C-2 and C-4 of both **3** and **4** were recorded at −40 °C. Next, the mixture of **3** and **4** was desilylated with methyllithium (−40 °C, 4 h), the solvent removed (0 °C, 10^{-6} torr), and the enolate mixture redissolved in THF-d_8, and the ^{13}C chemical shift values at C-2 and C-4 of the lithium enolates **1** and **6** were recorded at −40 °C. In the case of the ketene acetal (*Z*)-enamine **4** and its enolate analogue **6**, upfield shifts at C-2 of 13.2 ppm (75.7 to 62.6) and at C-4 of 4.9 ppm (106.4 to 101.5) were observed on conversion of **4** into **6**. In marked contrast, conversion of the ketene acetal (*E*)-enamine **3** into its lithium enolate **1** resulted in an upfield shift at C-2 of 11.3 ppm (74.5 to 63.2) while at C-4 only 0.9 ppm (92.4 to 91.5) of upfield shift was observed.[11] These data, with respect to the NMR time scale, support the notion that the (*E*)-enamine containing systems **3** and **1** are considerably twisted around the C-2–C-3 bond compared to the (*Z*)-enamine containing systems **4** and **6**.[12]

Interestingly, the aldol reactions of **1** occurred exclusively at C-4 and not at C-2 even though the electron density at C-2 was observed to be greater than at C-4 in the ^{13}C NMR. This called into question the pathway by which these aldol products were formed. Specifically, was the reaction at C-4 kinetic or thermodynamic, and was this condensation subsequent to a reversible aldol process at C-2?[13] We began to study this point by reacting **1** with an equivalent of isobutyraldehyde at −78 °C for periods varying from 15 s to 30 min. These reactions gave, in excellent yield, compounds **7** and **8**, which are C-4 aldol adducts that hold only anti geometry at C-4–C-5, differing as *E*/*Z* isomers about the C-2–C-3 olefinic moiety.[14] The condensation of **1** with pivalaldehyde also was examined. In this instance, the adducts **9** and **10**, as *E*/*Z* isomers possessing only anti geometry at C-4–C-5, were formed.

We were curious to see if the anti geometry at C-4–C-5 was maintained on cyclization of these adducts. This was examined in two ways; either by generating the adducts at −78 °C and allowing them to slowly cyclize at −78 °C or by raising the temperature, after 5 min, to 0 °C to allow rapid cyclization. The adducts **7** and **8** (*E*/*Z* isomers) cyclized under either protocol (90% yield) to give a 20:1 mixture of anti lactone **11** and syn lactone **12**, respectively. This is a detectable (^1H NMR) corruption of C-4–C-5 anti geometry during cyclization. More spectacularly, the adducts **9** and **10** cyclized at −78 °C to give an 18:1 ratio of anti lactone **13** and syn lactone **14**, while at 0 °C the ratio was 7.8:1.[15] These data indicate that the aldol reactions of **1** occur at C-4 to afford anti geometry via a kinetic process. However, lactonization of these adducts leads to some compromise of stereochemistry, presumably by a retro aldol process.[16]

The above data do not address the possibility that the C-4 reactivity observed for **1** could be preceeded by reversible aldol process at C-2 of the enolate. Hence, we condensed **1** with the aldehyde ester **15** feeling that the ester residue carried by **15** stood an excellent chance of intercepting the aldol generated alkoxide anion faster than the retro aldol process. The reaction of **1** with **15** (−78 °C) for periods ranging from 15 s to 1 h gave only the C-4 aldol adducts **16** and **17** (85% yield). **16** and **17** are *E*/*Z* isomers around the C-2–C-3 olefin, and in this instance it proved possible by ^1H NMR to demonstrate that the barrier for this isomerization was 15.0 kcal/mol (T_c = 331 K, THF-d_8).[17] We repeated the above experiment by adding [2.1.1]kryptand (1.0 equiv) to the enolate **1** followed by addition of **15**. A mixture of the C-4 aldol adducts **16** and **17** was isolated (35% yield) in this instance. Along with these C-4 adducts, a product, **18**, reflecting condensation at C-2, was isolated (35% yield), indicating that under certain conditions, reaction at this position of **1** can be realized.[18]

We are attempting to determine the role that the lithium counterion plays in the reactions of **1** in order to comprehend the mechanism by which this enolate undergoes the aldol process.

