Acknowledgment. We acknowledge several important contributions to this work from Dr. Peter Lin, Dr. J. Venit, and Mr. Alan Adams. Financial support from the NIH and the Merck Corp. are gratefully acknowledged.

Supplementary Material Available: Experimental details of compounds and tables of the atomic positional and thermal parameters, bond distances and bond angles for 5 (14 pages). Ordering information is given on any current masthead page.

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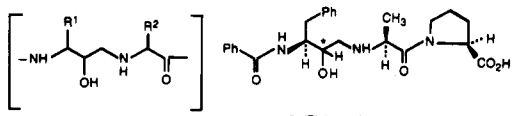
Synthesis of Peptide-Derived Amino Alcohols. 1. Potential Transition-State Inhibitors of Angiotensin Converting Enzyme

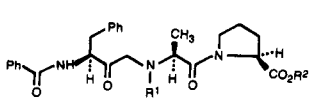
Summary: Synthetic methods and protection schemes were developed for "peptidyl amino alcohols" in which a novel "amino alcohol" design element is introduced into a peptide backbone to produce a new class of proteolytic enzyme inhibitors.

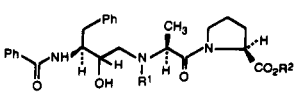
Sir: Recently we showed that a new "amino alcohol" design element, conceived to mimic the putative transition state of amide bond cleavage by proteolytic enzymes, could successfully be applied to the preparation of a new class of potent inhibitors of angiotensin converting enzyme (ACE).[1] The amino alcohol modification represented by 1 when integrated into the scissile bond position of substrates for ACE, such as *N*-benzoyl-Phe-Ala-Pro, gave rise to new series of ACE inhibitors that are typified by tripeptide amino alcohol **2** (I_{50} = 28 × 10^{-9} M). These structures provide the first examples of ACE inhibitors in which a hydroxyl group participates in an *essential* inhibitor/enzyme interaction.[2] Herein we describe newly developed chemical methodology useful in the synthesis of "peptidyl amino alcohols". Although we specifically describe the preparation of tripeptide-like ACE inhibitors, the fact that subunit 1 can be conveniently embedded in the form of a dipeptide surrogate within any peptide chain, offers the possibility of extending this inhibitor design concept to a variety of other proteolytic enzymes.



1

2 (R) I_{50}= 28 nM
3 (S) I_{50}= 10,000 nM





	R_1	R_2
4	-H	-benzyl
5	-H	-t-butyl
6	-Cbz	-benzyl
7	-Cbz	-t-butyl

	R_1	R_2
8	-H	-benzyl
9	-H	-t-butyl
10	-Cbz	-benzyl
11	-Cbz	-t-butyl

Reduction of amino ketones **4** or **5**[3-6] or the corresponding *N*-Cbz derivatives **6** and **7** (prepared from **4** and **5** by treatment with CbzCl/benzene/pyridine) with sodium borohydride in aqueous THF produced in high yield amino alcohols **8-11**, each as a pair of diastereoisomers. Deprotection of **10** $Pd(OH)_2/C$, H_2, HCl/EtOH) yielded the diastereisomeric pair of amino alcohols **2** and **3**. In order to ascertain the importance of hydroxyl stereochemistry on inhibitory potency, it was necessary to prepare each diastereoisomer **2** and **3** in pure form. Since the fully elaborated tripeptidyl amino alcohols **8-11** were not separable into pure isomers, other routes were investigated. Alkylation of L-Ala *tert*-butyl ester with *N*-benzamido chloro ketone **12**[6] followed by N-protection (CbzCl/benzene/pyridine) and ketone reduction ($NaBH_4$/aqueous THF) afforded alcohols **13** as a mixture of diastereoisomers (Scheme I), which were resolved by flash chromatography. Deprotection (TFA/CH_2Cl_2) of the C-terminal ester of either isomer of **13** did not produce desired acid **14** but led rather to lactone **15**. Hence, in order to derive pure **2** and pure **3** from **13**, a suitable hydroxyl protecting group is required to prevent lactonization. Deprotecting conditions applied to any OH blocking group must necessarily fall within the constraints of being orthogonal to the C-terminal ester employed.

