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Bioorganic & Medicinal Chemistry Letters 14 (2004) 2853–2856
Bioorganic & Medicinal Chemistry Letters

Silanediol peptidomimetics. Evaluation of four diastereomeric ACE inhibitors

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Received 25 January 2004; accepted 16 March 2004

Abstract—Four diastereomers of a Phe-Ala peptide mimic incorporating a central silanediol group have been individually prepared and tested as inhibitors of angiotensin-converting enzyme (ACE). Three of the silanediols exhibit levels of inhibition that are similar to those of corresponding ketones reported by Almquist. For the fourth diastereomer, with both stereogenic carbons inverted relative to the most active isomer, the ketone gives the least enzyme inhibition whereas the silanediol shows a surprisingly low IC_{50} value.
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Silanediols are a new central subunit for design of protease inhibitors, replacing for the scissile amide carbonyl of the protease substrate. This nonhydrolyzable mimic of a carbonyl hydrate has been incorporated into several inhibitor structures, replacing ketone,[1,2] hydroxyl,[3] and phosphinic acid groups,[4] and the resulting structures have been effective inhibitors of both metallo and aspartic proteases. We report here the first set of silanediol structures, four diastereomers that are directly comparable to ACE inhibitor **2** and its diastereomers.

As a transition state analogue, the silanediol presents two hydroxyl groups corresponding to a hydrated amide carbonyl at the enzyme active site. In this way it is similar to a fluorinated ketone hydrate,[5–7] although slightly larger,[8] and comparable to a phosphinic acid,[9,10] but would not be ionized at physiological pH.[11,12] The first silanediol protease inhibitor **1** was assembled as an analogue of Almquist's ketone-based ACE inhibitor **2**.[13] While **1** was an effective inhibitor, direct comparison with **2** was difficult because it contained an isobutyl group where **2** has a benzyl group and was an inseparable mixture of four diastereomers (Fig. 1).

Inhibition of ACE is an established therapy for hypertension.[14,15] All commercial ACE inhibitors incorporate a group to interact with the active site zinc ion, such as the thiol found in captopril **3** or an anionic carboxylate or a phosphinate.[14] Ketone **2** presumably chelates the active site zinc as the tetrahedral hydrate,[5] with an IC_{50} of 1 nM,[13] and the silanediol was expected to act in the same way. Mixture **1** was found to inhibit ACE with a IC_{50} of 14 nM.[2] Presumably only one of the four diastereomers of **1** was responsible for most of this

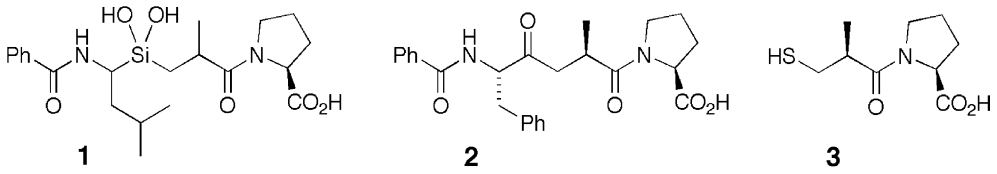

Figure 1. Three inhibitors of ACE.

Keywords: Protease; Inhibitor; Silane; ACE.
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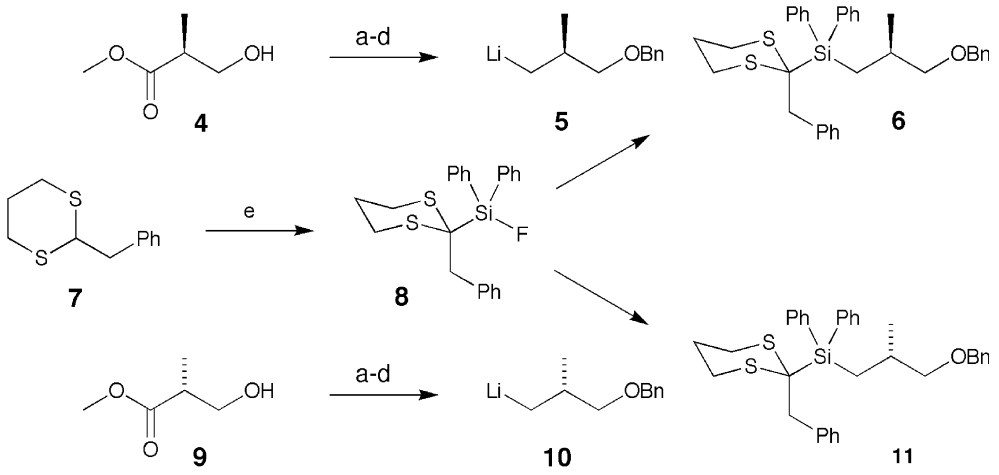
doi:10.1016/j.bmcl.2004.03.042

