and VOC esters. For example, titration of VOC-NR_2 with Br_2 yields $BrCH_2CHBrOCONR_2$, while the same reaction of $H_2C{=}CMeOCONR_2$ gives $BrCONR_2$.[5]

Synthesis of 4-Amino-3-hydroxy-6-methylheptanoic Acid by a Modified Reformatsky Reaction

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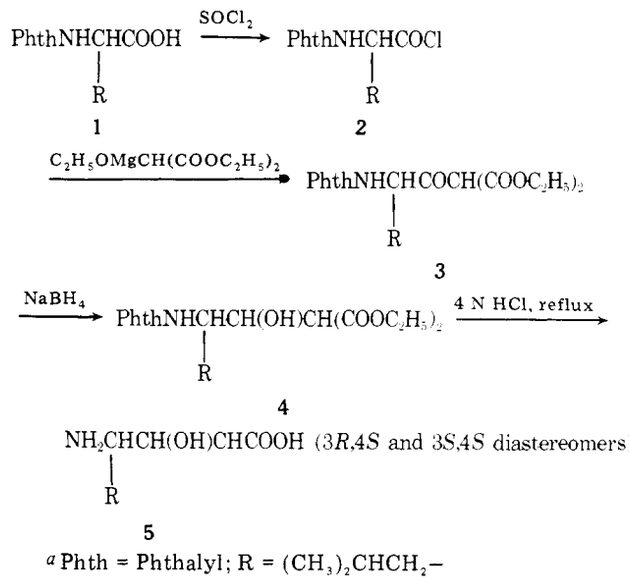
Pepstatin is a naturally occurring low-molecular-weight peptide that is a potent inhibitor of acid proteases.[1] The natural pentapeptide contains two residues of (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA), although a tripeptide containing only one residue of AHMHA at the C terminus retains its potency as an inhibitor of pepsin.[1] Since pepstatin is an effective inhibitor of renin, pepsin, and tissue cathepsin D's, there is a need for synthesis of analogues and derivatives that might be selective among these enzymes. The only derivatives reported have been prepared from AHMHA isolated from acid hydrolysates of pepstatin. AHMHA is unstable under conditions of acid hydrolysis, so it is not a good method for obtaining this amino acid. Synthesis of the 3*S*,4*S* and 3*R*,4*S* diastereomers (**5**) has been reported.[2] No yields or experimental details were given, but the yields were undoubtedly low (vide infra). All four of the possible stereoisomers have been synthesized by a method unsuitable for preparative work.[3] We report below the preparation of AHMHA in greatly improved yield via a modified Reformatsky reaction.

Results and Discussion

As a starting point, we repeated the reported[2] method for the preparation of AHMHA (Scheme I). We obtained an approximately equimolar mixture of diastereomers in 3.2% overall yield estimated by amino acid analysis of the crude

Scheme I[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

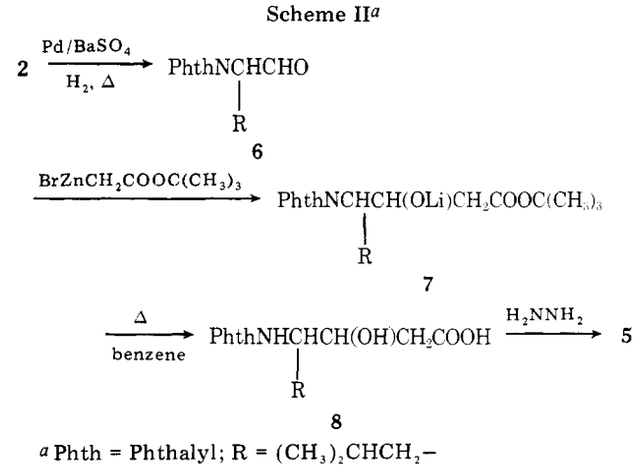
product. The intermediates **3** and **4** were obtained in good yield; their structures were confirmed by NMR analysis and by the fact that **3** is acidic and can be purified by extraction. Nearly all of **5** is lost during the hydrolysis step. The instability of **5** to acid-hydrolysis conditions was confirmed by heating a purified sample in 6 N HCl at 110 °C for 24 h which resulted in a loss of 58%. The yield of AHMHA from hydrolysis of pepstatin was about 50%.