Reconsideration of the protecting group problem suggested a new strategy which was implemented as follows. Reaction of L-alanine (trimethylsilyl)ethyl ester[7] with chloro ketone **12** gave an amino ketone, which was immediately treated with benzyl chloroformate (50%) and subsequently reduced ($NaBH_4$/aqueous THF/0 °C). This sequence produced **16** as a nearly equal mixture of diastereoisomeric alcohols that were separable by chromatography and, importantly, showed no tendency to form lactone **15** (Scheme II). Reaction of individual isomers **16A,B** with 2-methoxypropene/pyridinium 4-toluenesulfonate[8] (CH_2Cl_2) led to the *N*-acyloxazolidines **17**.[9] The oxazolidine system was expected to readily undergo acidic hydrolysis and thus might serve as a useful form of protection in construction of the amino alcohol inhibitor systems. Deesterification of **17** (*n*-$(Bu)_4N^+F^-$/DMF/<10 min) proceeded rapidly to give the desired acids in nearly quantitative yield.[7] Completion of the sequence was accomplished by coupling of **17** and L-proline benzyl ester (2-morpholinoethyl isocyanide/HOBT/THF (65%)[10]), hydrolysis of the oxazolidine ring of **18** (THF/HOAc/10% HCl (6:4:4), 1-24 h, 26 °C (90% yield)), followed by simultaneous removal of the Cbz and benzyl groups (H_2,

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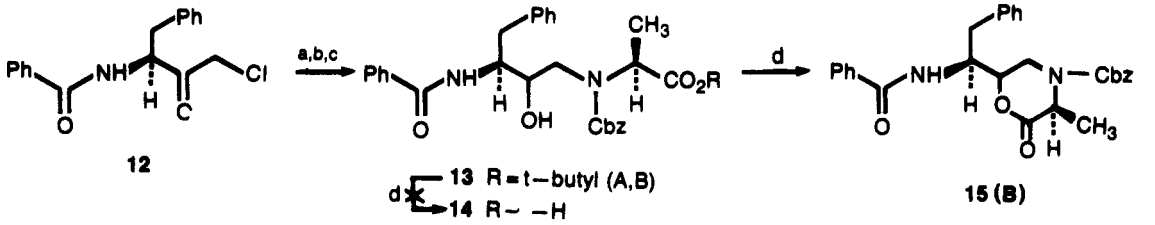
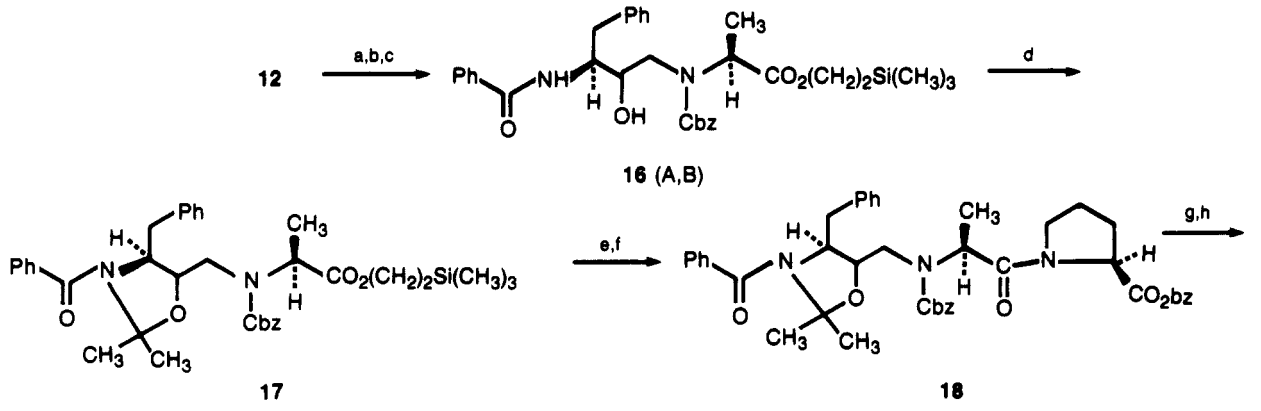
Scheme I[a]



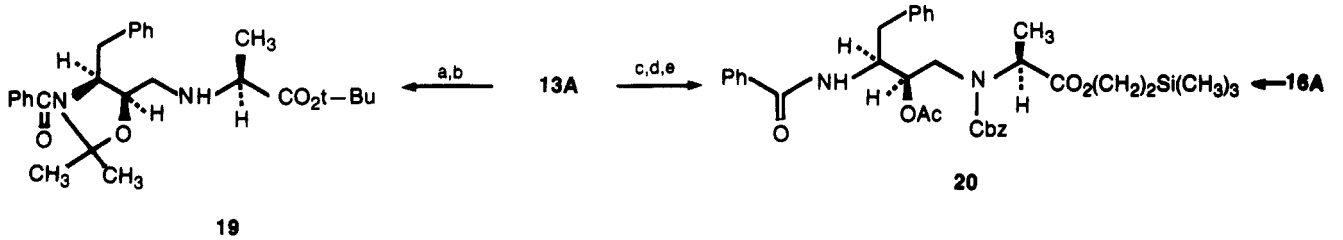
[a] (a) L-Ala-*tert*-butyl ester/DMF/NaI/$NaHCO_3$; (b) CbzCl/benzene/pyridine; (c) $NaBH_4$/THF/water; (d) TFA.

