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# DESIGN AND SYNTHESIS OF NOVEL, PSEUDO *C2* SYMMETRIC INHIBITORS OF HIV PROTEASE

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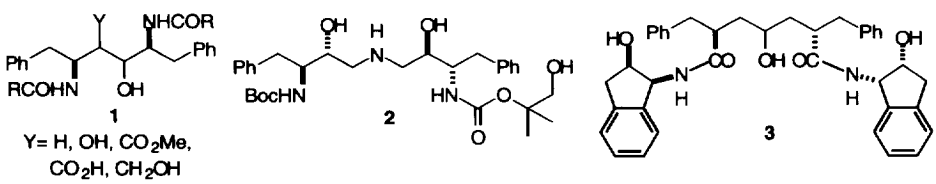
**Abstract**: A novel series of chain-extended, pseudo *C2* symmetric 1,5-diaminoalcohol analogs was designed and synthesized using an efficient nitroaldol condensation mediated by triethylsilyl triflate and TBAF.x$H_2O$. Prototypical acyclic compounds harboring a central spirolactam or a nitro group, and amide variants of an off-center 1,5-diaminoalcohol analog were synthesized and their activities against HIV protease evaluated.


Inhibition of HIV protease has become a strategically important and therapeutically viable approach toward the control of HIV infection.[1,2] Of particular relevance are the recently reported potent HIV protease inhibitors with *C2* and pseudo *C2* symmetrical structures, as exemplified by the Abbott diol **1** (Y = OH),[3a] the aminodiol **2**,[3b] several branched or chain-extended variants such as **1** (Y = $CO_2H$, $CO_2Me$, $CH_2OH$),[3c] and **3**[3d] (Figure 1). Capitalizing on recent methodology in stereocontrolled nitroaldol condensations of α-aminoaldehydes developed in our laboratories,[4] we extended our studies to the synthesis of the novel acyclic molecules illustrated in Figure 2.

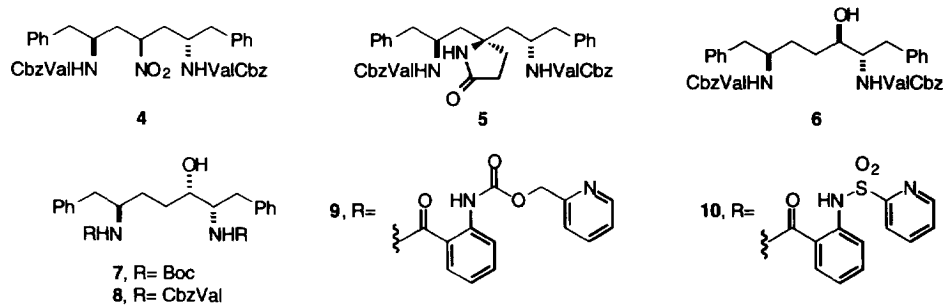
Figure 1




**Design considerations**: It has been suggested from X-ray crystallographic studies[3d] that the central unit (carboxyl, amino, etc.) in *C2* and pseudo *C2* symmetric inhibitors is involved in displacing a water molecule in the catalytic active site of the enzyme with the flanking units occupying two equivalent, hydrophobic S1 sites in a favorable binding interaction. It is also apparent that the enzyme shows some conformational flexibility in its binding modes allowing for manipulation in this central unit.

From a consideration of structures **1**, **2**, and **3**, it is evident that some latitude exists in the relative disposition of the hydroxyl group(s) and the aminoacyl units with regard to biological activity. The design of molecules **4-10** was predicated upon the inclusion of prototypical functional, stereochemical, and symmetry elements that could be conducive to the manifestation of HIV protease inhibitory activity based on data from related structures.