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Registry No. **1**, 102779-94-2; **2**, 102779-95-3; **3**, 102779-96-4; **4**, 102779-97-5; **5**, 102779-98-6; **6**, 102779-99-7; **7**, 102780-00-7; **8**, 102780-01-8; **9**, 102780-02-9; **10**, 102780-03-0; **11**, 102780-04-1; **12**, 102780-05-2; **13**, 102780-06-3; **14**, 102780-07-4; **15**, 51445-11-5; **16**, 102780-08-5; **17**, 102807-65-8; **18**, 102780-09-6; isobutyraldehyde, 78-84-2; pivaldehyde, 630-19-3.

(11) Methyl 3-pyrrolidino-2-butenoate could not be examined since it does not form a ketene acetal enamine, see: Chan, T. H.; Kang, G. J. *Tetrahedron Lett.* **1982**, *23*, 3011–3014.

(12) The species **4** and **6**, based on nonbonded interactions, are also twisted; however, the extent of twist in **4** and **6** must be less extreme than that observed for **3** and **1**.

(13) Reversible reactions at either C-2 or C-4 could result in *E*/*Z* isomerization of the enolate at the C-1–C-2 or C-3–C-4 bonds, rendering an accounting of the anti selective behavior of **1** futile. For appropriate examples, see: (a) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162. See also ref 16.

(14) The degradation sequence used to confirm anti geometry at the C-4–C-5 bond was similar to that described by: Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.

(15) Benzaldehyde was also examined and found to behave like pivaldehyde.

(16) To further demonstrate a retro aldol process, crossover experiments between pivalaldehyde and isobutyraldehyde were carried out. It was possible to exchange pivalaldehyde with isobutyraldehyde but not to exchange isobutyraldehyde with pivalaldehyde. Since this retro aldol process could have isomerized the (*E*)-enamine geometry of **1**, we conducted the following experiment to probe this possibility. **1** (1 equiv) in THF at −78 °C was treated with 0.5 equiv of pivalaldehyde. The reaction was brought to 0 °C, then cooled to −78 °C, and quenched with Et_3SiCl. After removal of the volatiles, the ^1H NMR of the residue was examined. Aside from **13** and **14** (7.8:1) and **2**, a Et_3Si-derived ketene acetal enamine was present. This substance possessed only (*E*)-enamine geometry and was identical with the ketene acetal enamine obtained by reacting **1** with Et_3SiCl.

(17) **16** and **17** exist as a 15:1 anti/syn mixture, respectively, of isomers at the C-4–C-5 bond. The anti/syn ratio obtained on reaction of **1** with butyraldehyde was 11:1.

(18) **18** arises on workup with aqueous NH_4Cl. The anti/syn ratio of **16** and **17** in this reaction changes from 15:1 to 2:1.

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An Enantio- and Erythro-Selective Lithium Enolate Derived from a Vinylogous Urethane: Its Application as a C_4 Synthon to the Virginiamycin M_2 Problem

Summary: A brief and efficient construction of the virginiamycin M_2 fragment **2** using an enantio- and erythro-selective lithium enolate derived from the vinylogous urethane **3** is described.