Scheme II[a]



[a] (a) L-Ala-$OCH_2CH_2Si(CH_3)_3$/DMF/NaI/$NaHCO_3$; (b) CbzCl/ benzene/pyridine; (c) $NaBH_4$/THF/water; (d) 2-methoxypropene/pyridinium 4-toluenesulfonate; (e) $(n\text{-butyl})_4N^+F^-$/DMF; (f) 2-morpholinoethyl isocyanide/L-proline benzyl ester: (g) THF/HOAc/10% HCl; (6:4:4), 25 °C; (h) H_2/Pd/C, HCl/EtOH.

Scheme III[a,b]



[a] (a) 2-Methoxypropene/pyridinium 4-toluenesulfonate; (b) H_2/$Pd(OH)_2$/C; (c) Ac_2O/DMAP/benzene/pyridine; (d) TFA/CH_2Cl_2; (e) trimethylsilyl ethanol/DCC/DMAP. [b] A series: β-OH, *R* series. B series: α-OH, *S* series.

Pd/C, HCl/EtOH (100% yield)) to afford pure peptidyl amino alcohol hydrochloride salts **2** ($[\alpha]^{25}_D$ −84.2° (*c* 1.13, CH_3OH)) and **3** ($[\alpha]^{25}_D$ −110.2° (*c* 1.12, CH_3OH)).

Analysis of compression effects in the ^{13}C NMR spectra of related oxazolidones[8] has been previously used to assign hydroxyl configuration in pepstatin analogues,[11] and analysis of ^1H NMR coupling constants was used to determine stereochemistry in 4,5-disubstituted 2-oxazolidones.[12] In the present case, NMR techniques did not lead to a definitive result. Hence the absolute configuration of the carbinol carbon which neighbors the chiral center derived from L-phenylalanine was determined by X-ray crystallographic analysis of pure diastereomer **19**, derived from **13A** as indicated in Scheme III.

In order to chemically relate the absolute configuration of **19** to amino alcohols **2** and **3**, a series of transformations were executed as shown in Scheme III. Substance **13A** was converted to **20** as shown. The product from O-acetylation (Ac_2O/DMAP/pyr/benzene) of diastereoisomers (**A,B**) of **16** indicated that isomer **16A**, the precursor to **2**, gave an acetate which was identical by spectral and physical means with **20** derived directly from **13A**. This establishes the absolute configuration of the hydroxyl bearing carbon of **2** as *R*.

The absolute configuration at the hydroxyl-bearing center was found to be crucial to inhibitory activity. In vitro assay of **2** and **3** revealed an approximately 400-fold difference in inhibitory potency between the two isomers (*R*, 28 nM; *S*, 10 000 nM).[1] This divergence must reflect important distinctions in the mode of binding of these substances with angiotensin converting enzyme.[4]

In conclusion, we have described a flexible chemical methodology for synthesis of peptidyl amino alcohols of type **2**, a new new class of ACE inhibitors. Similiar procedures, in which the N-terminal amide substituent is replaced by commonly used N-protecting groups have been employed to obtain peptide analogues possessing free N-terminal amino groups.[13] More recently, peptide chain extension from the N-terminal position of such intermediates has been applied to the preparation of a novel series

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of renin inhibitors.[14] Future reports will describe the application of this strategy to synthesis of inhibitors of other proteolytic enzymes.

Acknowledgment. We thank Dr. J. Gougoutas and Mary Malley for X-ray crystallographic determinations and the Squibb Institute Analytical Department for assistance in obtaining and interpreting spectral information.

Supplementary Material Available: Experimental data for **2**, **3**, **13A,B**, **15**, **16A,B**, **17A,B**, **18A,B**, **19**, and **20** (16 pages). Ordering information is given on any current masthead page.

* To whom requests for reprints should be sent.

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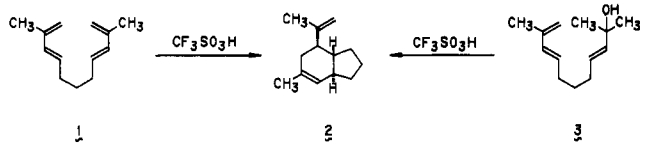
Control of Regiospecificity in Ionic Diels-Alder Reactions. The Use of Allylic Alcohols and Allylic Ethers as Precursors of Dienophilic Allyl Cations

Summary: Allylic alcohols and allylic ethers have been used as precursors of allyl cations in an intramolecular "ionic Diels-Alder reaction" in order to gain complete control of the regiochemistry of the cycloaddition.