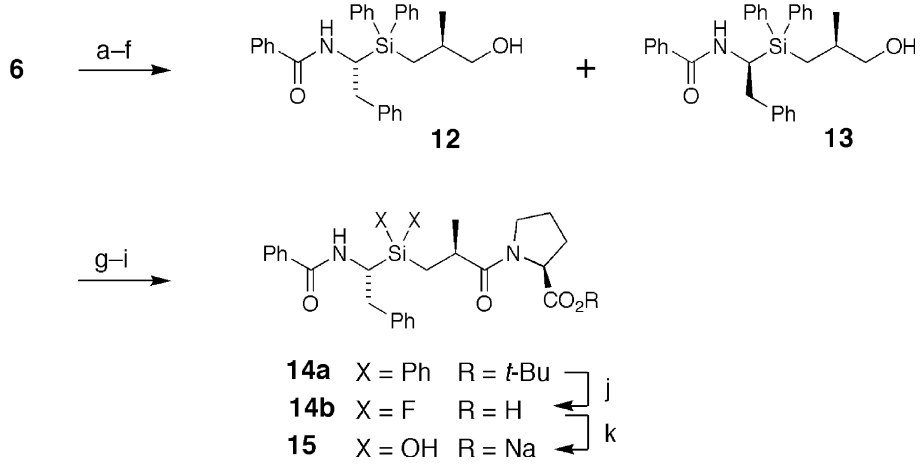


Scheme 1. Assembly of enantiomerically pure intermediates. Reagents and conditions: (a) $BnOC(NH)CCl_3$, TfOH, 0 °C; (b) $LiAlH_4$, 0 °C; (c) I_2, Ph_3P, imidazole, 0 °C; (d) 2 *tert*-butyllithium, −78 °C, **8**, to rt; (e) *n*-butyllithium, −78 °C, Ph_2SiF_2, to rt.

inhibition. The IC_{50} data for **1** and related silanols was consistent with an interaction with ACE in a manner similar to that of ketone **2**.[2] For example, replacement of one silanol of **1** with a methyl group (to give a methylsilanol) eliminated the enzyme inhibition. To probe this relationship further, we have prepared four silanediol diastereomers that more closely resemble **2**, inhibitors that could be directly compared to diastereomers reported by Almquist.

The synthesis of silanediol-based analogues of **2** was predicated on the use of a diphenylsilane as an acid-hydrolyzable silanediol precursor.[2,16] The synthesis of the diastereomers began with the commercially available (*S*)-3-hydroxy-2-methyl propionate **4** and its enantiomer (*R*)-**9**, Scheme 1. Following the method of White and Kawasaki,[17] the alcohol was converted to a benzyl ether with benzyl 2,2,2-trichloroacetimidate and triflic acid (82%), and the resulting ester was then reduced to an alcohol (87%). Conversion of the alcohol to an iodide with iodine and triphenylphosphine (85%) was followed by metal–halogen exchange at −78 °C using *tert*-butyllithium,[18,19] yielding lithium reagents **5** and **10**. These reagents were coupled with fluorosilane **8** to produce **6** and **11** (65%). Fluorosilane **8** was readily prepared by the reaction of difluorodiphenylsilane with the anion of 2-benzyl-1,3-dithiane **7**[20] (83%).

Elaboration of the dithianes **6** and **11** to the desired α-aminosilane groups was accomplished by hydrolysis of the dithiane to sensitive silylketones[21–23] (Scheme 2, 73%), which were then reduced with lithium aluminum hydride to give a 1:1 mixture of diastereomeric alcohols (quantitative). These diastereomeric mixtures were carried through several steps without separation: the alcohol was displaced with phthalimide using Mitsunobu conditions[24] (63%), followed by removal of the phthalimide with hydrazine; treatment with benzoyl chloride gave the benzamide (91%, two steps), and benzyl ether cleavage with boron tribromide led to the corresponding



Scheme 2. Synthesis of diastereomerically pure silanediols. Reagents and conditions: (a) $HgCl_2$, MeCN, H_2O, rt; (b) $LiAlH_4$, 0 °C; (c) PhthNH, Ph_3P, DEAD, 0 °C to rt; (d) N_2H_4, ethanol, reflux; (e) PhCOCl, $NaHCO_3$, 0 °C; (f) BBr_3, CH_2Cl_2, −78 °C to rt; (g) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-butanol; (i) L-proline-*O*-*tert*-Bu, DEPC, Et_3N, DMF; (j) (i) TfOH, CH_2Cl_2, 0 °C; (ii) NH_4OH; (iii) 48% HF; (k) 3 NaOH.

alcohols (90%). Separation of the diastereomers using standard column chromatography[25] was most readily accomplished after removal of the benzyl ether, giving stereochemically pure isomers **12**, **13**, and their enantiomers. The identity of **12** was secured by X-ray crystallography,[26] which thereby defined all four diastereomers, based on their origin from **4** and **9** and their chromatographic properties.