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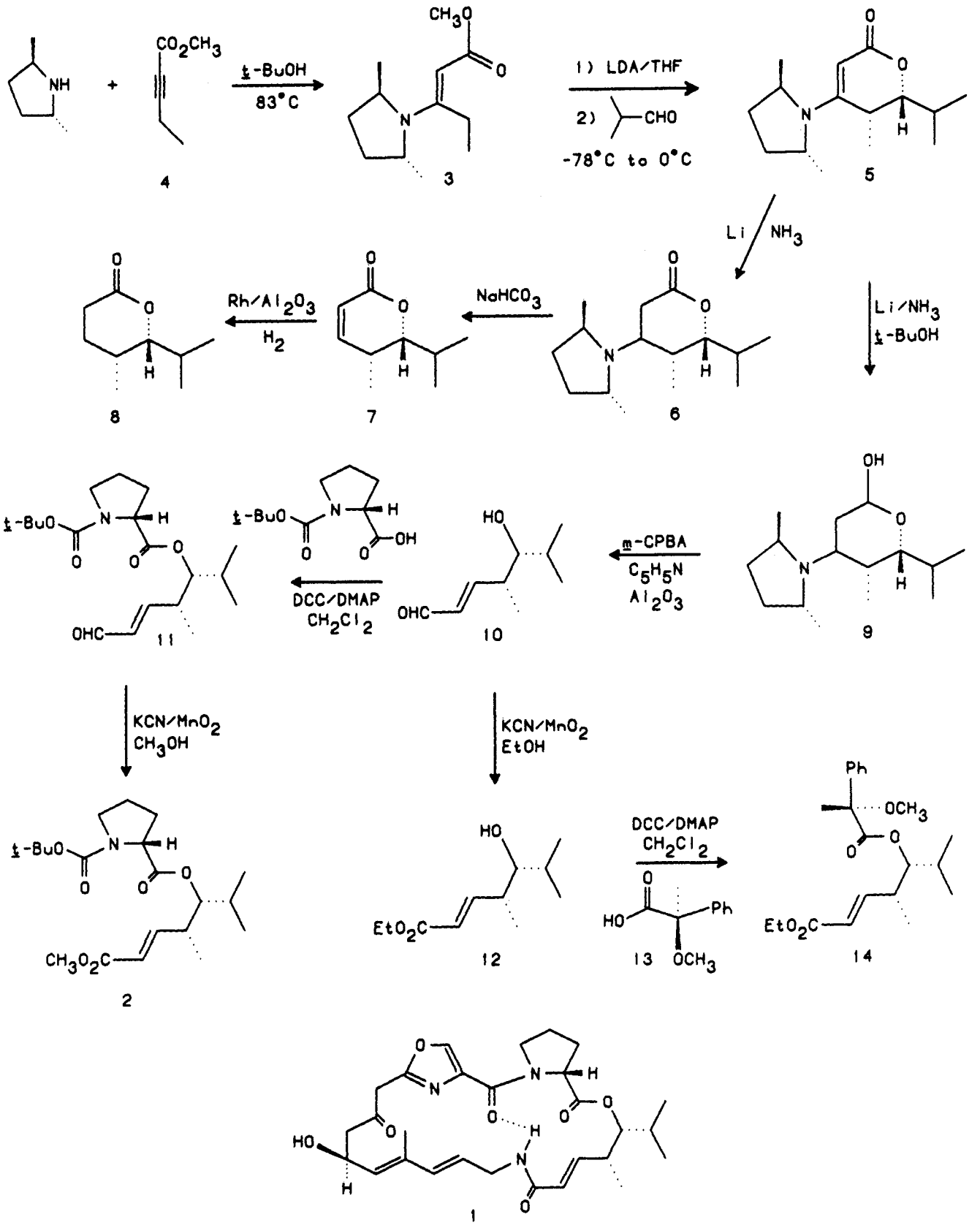
Sir: The virginiamycin family of antibiotics, personified by virginiamycin M_2 (1)[1] provide the chemist with a variety of interesting constructional tasks.[2] Within this context, we describe an efficient and brief preparation of the virginiamycin M_2 fragment, 2. This effort was facilitated by use of the vinylogous urethane 3, which as its lithium

Scheme I



(1) Bycroft, B. W. *J. Chem. Soc., Perkin Trans. 1*, 1977, 2464 and references cited therein.

(2) Meyers, A. I.; Spohn, R. F.; Linderman, R. J. *J. Org. Chem.* 1985, *50*, 3633 and references cited therein.

enolate, undergoes both an enantio- and erythro-selective aldol lactonization reaction with isobutyraldehyde.

(*R*)-(−)-2,5-Dimethylpyrrolidine,[3] in combination with the acetylenic ester **4** (*tert*-butyl alcohol, 83 °C, 5 h), afforded the vinylogous urethane **3** (90% yield) $[\alpha]^{22}_D$ +398.0° (*c* 2.0, CH_2Cl_2).[4] Deprotonation of **3** with lithium diisopropylamide (LDA) in THF solution at −78 °C generated the lithium enolate of **3**[5] which on reaction with isobutyraldehyde gave a single lactone product, **5** (86% yield), $[\alpha]^{22}_D$ +71.14° (*c* 2.0, CH_2Cl_2). This adduct, much to our gratification, was unambiguously demonstrated by X-ray analysis to possess erythro stereochemistry in the correct absolute configuration to permit its ultimate conversion into the substance **2**.[6]

The extent of enantiomeric selection accompanying the formation of **5** was evaluated in the following manner. Reduction of **5** with lithium in liquid ammonia afforded the β-amino lactone **6**. This substance was then treated with saturated aqueous $NaHCO_3$ to give the unsaturated lactone **7**, which it in turn was hydrogenated over rhodium on alumina (250 psi) to yield the saturated lactone **8**. Compound **8**, prepared from a natural source, has a rotation of $[\alpha]^{22}_D$ +96.0°;[7] whereas, a rotation of $[\alpha]^{22}_D$ +89.5° (*c* 2.0, $CHCl_3$) was observed for synthetically derived **8**.[8] This represents a 93% ee value for the synthetic lactone.

