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A New Method for Hydroxymethylene Peptide Isostere Synthesis: Asymmetric Synthesis of Statine

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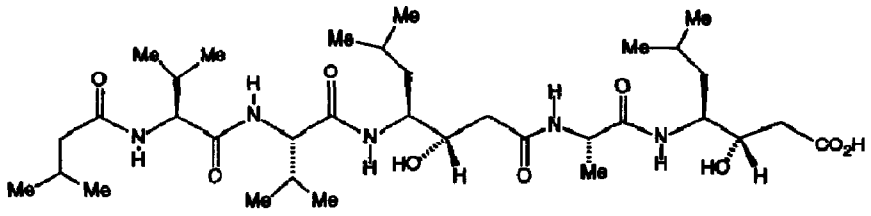
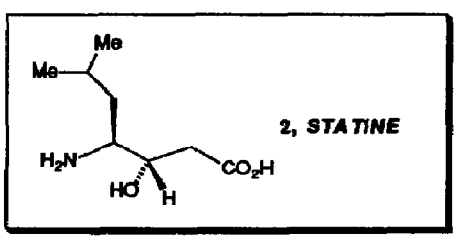
Abstract: *The asymmetric synthesis of (-)-Statine is described. The key step of the synthesis involves the coupling of hemi-acetal 6 with the ketene silyl acetal of methyl acetate.*

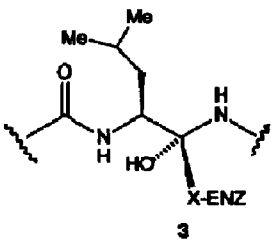
Since the discovery of pepstatin by Umezawa in 1970,[1] there has been a tremendous level of interest in the design and synthesis of non-scissile peptide mimics. Pepstatin (**1**) is a naturally occurring peptide produced by various *Streptomyces* sp. that was demonstrated [2] to be a potent inhibitor of aspartic proteases such as, pepsin, renin and cathepsin D. Pepstatin contains the unusual amino acid statine (**2**) which has become the prototypical hydroxymethylene isostere of the putative tetrahedral transition state (**3**) for peptide bond hydrolysis. Most syntheses of statine and related hydroxymethylene peptide isosteres utilize the natural amino acid (in the case of statine, leucine) as a starting material which is homologated by two carbons.[3] As part of a program aimed at significantly broadening the scope of functionality and stereochemistry that could be incorporated into the hydroxymethylene manifold, we report in this paper, a new and potentially very general method for constructing this class of peptidomimetics.