The problem with Scheme I could have been solved by changing to *tert*-butyl ester blocking groups which could be removed by anhydrous acid, allowing removal of the phthalyl blocking group by hydrazinolysis. However, the Reformatsky reaction sequence in Scheme II was appealing in view of the reported success in obtaining β-hydroxy acids using the zinc enolate of *tert*-butyl acetate.[4]

The acid chloride **2** was obtained in quantitative yield as an oil that was used without further purification. Reduction gave the aldehyde **6** in 85% yield after removal of unreacted **2** by stirring the mixture with aqueous sodium bicarbonate and was used without further purification. Performing the Reformatsky reaction in the usual manner gave **8** in only 20% yield, due primarily to reaction of the enolate at the phthalyl carbonyl groups. The yield of **8** was improved to 40% with no side reaction at the blocking group by preparing the enolate separately and adding it to a cooled solution of the aldehyde. Hydrazinolysis proceeded in quantitative yield, giving a 55:45 mixture of **5** (3*S*,4*S*:3*R*,4*S*).

Although separation of the diastereomers **5** was reported

Scheme II[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

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using ion-exchange chromatography,[2] we have not been successful in separating them by this technique. We are investigating separations of the mixtures with **7** (alcohol) and **8** or at the stage of peptides prepared from the mixture **5**.

It is likely that the yield of **8** can be optimized, but even without a higher yield this synthesis is applicable to the preparation of AHMHA in quantity. In addition, the optical rotation of the mixture **5** indicates no more than 2% racemization, an important consideration in the preparation of enzyme inhibitors.

Experimental Section

Amino acid analyses were performed on a Beckman 120-C amino acid analyzer using standard short and long columns and pH 4.25, 0.2 M sodium citrate buffer.[5] The mixture **5** eluted as a single symmetrical peak on the short (33 min) or long (308 min) columns as did natural AHMHA in hydrolysates from pepstatin. The ninhydrin constant is 36% of that of L-leucine.

4-Amino-3-hydroxy-6-methylheptanoic Acid (5). Under anhydrous conditions, 48.7 g (0.25 mol) of *tert*-butyl α-bromoacetate[4] and 19.6 g (0.3 mol) of activated zinc[6] were refluxed in 100 mL of dry tetrahydrofuran for 1.5 h. The solution was cooled, decanted into a dropping funnel, and added dropwise during 45 min, with stirring, to a solution of 41.7 g (0.17 mol) of *N*-phthalyl-L-leucinal[7] maintained at 0–5 °C. After an additional 30 min of stirring, the solvent was removed by distillation and the residue was refluxed in 200 mL of dry benzene for 5 h. The solvent was removed in vacuo, 200 mL of 2 N hydrochloric acid was added, and the solution was extracted with three 150-mL portions of ethyl acetate. The combined organic extracts were extracted with two 100-mL portions of 5% sodium bicarbonate. The basic extracts were acidified to pH 1 with hydrochloric acid and the product was extracted with two 100-mL portions of ether. The extracts were dried over sodium sulfate and evaporated to give 20.7 g (40% yield) of crude **8**. Deblocking was effected by refluxing the product (0.068 mol) with 2.3 g (0.068 mol) of 95% hydrazine hydrate for 1.5 h in 100 mL of ethanol. The solvent was removed in vacuo, the residue was stirred with 200 mL of 2 N hydrochloric acid, the phthalylhydrazide was filtered off, and the filtrate was evaporated to dryness. The residue was taken up into 200 mL of water and amino acid analysis of the solution indicated a quantitative yield in the deblocking step. The solution was applied to a 2.5 × 79 cm column of Dowex 50-X8 ion-exchange resin equilibrated with 0.1 M pyridine adjusted to pH 5 with acetic acid. Elution with this buffer yielded 11.5 g (38%) of the mixture **5**. The NMR spectrum agrees with that reported[2,8] for the 3*R*,4*S* and 3*S*,4*S* diastereomers and revealed a 45:55 mixture of the two: $[\alpha]^{21}_{365}$ −47.9° (Cl, H_2O) [reported[3] for 3*R*,4*S* and 3*S*,4*S* $[\alpha]^{21}_{365}$ −49° (Cl, H_2O)].