The preceding results permitted us to commence preparation of the virginiamycin M_2 fragment **2** from the lactone **5**. Reduction of **5** with lithium in liquid ammonia containing *tert*-butyl alcohol (10.0 equiv) gave (95% yield) the β-amino lactol **9**, $[\alpha]^{22}_D$ +1.27° (*c* 4.0, CH_2Cl_2). In one reaction vessel, this material was sequentially treated with *m*-chloroperbenzoic acid (1.05 equiv, 0 °C, THF, 3–5 min), followed by addition of pyridine (2.0 equiv, 22 °C, 5 min), and finally alumina (Super Grade 1, 40 °C, 2 h).[9] Filtration of the reaction mixture through a pad of silica gel gave a solution of the unstable aldehyde alcohol **10**, which after removal of the solvent was reacted with a mixture of *N*-(*tert*-butyloxycarbonyl)-D-(+)-proline (1.1 equiv), DCC (2.0 equiv), and DMAP (0.2 equiv) in CH_2Cl_2 solution (0–22 °C, 2 h) to give compound **11**, $[\alpha]^{22}_D$ +49.4° (*c* 1.0, CH_2Cl_2) in 60% overall yield from the lactol **9**. Finally, the aldehyde residue of **11** was converted (75% yield) into its corresponding methyl ester **2**, $[\alpha]^{22}_D$ +40.9° (*c* 2.0, CH_2Cl_2) by treatment of the aldehyde with a mixture of potassium cyanide (5.0 equiv) and manganese dioxide (20 equiv) in methanol solution (0 °C, 2 h).[10]

Careful ^1H NMR examination of **2** suggested this compound to be essentially one stereoisomer. We depict **2** in the indicated absolute configuration based on the observation that compound **5** leads not only to **2** but also, by a different pathway, to **8**.[7] To certify the stereointegrity of the synthetic route to **2**, we treated the aldehyde alcohol **10** with a mixture of potassium cyanide (5.0 equiv) and manganese dioxide (20.0 equiv) in ethanol solution (0 °C, 2 h) to obtain the unsaturated ethyl ester alcohol **12** in excellent yield. **12** was then esterified with the acid **13**[11] using DCC (2.0 equiv) and DMAP (0.2 equiv) in CH_2Cl_2 solution (0–22 °C) to afford **14**, also in excellent yield.

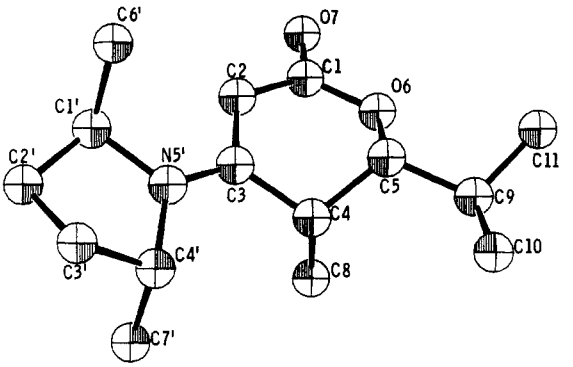


Figure 1. Computer-generated drawing of **5** derived from the X-ray coordinates with hydrogens omitted for clarity.

Compound **14** was carefully examined, via its ^1H NMR spectrum, and this spectrum in turn was compared to a published spectrum of **14**.[2] This comparison enabled us to confirm the absolute configuration of **14** to be as written. Further, we were able to determine that **14** was free of contamination by its threo analogue,[12] and, in addition, that it was formed in at least 93% optical purity. Since essentially the same reactions that lead to **14** also lead to **2**, we feel confident that **2** has the absolute configuration indicated and that it was formed with comparable diastereo and optical purity to that observed for **14**.