1, *PEPSTATIN*



2, *STATINE*

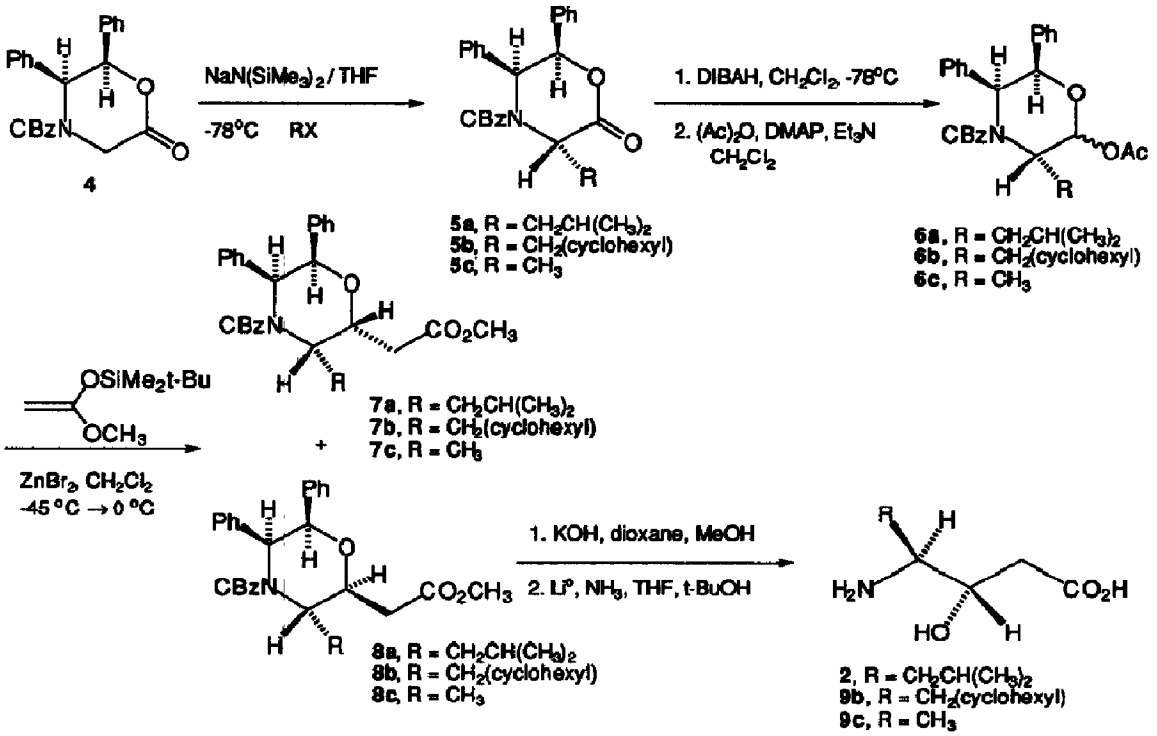


3

The method employed relies on the ready availability [4] of the alkylated oxazinones (**5**) that can be prepared from the commercially available [5] glycine templates (**4**). A wide variety of α-"R" groups can be introduced via

electrophilic and nucleophilic C-C bond-forming reactions on the lactones **4**. To illustrate this method, the synthesis of statine (**2**) and two related hydroxymethylene peptide isosteres (**9b** and **9c**) are reported herein. As shown in Scheme 1, the sodium enolate of optically active lactone **4** was alkylated with 1-isobutyl triflate to afford the alkylation product **5a** in 78% yield. [6] The *anti*-isomer (**5a**, shown) was the only diastereomer that

SCHEME 1



could be detected by ^{1}H nmr analysis. Reduction of the lactone carbonyl with diisobutylaluminum hydride (DIBAH) in methylene chloride at low temperature gave the corresponding lactol which was immediately acetylated with acetic anhydride in the presence of N,N-dimethylaminopyridine (DMAP) and triethylamine to give the hemi-acetal **6a** in 79% overall yield from **5a**. The acetates were formed (in all cases) as a roughly equimolar mixture of diastereomers and were used in the subsequent couplings as a mixture. [7] The t-butyldimethylsilyl ketene acetal [8] of methylacetate was condensed [9] with **6a** in the presence of zinc bromide in methylene chloride at -45 °C → 0 °C to furnish the separable coupling products **7a** and **8a** in a 1 : 4 ratio in 65% combined yield. The major diastereoisomer (**8a**) was shown to have the desired 2S,3S-stereochemistry by conversion into statine. Thus, hydrolysis of the methyl ester into the corresponding acid was accomplished with aqueous, methanolic KOH in dioxane; the crude acid was subsequently reduced with lithium in liquid ammonia to provide essentially optically pure (-)-statine (**2**) in 69% yield. The synthetic and authentic [10] materials were shown to be identical by ^{1}H nmr, mobility on HPLC and optical rotation.

Application of this method to other hydroxymethylene isosteres is also illustrated in Scheme 1. Table 1 summarizes the yields and diastereoselectivities for the synthesis of the methylcyclohexyl series (**5b-9b**) and the

methyl series (**5c-9c**). The diastereoselectivity of the ketenesilyl acetal coupling to the methylcyclohexyl derivative **6b** closely paralleled the level of selectivity observed for **6a**. However, the methyl derivative (**6c**) gave a preponderance of the *anti*-diastereoisomer **7c** over the *syn*-diastereoisomer **8c** (3 : 2 ratio). The change in diastereoselectivity can be rationalized by considering the conformations of the two relevant oxonium ions (**10a** and **10b**) that are presumably generated from **6** in the Lewis acid-mediated couplings.[7] In the isobutyl and methylcyclohexyl systems, the steric bulk of the branched side chain is envisioned to favor conformer **10a** which places the CH_2R' group in a pseudoaxial disposition and minimizes A-1,3 strain and 1,3-diaxial compression between the CH_2R' group, the carbobenzyloxy group and the C-5 ring methine, respectively (see **10a**); attack of the ketenesilyl acetal should proceed from the pro-(S) face. In the methyl system (**6c**), it appears that the equilibrium between the conformers (**10a / 10b**) is shifted to favor **10b** where, the less bulky methyl group adopts a pseudo-equatorial orientation and positions the C-6 phenyl ring axial and thus shielding the pro-(S) face from nucleophilic attack (Scheme 2).

