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Addition of Allylic Metals to α-Aminoaldehydes. Application to the Synthesis of Statine, Ketomethylene and Hydroxyethylene Dipeptide Isosteres

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Summary: A general and stereoselective method to statine, ketomethylene and hydroxyethylene dipeptide isosteres is described. The key reaction is the diastereoselective allyl metal addition to α-aminoaldehydes.

Many potent inhibitors of proteolytic enzymes[1] have been designed by replacing the scissile amide bond in a substrate with a hydrolytically stable functionality, such as the statine or ketomethylene and hydroxyethylene isosteres.[2] Numerous synthetic methods to make these important isosteres have been reported,[3,4] but many are not sufficiently general and stereoselective, or else use chiral auxiliaries to achieve good stereoselection. New methods to synthesize these isosteres are needed since these are used to prepare potent inhibitors of therapeutically important aspartic proteinases,[1] e.g. HIV protease.[5] We report herein a stereoselective synthesis of a key intermediate that can be used to prepare statine and its analogs, and ketomethylene and hydroxyethylene isosteres, starting from commercially available N-protected α-aminoacids. The key reaction is the diastereoselective allyl metal addition to α-amino aldehydes.

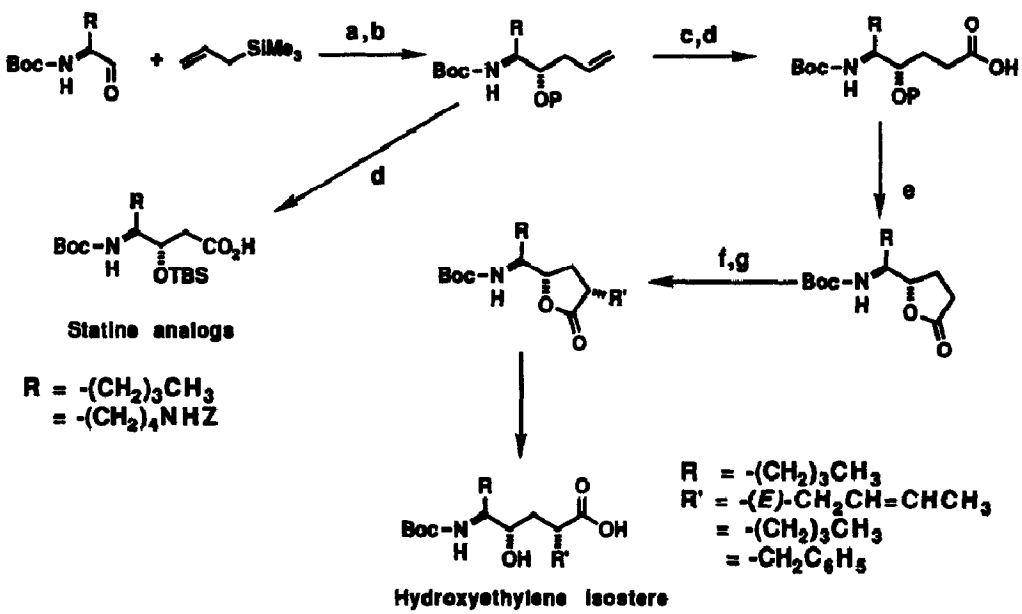
Condensation of allylic metals (e.g.; M: Si, Ti, Sn, B, Cr) with various carbonyl compounds can be used to achieve acyclic stereoselection[6], and has been applied to the synthesis of natural products.[7] Initially, we systematically examined the reaction of α-amino aldehydes[8] with achiral allylic metals to determine the diastereoselectivity of the reaction. The results are shown in Table I. Except for prolinal derivatives, diastereoselectivity[9] could best be achieved with allyltrimethylsilane in the presence of tin tetrachloride[10] (entries 1-4, and 7). Increased steric bulk in the protective group (entries 6 and 7) and in the R group (entries 7-10) gave better diastereoselection. Choice of Lewis acid is also important as noted by entries 3-6 and 11-13 . In all cases, the major product results from a chelation controlled reaction that gives mainly the threo isomer. In the case of Boc-prolinal, which does not add Grignard regent stereoselectively[11], the allyltrimethylsilane method gave good diastereoselectivity (entries 11-13). Titanium tetrachloride gave superior results to the use of tin tetrachloride.[10]

The diastereomerically pure homoallylic alcohols[12,13] were converted to statine analogs

(Scheme I) by protection as the TBS ether[14] followed by oxidation using a catalytic amount of ruthenium trichloride and sodium periodate[15].