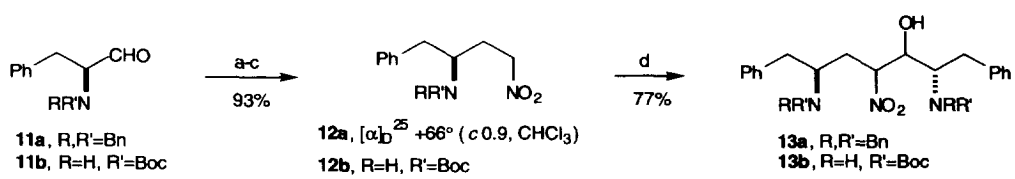
Figure 2




To the best of our knowledge, a nitro group has not replaced the central polar group in HIV protease inhibitors of the types shown in structures **1-3** (Figure 1). Although the nitro group can only be a H-bond acceptor in analog **4**, its influence, if any, on binding to the enzyme was of interest. The novel spirolactam **5** offers hydrogen-bonding donor and acceptor sites in a spatially unique position. The effect of an "off-center" hydroxy group in compounds **6-10** was of interest particularly with regard to any stereochemical preferences *vis-a-vis* the epimeric alcohols **6** and **8**. We chose to place a Cbz-valine moiety on the nitrogen atoms of compounds **4**, **5**, **6**, and **8**, given the marked improvement in activity of the Abbott diaminodiol HIV protease inhibitor **1** (Y = OH) when Boc groups were replaced by Cbz-valine.[3a]

**Synthesis**: N, N-Dibenzyl-L-phenylalaninal[5] **11a** was condensed with nitromethane[6] to obtain a mixture of *syn* and *anti* nitroalcohols (Scheme 1).[4]

Scheme 1




**11a**, R,R'=Bn
**11b**, R=H, R'=Boc

**12a**, $[\alpha]_D^{25}$ +66° (*c* 0.9, $CHCl_3$)
**12b**, R=H, R'=Boc

**13a**, R,R'=Bn
**13b**, R=H, R'=Boc

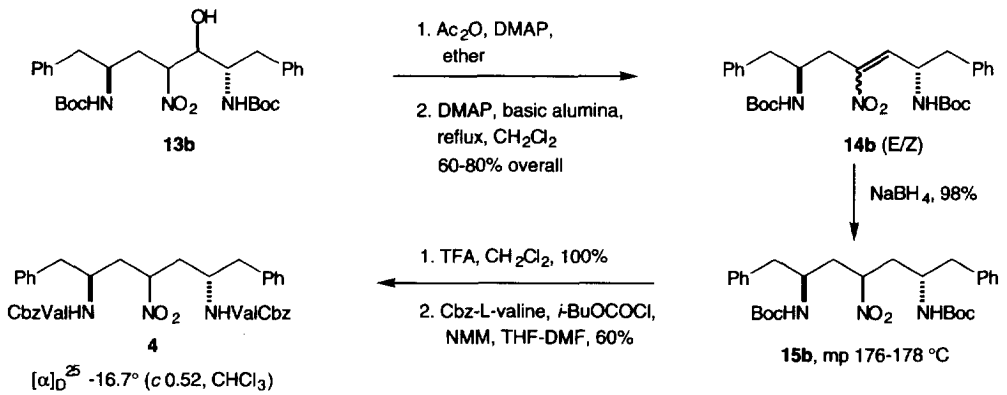
Conditions and yields for series **a**: (a) $CH_3NO_2$, TBAF.x$H_2O$, THF, 0 °C; (b) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C--> rt; (c) $NaBH_4$, $CHCl_3$:*i*-PrOH, silica gel; (d) For **13a**: **11a**, TBAF.x$H_2O$, TESOTf, $Et_3N$, THF, 0 °C--> rt, 1 h; For **13b**: **11b**, TBAF.x$H_2O$ (2 equiv), THF, 69% (see note 7); TBAF.x$H_2O$ was purchased from Aldrich Chemical Co.

This mixture was subjected to elimination first by mesylation and then reduction with $NaBH_4$ under Borchardt's conditions[8] to obtain nitroalkane **12a**. Compound **12a** was then condensed with aldehyde **11a** under triflate-mediated conditions as previously described[4] to afford a diastereomeric mixture of nitroalcohols **13a**. The condensation of two sterically hindered subunits **11a** and **12a** was best achieved under optimal conditions that required 1.5 equivalents of **11a** per mole of **12a** with one equivalent each of TBAF.x$H_2O$, TESOTf, and $Et_3N$.