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.83; H, 9.77; N, 7.99. Found: C, 54.77; H, 9.68; N, 7.89.

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Registry No.—(3*R*,4*S*)-**5**, 49642-13-9; (3*S*,4*S*)-**5**, 49642-07-1; **6**, 64490-39-7; (3*R*,4*S*)-**8**, 64490-38-6; (3*S*,4*S*)-**8**, 64490-37-5; *tert*-butyl α-bromoacetate, 5292-43-3.

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Metal–Ammonia Reduction of *cis*-8,10-Dimethyl-1(9)-octal-2-one[1]

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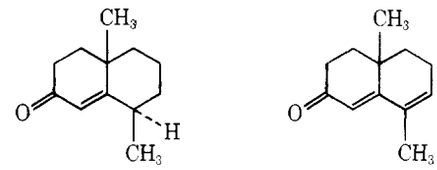
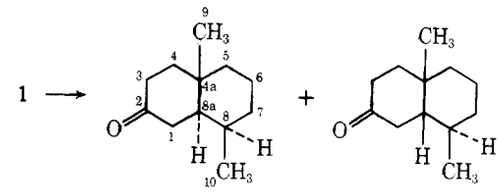
Recently, we reported the synthesis of *cis*-8,10-dimethyl-1(9)-octal-2-one (**1**) by transfer hydrogenation of the bicyclic dienone **2**.[2] The continued interest in the influence of substituents upon the metal–ammonia reductions of 1(9)-octal-2-ones[3] has prompted us to investigate the stereochemistry of the reduction of **1** with lithium and other metals in liquid ammonia.



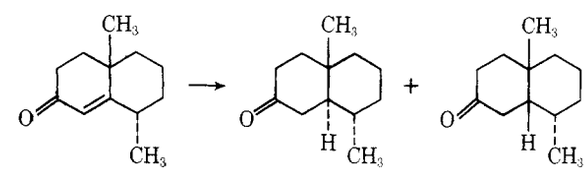
1 **2**

Reduction of **1** with lithium in liquid ammonia containing 1 equiv of *tert*-butyl alcohol under the usual conditions gave a 6.4:1 mixture of the known *trans*-decalone **3**[4] and an isomer which has been assigned the *cis*-decalone structure **4** in 85–91% yield. It was also found that catalytic hydrogenation of **1** using 10% paladium on carbon in 95% ethanol gave a 65:35 mixture of **3** and **4** in essentially quantitative yield.[5]



	3	**4**
Li/NH_3, ether, 1 equiv *t*-BuOH	87%	13%
H_2, Pd(C), 95% EtOH	65%	35%

In order to ascertain that isomerization of **1** into the thermodynamically more stable *trans*-octalone **5**[6] was not occurring prior to chemical (or catalytic) reduction, the latter enone was converted to the corresponding decalone derivatives. As expected lithium–ammonia reduction of **5** gave exclusively the *trans*-decalone **6**[4b] and a 5:95 mixture of **6** and the cis isomer **7**[7] was produced by catalytic hydrogenation of **5** in acidic 95% ethanol using 5% palladium on carbon as the catalyst. The isomeric decalones **3**, **4**, **6**, and **7** were readily separated from each other by GLC using a Carbowax column. Thus no significant isomerization of **1** into **5** occurred under either set of reduction conditions.[5]



5 **6** **7**

	6	**7**
Li/NH_3, ether 1 equiv *t*-BuOH	100%	—
H_2, Pd(c), 95% EtOH, HCl	5%	95%

The structural assignment of **4** is based upon the fact that