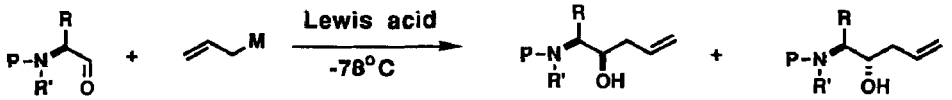
The pure homoallylic alcohol also could be converted to various hydroxyethylene isosteres. The hydroxyl group was protected as a silyl ether (TBS or TBDPS), and hydroboration followed by oxidation afforded the corresponding primary alcohol. This was oxidized under Sharpless conditions[15] to yield the acid, which upon treatment with methanolic hydrogen chloride or tetrabutylammonium fluoride gave the corresponding lactones in excellent yield. The lactones thus obtained were alkylated with allyl or benzyl bromide to form the corresponding alkylated lactones in excellent diastereomeric purities.[4b] These lactones can be converted to the corresponding hydroxyethylene acids by the procedures reported in the literature.[4a,4c] Work is in progress to extend this strategy to synthesize other types of hydroxyethylene dipeptide isosteres and protease inhibitors.

Scheme I:



Reaction Conditions: a) Tin tetrachloride, -78°C, 4h; b) *tert*-Butyldimethylsilyl chloride (P = TBS) or *tert*-butyldiphenylsilyl chloride (P = TBDPS), DMF, Imidazole, RT; c) BH_3-THF, RT, 3h followed by NaOH, H_2O_2, RT, 6h; d) $RuCl_3$-hydrate, $NaIO_4$, CH_3CN:CCl_4:H_2O 2:2:3, RT, 2h; e) 3N HCl in MeOH, RT, 1h or TBAF, THF, RT, overnight; f) lithium bistrimethylsilylamide, -78°C, 0.5h; g) *E*-crotyl bromide, or benzyl bromide, -78°C, 2h.

Table I. Reactions of α-Aminoaldehydes with Achiral Allylmetal Reagents[a]



P = Protective group; M = Metal

Entry	P	R	R'	Lewis Acid[b]	M	Ratio of diastereomers[c] Erythro/Threo(Yield)[d]
1	Boc	n-Bu	H	-	MgBr[e]	1 : 4
2	Boc	n-Bu	H	-	B-9-BBN	1 : 1.3
3	Boc	n-Bu	H	$TiCl_4$	$SnBu_3$	1 : 2.7
4	Boc	n-Bu	H	BF_3-OEt_2	$SnBu_3$	1 : 4.5
5	Z	n-Bu	H	$TiCl_4$	$SiMe_3$	1 : 3.4
6	Z	n-Bu	H	$SnCl_4$	$SiMe_3$	1 : 6.9 (77)
7	Boc	n-Bu	H	$SnCl_4$	$SiMe_3$	1 : 11 (80)
8	Boc	Bn	H	$SnCl_4$	$SiMe_3$	1 : 6 (65)
9	Boc	i-Bu	H	$SnCl_4$	$SiMe_3$	1 : 20.6 (68)
10	Boc	$(CH_2)_4NHZ$	H	$SnCl_4$	$SiMe_3$	1 : 10 (85)
11	Boc	$-(CH_2)_3-$		$BF_3.OEt_2$	$SnBu_3$	1.3 : 1
12	Boc	$-(CH_2)_3-$		$SnCl_4$	$SiMe_3$	1 : 2.8
13	Boc	$-(CH_2)_3-$		$TiCl_4$	$SiMe_3$	1 : 28 (63)[f]

[a]All the reactions were performed at -78°C and quenched with brine after 4 h. [b]Two equivalents of Lewis acid were used. [c]Determined by ^{1}H-NMR analysis of the corresponding acetonides. [d]Isolated yield after silica gel chromatography. [e]The Grignard reactions were initiated at -78°C, stirred at -78°C for 4 h; then slowly warmed to room temperature. [f]Taken from Ref.10.

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9. Diastereomeric ratio was determined by 300-MHz ^{1}H-NMR analysis of the corresponding acetonides. Acetonides are prepared by treating the homoallylic alcohols with p-toluene sulfonic acid in 2,2-dimethoxypropane. Moreover, stereochemistry of the products was independently established by decoupling ^{1}H-NMR experiments using a Bruker AM-300 NMR spectrometer. It was also found that the use of 2eq. of tin tetrachloride gave the best diastereoselectivity.

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