Sir: Recently, we demonstrated that both intramolecular[2] and intermolecular[3] 2 + 4 cycloaddition reactions of allyl cations to 1,3-dienes could be accomplished at low temperature in high yield and with excellent stereospecificity.[4] This "ionic Diels-Alder reaction" is exemplified by the intramolecular cyclization of **1** to **2** in 88% yield using trifluoromethanesulfonic (triflic) acid as a catalyst. Due



1 2 3

to the symmetry of **1**, protonation of either diene produces the same allyl cation. However, in an unsymmetrical tetraene, a complication exists because the site of initial protonation, which determines which portion of the molecule becomes the allyl cation (dienophile), cannot be rigorously controlled. In order to circumvent this problem, we sought other precursors for the allyl cation portion of the intermediate leading to **2**. We now wish to report that intramolecular ionic Diels-Alder reactions may be accomplished in high yield, stereospecifically and regiospecifically, through the use of allylic alcohols or allylic ethers as specific allyl cation precursors.

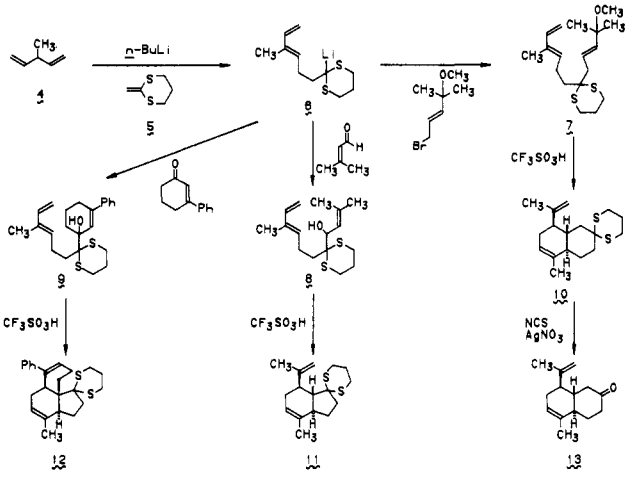
Table I. Yields and Reaction Conditions for the Intramolecular Ionic Diels-Alder Reaction of 7-9

substrate	catalyst,[a] mol %	conditions: temp, °C	conditions: time, min	product	% yield
7	12[b]	10	20	**10**	31
8	37[b]	25	15	**11**	56
9	5	−23	2	**12**	80

[a] The triflic acid catalyst was added as a freshly prepared solution in 1,1,2-trichlorotrifluoroethane. [b] The catalyst was added in three equal portions at 5-min intervals.

In order to establish the plausibility of our approach, we first studied the intramolecular cyclization of **3**.[5,6] As previously observed with **1**,[2] triflic acid was an excellent catalyst for cyclization. Treatment of a dilute solution of **3** in methylene chloride with 5 mol % of triflic acid for 20 min at −23 °C gave a 77% yield[6] of **2** (98% isomeric purity). Significantly, no hydroxylic products resulting from capture of water by the intermediate cations were observed.[4b,c] This confirmed the viability of using allylic alcohols as allyl cation precursors in the intramolecular ionic Diels-Alder reaction.

In order to demonstrate the versatility of our approach, a variety of substrates were synthesized and their cyclization was investigated. Treatment of 3-methyl-1,4-pentadiene (**4**) with *n*-butyllithium gave (3-methylpentadienyl)lithium.[9] Addition of 2-methylene-1,3-dithiane (**5**)[10] then generated **6**, which on subsequent addition of appropriate unsaturated electrophiles afforded **7**, **8**, and **9** in 74%, 74%, and 48% yields, respectively.[11,12]



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(5) Treatment of methyl (*E*)-7-oxo-2-heptenoate[7] with the ylide derived from methallyltriphenylphosphonium chloride[8] gave methyl (2*E*,7*E*)-9-methyl-2,7,9-decatrienoate (44% yield). Three successive treatments of this triene with methyllithium gave **3** in 89% yield.

(6) Satisfactory elemental analyses and exact mass molecular weights have been obtained on all new compounds. In all cases, ^1H and ^{13}C NMR and IR spectral data were consistent with the assigned structures.

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(11) This "one-pot" reaction sequence should have extensive utility outside of the examples cited herein.

(12) The *E* stereochemistry of **7-9** was assigned according to the literature methods: Cardenas, C. G. *Tetrahedron Lett.* **1969**, 4013.

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