The corresponding Boc-protected nitroalkane **12b** was synthesized under identical conditions in 55% overall yield. Best yields for the nitroaldol condensation between **11b** and **12b** were obtained in the presence of two equivalents of TBAF.x$H_2O$. The triflate-mediated protocol failed to give reasonable yields of **13b**

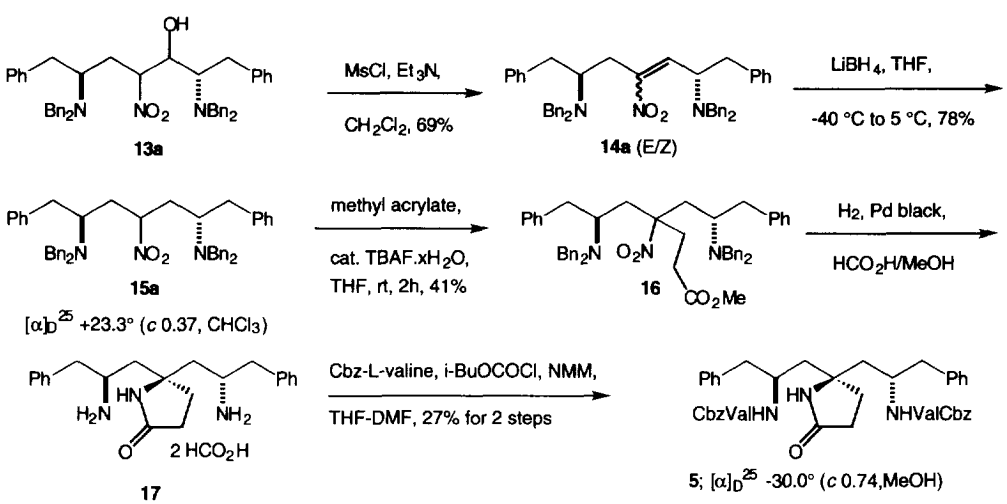
possibly due to the generation of triflic acid in situ under the reaction conditions resulting instead in cleavage of the Boc groups.

Scheme 2




The Schmidt–Rutz dehydration of **13b** under conditions modified by Ballini and Palestini[9] proceeded in good yields (Scheme 2). Subsequent reduction with $NaBH_4$ afforded the pseudo *C2* symmetric crystalline nitroalkane **15b** in 98% yield. This was quantitatively deprotected in the presence of $TFA/CH_2Cl_2$ and the product coupled under standard conditions[10] with Cbz-L-valine to afford analog **4** in 60% yield.

Scheme 3

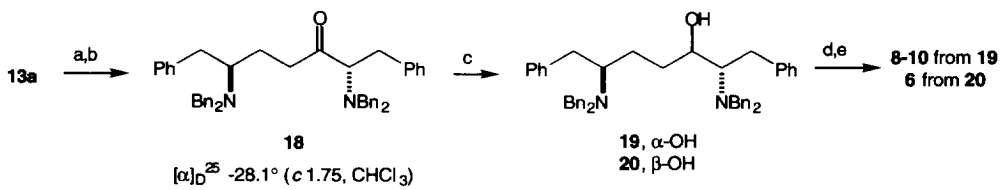



From a synthetic standpoint, the versatility of the nitro group is best illustrated in the synthesis of analog **5** (Scheme 3). Subjecting the nitroalcohol mixture **13a** to an elimination-reduction sequence yielded the pseudo *C2* symmetric nitrodiamine **15a**. Compound **15a** underwent smooth Michael addition[11] to methyl acrylate in the presence of a catalytic amount of $TBAF.xH_2O$ to give nitroester **16**. Reduction with Pd black in

the presence of formic acid[12] was accompanied by γ-lactamization to yield the spirolactam **17**. Functionalization of the amine groups in the usual manner afforded analog **5**.[13]

The hydroxypropyl-linked diamine analogs **6-10** were obtained from **13a** (Scheme 4). Swern oxidation of **13a** led to several side-products probably resulting from elimination to the corresponding nitroalkene. Dess–Martin oxidation,[14] on the other hand, led to the corresponding nitroketone in 90% yield.

