ORGANIC LETTERS

2002
Vol. 4, No. 16
2683−2685

A Concise Synthesis of Silanediol-Based Transition-State Isostere Inhibitors of Proteases

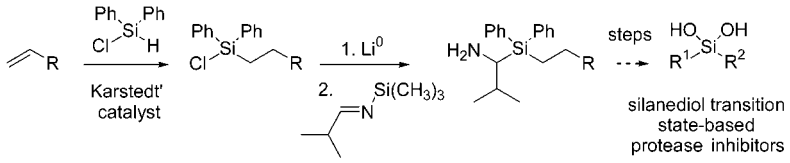
Michael G. Organ,*,† Christophe Buon,† Carl P. Decicco,‡ and Andrew P. Combs*,‡

The Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario M3J 1P3, Canada, and Discovery Chemistry, Bristol-Myers Squibb Company, Experimental Station, P.O. Box 80500, Wilmington, Delaware 19880-0500

organ@yorku.ca

Received May 16, 2002

ABSTRACT



An efficient synthesis of silanediol-based transition-state inhibitors of proteases is described. A new convergent synthesis has been optimized by using a two-step sequence of hydrosilylation followed by the addition of a silyllithio species to an imine. The method should be applicable to the synthesis of a wide variety of silanediol isosteres to probe the utility of this unique transition-state isostere.

Introduction. Medicinal chemists design and synthesize peptidiomimetic inhibitors to mimic the topography of the enzyme-bound peptide conformations in efforts to identify novel molecules with pharmacokinetic properties suitable for once-a-day oral dosing. The most common uses of peptidomimetics are as selective inhibitors of proteolytic enzymes (proteases).[1] There are four major classes of proteases: aspartic, serine, cysteine, and metallo. One approach to protease inhibition that has proven very successful is the incorporation of a non-hydrolyzable isostere of the tetrahedral intermediate of amide hydrolysis (Figure 1, structure **1**). Ketone or aldehyde hydrates (**2**) are examples which effectively mimic the tetrahedral intermediate, but such structures are often reactive and form undesirable covalent bonds with other nucleophilic species *in vivo*.[2] The hydroxyl group (**3**) has been incorporated successfully into many potent peptidomimetic inhibitors (norstatines, statines, cyclicureas, etc.) to alleviate this untoward reactivity.[3]

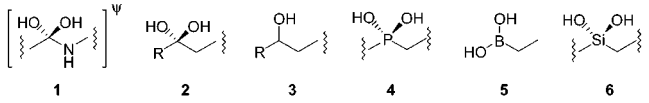


Figure 1. Representative peptide bond hydrolysis isosteres.

Other molecular structures that mimic the "geminal diol motif" (e.g., **4**, **5**, or **6**) have also been incorporated into peptide-derived peptidomimetics and also have been shown to serve as effective isosteres. Silicon in the form of a dialkylsilanediol (e.g., **6**) is a stable isostere providing the diol component is hindered enough to prevent siloxane polymer formation. In fact, it has been demonstrated recently that silanediol-based dipeptide analogues are potent inhibitors of metallo and aspartic proteases.[4] Compound **7** (Figure 2)

† York University.
‡ Bristol-Myers Squibb Company.

(1) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43* (3), 305−341.
(2) Sanderson, P. E. *Med. Res. Rev.* **1999**, *19*, 179−97.
(3) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45* (3), 541−558.
(4) McN. Sieburth, S.; Nittoli, T.; Mutahi, A.; Guo, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 811−814.

10.1021/ol026195s CCC: $22.00
Published on Web 07/13/2002

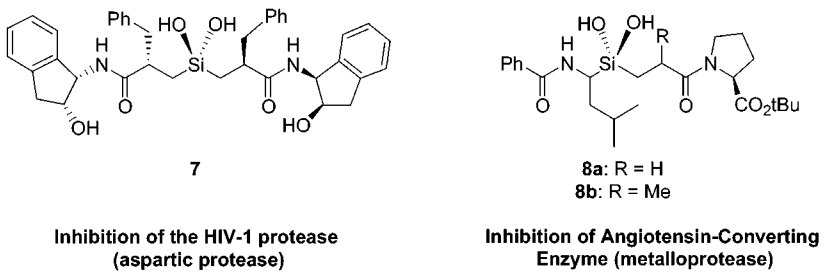
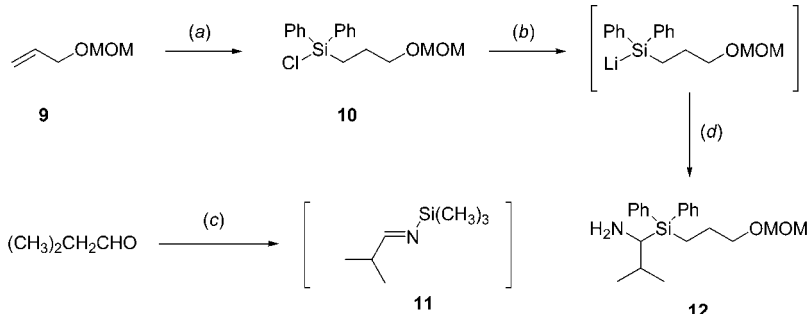