Starting from the acetylenic ester **4**, the reaction sequence resulting in the production of **2** requires six steps and proceeds in 33% overall yield, evincing the utility of the lithium enolate derived from **3** to be an effective enantio- and erythro-selective C_4 synthon.

X-ray Crystal Structure Analysis of 5. Suitable crystals of **5** ($C_{15}H_{25}NO_2$) for X-ray diffraction studies formed from hexane/ether mixtures with space group symmetry of $P2_12_12_1$ and cell constants of a = 7.348 (2) Å, b = 9.945 (1) Å, and c = 20.636 (4) Å for Z = 4 and a calculated density of 1.107 g/cm^3. Of the 994 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 900 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques.[13] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.044. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer generated perspective drawing of **5** from the final X-ray coordinates showing the correct stereochemistry.

(3) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. (b) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663.

(4) Satisfactory spectral and physical data were obtained for all new compounds reported herein.

(5) The structure and mechanism by which this enolate species reacts with aldehydes will be reported in the near future.

(6) For an example of the threo-selective analogue of this reaction, see: Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777 and references cited therein.

(7) Lactone **8**, +96.0°, from a natural source has been described by Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, D. G. I.; Sarin, P. S.; Todd, Lord; Williams, D. H. *J. Chem. Soc. C* **1966**, 1653.

(8) Lactone **8**, +56.0°, has been prepared by Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707.

(9) For a leading reference on amine oxide elimination reactions, see: Cram, D. J.; Sahyun, M. R. V. *J. Am. Chem. Soc.* **1963**, *85*, 1263.

(10) For a leading reference, see: Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(11) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

(12) This determination was possible due to the fact that the published spectrum of **14** was found by the authors of that paper (ref 2) to contain 5% of the threo isomer.

(13) The following library of crystallographic programs was used: MULTAN80, P. Main et al., University of York, York, England (1980); ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN (1970); SDP Plus 1.1, Y. Okaya et al., B. A. Frenz and associates, College Station, TX (1984).

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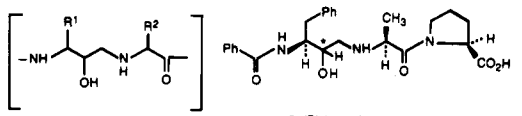
Synthesis of Peptide-Derived Amino Alcohols. 1. Potential Transition-State Inhibitors of Angiotensin Converting Enzyme

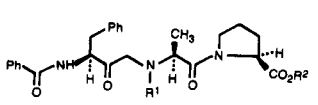
Summary: Synthetic methods and protection schemes were developed for "peptidyl amino alcohols" in which a novel "amino alcohol" design element is introduced into a peptide backbone to produce a new class of proteolytic enzyme inhibitors.

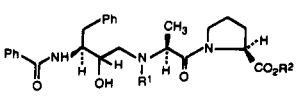
Sir: Recently we showed that a new "amino alcohol" design element, conceived to mimic the putative transition state of amide bond cleavage by proteolytic enzymes, could successfully be applied to the preparation of a new class of potent inhibitors of angiotensin converting enzyme (ACE).[1] The amino 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,

(1) Gordon, E. M.; Godfrey, J. D.; Pluscec, I.; Von Langen, D.; Natarajan, S. *Biochem. Biophys. Res. Commun.* **1985**, *126*, 419.
(2) Petrillo, E. W., Jr.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1-41.
(3) Natarajan, S.; Gordon, E. M.; Sabo, E. F.; Godfrey, J. D.; Weller, H. N.; Pluscec, J.; Rom, M. B.; Cushman, D. W. *Biochem. Biophys. Res. Commun.* **1984**, *124*, 141.
(4) Gordon, E. M.; Natarajan, S.; Pluscec, J.; Weller, H. N.; Godfrey, J. D.; Rom, M. B.; Sabo, E. F.; Engebrecht, J.; Cushman, D. W. *Biochem. Biophys. Res. Commun.* **1984**, *124*, 148.
(5) Natarajan, S.; Gordon, E. M.; Sabo, E. F.; Godfrey, J. D.; Weller, H. N.; Pluscec, J.; Rom, M. B.; Cushman, D. W.; DeForrest, J. M.; Powell, J. R., Presented at the Ninth American Peptide Symposium, Toronto, Canada, June 23-28, 1985.
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