Scheme 4




(a) Dess–Martin periodinane, $CH_2Cl_2$, 90%; (b) $Ph_3SnH$, AIBN, benzene, 56%; (c) $LiBH_4$, ether, rt, 6 h, 94% (3:1) or L-Selectride™, THF, -78 °C, 2 h--> rt, 12 h, 34% for 2 steps (>99:1); (d) $H_2$, Pd black, 10% $HCO_2H$/MeOH, 78%, ref 10; (e) Cbz-L-valine, BOP, DIEA, $CH_3CN$-DMF, 46% (yield for **8**)

Radical-induced denitration[15] was best accomplished using $Ph_3SnH$/AIBN. Complete *syn* selectivity in the reduction of ketone **18** was achieved with L-Selectride™ or $NaBH_4$ to obtain **19** based on literature precedents.[16] Alternatively, alcohols **19** and **20** were obtained as a 3:1 mixture (*syn*:*anti*) in 94% yield in the presence of $LiBH_4$. The α- and β-alcohols were easily separable by flash chromatography and they were individually subjected to debenzylation, and amide formation mediated by BOP/DIEA[17] to yield analogs **8-10**. For the synthesis of compound **6**, coupling was performed in the presence of i-BuOCOCl/NMM.[10] No epimerization was detected by HPLC during the coupling.

**Results and Discussion**: A preliminary biological evaluation of the novel compounds **4**, **5**, and **8** identified compound **8** as a subnanomolar inhibitor of HIV protease (Table 1). It displayed a potency equal to that of the Abbott standard A-77003[18] used in the assay. The lack of activity of compounds **4** and **5** may indicate that the nitro and the spirolactam groups do not serve as useful anchors in the active site. The off-center hydroxyl group in the chain-extended analog **8** has a beneficial effect, possibly as an effective site for H-bonding.

Recently, Randad et al.[19] published the synthesis of inhibitors of HIV protease containing anthranilamide P2/P2′ ligands with activities in the picomolar range. The 2-pyridylmethoxycarbonyl anthranil group was purported to enhance binding by H-bonding of amide NH of anthranilate with gly 48/148 and by additional P3/P3′ stacking interactions with the pyridine moiety along with water-mediated interactions of the pyridine nitrogens with the enzyme. Encouraged by the excellent inhibitory activity of **8**, we prepared the corresponding anthranil analog **9**. Furthermore, the 2-pyridylsulfonyl group[20] was placed on the anthranilate to probe the effect of a sulfonamide moiety in that region of the molecule.

As seen from Table 1, compound **9** ($IC_{50}$ = 14 nM) retained good inhibitory activity against HIV protease, although the anthranil ligands did not help enhance potency relative to the Cbz-valine derivative **8**. In light of a close structural resemblance between **9** and **10**, a complete loss of potency for analog **10** was unexpected. It is of interest that the (*R*)-alcohol **6** was found to be 400-fold less potent than the (*S*)-alcohol **8** (Table 1). The effects, if any, of epimeric alcohol analogs of **9** and **10**, were not studied.

Table 1

| Compound | $IC_{50}$ nM[a,b] |
|---|---|
| **A-77003** | <1 (57% at 0.5 nM) |
| **4** | 1500 |
| **5** | 2700 |
| **6** | 200 |
| **7** | 380 |
| **8** | <1 (62% at 0.5 nM) |
| **9** | 14 |
| **10** | >3000 |

a. For conditions of biological assays, see reference 18.

b. Average of 2-3 determinations.