Figure 2. Silanediol-based inhibitors of proteases.

Scheme 1[a]



[a] Reagents and conditions: (*a*) $Ph_2(Cl)SiH$, Karstedt's catalyst, 65 °C (98% yield). (*b*) Li, THF, rt. (*c*) LHMDS, THF, −30 °C (used directly in *d*). (*d*) **11**, −78 °C (47% yield for steps *b*, *c*, *d*).

inhibits HIV protease with a Ki of 2.4 nM and isomeric mixtures of **8a** and **8b** were tested as ACE inhibitors (IC_{50} values, 57 and 14 nmol, respectively). On the basis of these results, we were encouraged to investigate the preparation of a library of such inhibitors to probe the binding sites of several proteases currently being investigated in our laboratories.

A review of the literature revealed that the existing synthetic route(s) to structures resembling **7** or **8** were long (11 or more steps) and contained difficult chemistry, too much so to consider adapting such routes to high-throughput synthesis.[4,5] The most common strategy for introducing silicon into an organic structure, that is to form a C−Si bond, is via an electrophilic silane species such as a chlorosilane. While simple allylsilanes can be prepared effectively by using allyl anion chemistry, more elaborate structures cannot as remote alkyl (sp^3) anions are not generated readily. Further, enolates *O*-silylate and dithiane-anion chemistry, while effective for the preparation of acylsilanes, is quite unpleasant to carry out, especially on a large scale. The route developed by Sieburth's group in fact employs both allylmagnesium bromide and a dithiane to desymmeterize difluorodiphenylsilane.[4]

We felt that a much more practical route could be realized if more complex structure could be added directly to the silicon atom, rather than adding simple units that have to be subsequently elaborated with a linear strategy. We have optimized a new convergent synthesis using a two-step sequence of hydrosilylation followed by the generation of a silyllithio species, i.e., nucleophilic silicon, and adding it to an imine.[6] The approach is quite general and thus should allow for the construction of a library of the desired silanediol peptide-derived peptidomimetics discussed above.

Results and Discussion. Hydrosilylation of allyl ether **9** with chlorodiphenylsilane and Karstedt's catalyst (Pt_2-$[(H_2C{=}CHSiMe_2)O]_3$)[7,8] proceeded very cleanly to provide chlorosilane **10** (Scheme 1). The reaction also proceeded well with methyl acrylate and with methyl 2-methylacrylate. The existing method used to generate 2-substituted amides (e.g., R = alkyl on structure **8**), which are required for protein recognition and tight binding, is to alkylate the prerequisite carboxylic acid derivative. This is an additional step that also runs the risk of over-alkylating and/or alkylating the amide on the opposite side of the molecule as well.

The addition of organolithium, organocopper, and Grignard reagents to the carbon of an imine is a useful method for the preparation of amines.[6] However, steric hindrance and the reduced electrophilicity of the imine carbon often

(5) Chen, C.; McN. Sieburth, S.; Glekas; A.; Hewitt, G.; Trainor, G.; Erickson-Viitanen, S.; Garber, S.; Cordova, B.; Jeffry, S.; Klabe, R. *Chem. Biol.* **2001**, *8*, 1161−1166.

(6) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Chem. Soc.* **1944**, *66*, 82−84.

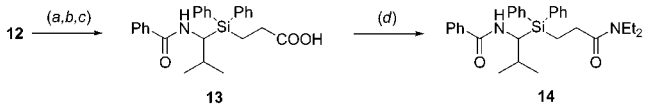
(7) Hitchcock, P. B.; Lappert, M. F.; Warhurst, N. J. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 438−440.