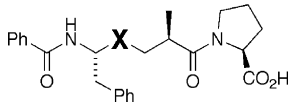
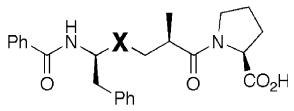
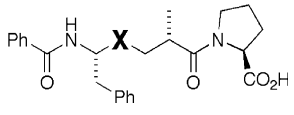
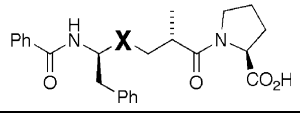
Oxidation of the alcohols to acids using TPAP[27] and sodium chlorite[28] (77%) was then followed by coupling with the *tert*-butyl ester of proline, yielding **13a** and the three other diastereomers (72–80%). With only deprotection of the ester and diphenylsilane remaining, we turned our attention to this final step. This hydrolysis is potentially problematic because of the well-known predilection of silanediols to undergo dehydration/polymerization, promoted by both acidic and basic conditions. Our original work utilized triflic acid for hydrolysis, followed by addition of ammonium hydroxide.[2,3] Ammonium hydroxide neutralizes the acid, provides water for silanediol formation, and ensures hydrolysis of any cyclized intermediates that may have resulted from amide participation in cleavage of the silicon–phenyl bonds. We found, during our preparation of a thermolysin inhibitor,[4] that including aqueous HF in the workup produced an isolable, monomeric difluorosilane intermediate, which subsequently undergoes a facile hydrolysis with aqueous base.

Treatment of **14a** and its diastereomers with 0.5 M triflic acid in methylene chloride at 0 °C for 1 h, followed by neutralization with ammonium hydroxide for 30 min, and then addition of 48% HF followed by evaporation gave a crystalline homogenous product (92%). When this difluoride in water was treated with 3 equiv of NaOH, both silyl fluorides rapidly hydrolyzed. Monitoring by ^{19}F NMR spectroscopy indicated that the conversion of the silyl fluorides to fluoride ion was complete within several minutes. The resulting silanediol carboxylate **15** and its diastereomers were monomeric, stable species, readily soluble in water.

Evaluation of the four silanediols was conducted using Holmquist's modification[29] of the enzyme assay described by Cushman and Cheung,[30] employing commercially available enzyme and fluorescent substrate.[31] For three of the silanediols, there is a close correlation of the IC_{50} data with the published values for the corresponding ketones, Table 1.[13] The most potent inhibitors, ketone **2**, and silanediol **15**, have the same absolute configurations. A similar relationship holds for diastereomeric ketones **16** and **18**, and their corresponding silanediols **17** and **19**. For these three inhibitor pairs, the relative potencies vary within a rather narrow range of 2.3–4.5, suggesting a similar mechanism of inhibition for the two structural types. Inverting the C2 stereogenic center of **15** to give **19** has a much greater effect (54x) than inverting the C5 stereochemistry (**17**, 5x).

Surprisingly, reversing both stereogenic centers of **2** and **15** gave very different results. Inhibition of ACE by ketone **20** is less effective by a factor of 3200 relative to ketone **2**, consistent with a mutually antagonistic effect of the two stereocenters. In contrast, the inhibition by silanediol **21**, relative to **15**, is reduced by only a factor of 20. Inverting the C2 and C5 stereochemistry is three times better than inverting only the C2 stereocenter. The anomalous level of inhibition of ACE by **21** may indicate that a conformation of this silane not accessible to the ketone can inhibit the enzyme, perhaps as a consequence of the longer C–Si bonds relative to C–C bonds and the slightly different bond angles surrounding a silanediol.[2] Tacke et al. have noted an attenuated effect

Table 1. Comparison of ketone and silanediol inhibitor IC_{50} values

X =			
	IC_{50} (nM), compound #		Relative potency
	1, **2**	3.8, **15**	3.8
	8.2, **16**	19, **17**	2.3
	46, **18**	207, **19**	4.5
	3200, **20**	72, **21**	0.023

of stereochemistry for biologically active organosilanes relative to comparable carbon systems.[32]

This study is the first assessment of the consequences of stereochemistry with a silanediol-based protease inhibitor. The most active silane **15** exhibits a good level of enzyme inhibition, and two epimers show the expected stereochemical dependence. Silanediol **21** has an unexpectedly low IC_{50} value, suggesting a special ability for the silanediol to adapt its conformation, a result that may become explicable with the very recent publication of an ACE crystal structure.[33] Additional studies are in progress.

Acknowledgements

Support for this research was provided by National Institutes of Health to whom we are grateful. We thank Dr. Patrick J. Carroll, University of Pennsylvania, for the crystal structure.

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26. Compound **12** crystallized in the monoclinic space group $P21/n$ with $a = 13.8822\ (8)\ \text{Å}$, $b = 8.4270\ (6)\ \text{Å}$, $c = 24.2031\ (14)\ \text{Å}$, $b = 92.353\ (5)\ \text{Å}$, $V = 2829.0\ (3)\ \text{Å}^3$. Final least squares refinement using 9016 unique reflections with $I > 3s(I)$ gave $R(R_w) = 0.0880$ (0.1810). This crystal structure will be reported elsewhere.
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