SCHEME 2

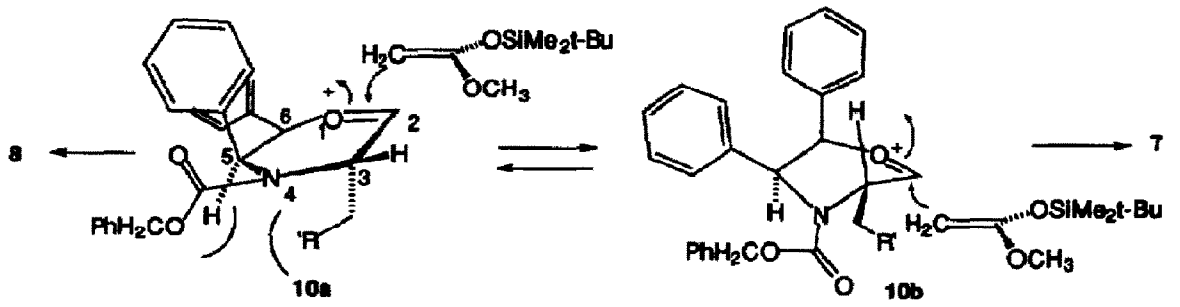


Table 1

Series	R	5 (%)	6 (%)	RATIO (7 : 8)	7 + 8 (%)	2 / 9 (%)
a	$CH_2CH(CH_3)_2$	75	82	1 : 4	58	69
b	CH_2(cyclohexyl)	70	85	1 : 4	75	82
c	CH_3	88	76	3 : 2	57	ND

Efforts are currently underway in these laboratories to further explore the utility of this approach to synthesizing a variety of hydroxymethylene, hydroxyethylene and related peptidomimetics in optically pure and stereodefined form; these studies will be reported on in due course.

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References and Footnotes

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2. a) Rich, D.H., *J.Med.Chem.* (1985) **28**, 263;b) Maibaum, J.; and Rich, D.H., *J.Org.Chem.* (1988) **53**, 869 and references cited therein; see also: Schuda, P.F.; Greenlee, W.J.; Chakravarty, P.K.; and Eskola, P. *J.Org.Chem.* (1988) **53**, 873; c) Morishima, H.; Takita, T.; Umezawa, H., *J. Antibiotics* (1973) **26**, 115; d) Rich, D.H.; Sun, E.T.; Boparai, A.S., *J.Org.Chem.* (1978) **43**, 3624.
3. For a review, see: Williams, R.M., in *"Biologically Active Peptides: Design, Synthesis and Utilization"*, Williams, W.V. and Weiner, D.B., Eds. Vol. 1, Chapter 8 (1993) Technomic Pub., Lancaster.
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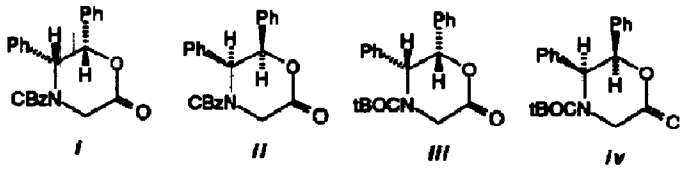
5. The requisite diphenyloxazinones utilized to prepare compounds **5** and stereochemical variants (*i - iv*) are commercially available from Aldrich Chemical Co.; *i*: catalog #33-185-6 (CAS Registry # 105228-46-4); *ii* catalog #33,187-2 (CAS Registry # 100516-54-9); *iii*: catalog #33-181-3 (CAS Registry # 112741-50-1); *iv*: catalog #33-184-8 (CAS Registry # 112741-49-8). We have not yet investigated this chemistry with the N-t-BOC compounds *iii* and *iv*; these studies are in progress.



I *II* *III* *IV*

6. 1-Isobutyl triflate was used for the preparation of **5a**; methylcyclohexyl triflate was used for the preparation of **5b**; see: Beard, C.D.; Baum, K.; Grakauskas, V., *J.Org.Chem.* (1973) **38**, 3673. Methyl iodide was used for the preparation of **5c**; see: ref. 4c.
7. Separation of the diastereomeric acetates (**6**) by silica gel chromatography, and subjecting each isomer separately to the coupling conditions gave the same ratio of diastereomers **7** / **8** as that obtained from the mixture; this observation has been interpreted as providing indirect evidence for the involvement of the oxonium ions (**10**) as the reactive electrophilic species.
8. Kita, Y.; Haruta, J.; Fujii, T.; Segawa, J.; Tamura, Y., *Synthesis* (1981) 451.
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10. An authentic sample of (-)-statine was purchased from Aldrich Chemical Co. Catalog # 34,823-6; Chemical Abstracts Registry # 49642-07-1.

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