(8) Kuhnen, T.; Ruffolo, R.; Stradiotto, M.; Ulbrich, D.; McGlinchey, M. J.; Brook, M. A. *Organometallics* **1997**, *16*, 5042−5047.

combine to make this a difficult reaction. Despite these limitations, the one-pot synthesis of a primary amine resulting from the reaction between an organometallic compound and an *N*-silylimine[9] would eliminate several functional group manipulations and protection/deprotection steps while providing the requisite aminomethylsilane (**12**) directly. To this end, the silyllithium derivative was formed from chlorodiphenylsilane **10** that was quenched with silylimine **11**, which was itself prepared *in situ* by treatment of isobutyraldehyde with lithium hexamethyldisilylamide (LHMDS).[10] The preparation of any silanol typically requires that the hydroxyl groups be masked or protected along the synthetic route. Phenyl groups were selected for this purpose because of their ability to assist in stabilizing the intermediate silyl anion and the possibility of removing these groups at the end with a strong acid.[4]

Benzoylation of **12** provides a representative amide moiety on the left-hand side of the structure by substitution chemistry (**12a**). This same transformation can be effected by using condensation chemistry as well, thus broadening the synthetic flexibility. Amide formation was followed by deprotection of the methoxymethyl ether to provide **12b** and PDC oxidation of the resulting alcohol provided carboxylic acid **13** (Scheme 2). Condensation of **13** with diethylamine gave the silanediol precursor **14**.

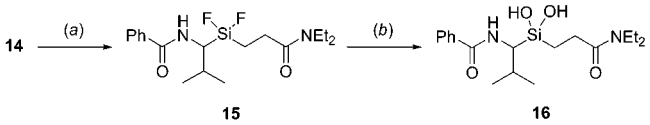
Scheme 2[a]



[a] Reagents and conditions: (*a*) PhCOCl, Et_3N, CH_2Cl_2, rt (68% yield). (*b*) HCl (cat.), MeOH, reflux (94% yield). (*c*) PDC, DMF, rt (63% yield). (*d*) Et_2NH, EDCI, CH_2Cl_2, 0 °C to rt (67% yield).

The phenyl protecting groups can be removed with triflic acid.[4,11] However, low, irreproducible yields for this reaction in our own hands encouraged us to seek an alternative method to liberate the silanediol.[12] Treatment of **14** with 50 equiv of BF_3·2AcOH[13] provided difluorosilane **15** in excellent yield (Scheme 3). Hydrolysis with potassium hydroxide in *i*PrOH[14] afforded the silanediol **16** in moderate yield

Scheme 3[a]



[a] Reagents and conditions: (*a*) BF_3·2AcOH, CH_2Cl_2, reflux (96% yield). (*b*) KOH, *i*PrOH, rt (35% yield).

(35%), but provided the product cleanly. The balance of the material in this transformation is simply returned difluoride. We are continuing our efforts to further optimize this deprotection.

In conclusion, a general and efficient method for the synthesis of silanediol-based transition-state isosteres has been developed. Noteworthy is the effective use of hydrosilylation to install the carboxyl-containing portion of the structure essentially intact and ready to diversify with a variety of amines. The choice to utilize a nucleophilic silicon species to effect Si−C bond formation on the amino side accomplished a number of goals. It eliminates the need to generate nonstabilized alkyl anions that are not only difficult to create, but to control the reactivity due to their strong basicity. Further, this approach allows for the one-pot incorporation of a variety of amines via the corresponding silylimine species. This strategy is currently being adapted to a parallel synthesis format for the preparation of a variety of silanediol peptidomimetics.

Acknowledgment. This work was funded by a research grant from the Ontario Research and Development Challenge Fund (ORDCF).

Supporting Information Available: Experimental procedures and spectral data for compounds **10**, **12**, **12a**, **12b**, **13**, **14**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026195S

(9) Leboutet, L.; Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1991**, *420*, 155−161.
(10) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 5369−5372.
(11) (a) Uhlig, W. *Chem. Ber.* **1996**, *129*, 733−739. (b) Bassindale, A. R.; Stout, T. *J. Organomet. Chem.* **1984**, *271*, C1−C3.
(12) For Tamao oxidation, see: (a) Tamao, K.; Kakui, K.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983−990. (b) Fleming, I.; Henning, R. R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317−337.
(13) Knölker, H.-J.; Jones, P. G.; Wanzl, G. *Synlett* **1998**, 613−616.
(14) Nakadaira, Y.; Oharu, K.; Sakurai, H. *J. Organomet. Chem.* **1986**, *309*, 247−256.