**Conclusions**: A novel chain-extended series of HIV protease inhibitors has been synthesized using an efficient sequence involving nitroaldol reactions and manipulations of the nitro group. The most potent compounds in this set were analogs **8** and **9** with $IC_{50}$ values of 0.5 and 14 nM, respectively. Also, a comparison of the in vitro activities of diastereomeric alcohols **6** and **8** has revealed a clear preference for the *S* stereochemistry at the alcohol stereogenic center. It is evident that some flexibility in terms of number of atoms between the amine centers is tolerated as long as a hydroxyl group in the central region serves as a H-bonding anchor. Preliminary tests on **8** in a standard cell-based assay against HIV-$1_{3B}$ in MT4 cells showed <50% activity up to 100 μM, which may be due to its extremely low solubility in water. Further refinements in the structures of chain-extended motifs related to **8** with the objective of obtaining less hydrophobic analogs are a logical extension of this work.

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**References and Notes**

1. (a) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (b) Thaisrivongs, S. Chapter 14. *Annu. Rep. Med. Chem.* **1994**, *29*, 133. (c) Tomasselli, A. G.; Howe, W. J.; Sawyer, T. K.; Wlodawer, A.; Heinrikson, R. L. *Chim. Oggi* **1991**, *9*, 6. (d) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543. (e) Clare, M. *Perspect. Drug Discovery Des.* **1993**, *1*, 49. (f) Meek, T. D. *J. Enzyme Inhib.* **1992**, *6*, 65. (g) Norbeck, D. W.; Kempf, D. J. *Annu. Rep. Med. Chem.* **1991**, *26*, 141. (h) Lang, M.; Roesel, J. *Arch. Pharm.* (Weinheim, Ger) **1993**, *326*, 921. (i) Darke, P, L.; Huff, J. R. In *Advances in Pharmacology*; August, J. T.; Anders, M. W.; Murad, F., Eds.; Academic: San Diego, 1994; vol 25, pp 399. (j) Martin, J. A. *Antiviral Res.* **1992**, *17*, 265. (k) Debouck, C. *AIDS Res. Human Retroviruses* **1992**, *8*, 153.
2. Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A.; Scolnick, E. M.; Sigal, I. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 4686.
3. (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N.; Paul. D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W, Jr.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687. (b) Barrish, J. C.; Gordon, E.; Alam, M.; Lin, P.-F.; Bisacchi, G. S.; Chen, P.; Cheng, P. T. W.; Fritz, A. W.; Greytok, J. A.; Hermsmeier, M. A.; Humphreys, W. G.; Lis, K. A.; Marella, M. A.; Merchant, Z.; Mitt, T.; Morrison, R. A.; Obermeier, M. T.; Pluscec, J.; Skoog, M.; Slusarchyk, W. A.; Spergel, S. H.; Stevenson, J. M.; Sun, C-q.; Sundeen, J.

E.; Taunk, P.; Tino, J. A.; Warrack, B. M.; Colonno, R. J.; Zahler, R. *J. Med. Chem.* **1994**, *37*, 1758. (c) Ettmayer, P.; Hübner, M.; Billich, A.; Rosenwirth, B.; Gstach, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2851. (d) Bone, R.; Vacca, J. P.; Anderson, P. S.; Holloway, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 9382; Babine, R. E.; Zhang, N.; Jurgens, A. R.; Schow, S. R.; Desai, P. R.; James, J. C.; Semmelhack, M. F. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 541. (e) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenhouse, J. W.; Turon, M.; Wideburg, N.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul. D. A.; Knigge, M. *Science* **1990**, *249*, 527.

4. Hanessian, S.; Devasthale, P. V. *Tetrahedron Lett.* **1996**, *7*, 987.
5. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
6. For another example, see: Sasai, H.; Kim, W-S.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 6123.
7. All new compounds gave satisfactory $^{1}H$, $^{13}C$ NMR, MS, IR, CHN analysis or HRMS.
8. Sinhababu, A.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227.
9. Ballini, R.; Palestini, C. *Tetrahedron Lett.* **1994**, *35*, 5731.
10. (a) Meienhofer, J. In *The Peptides*, Gross, E.; Meienhofer, J., Eds.; Academic: New York, 1979; vol. 1, pp 263. (b) Chenera, B.; Boehm, J. C.; Dreyer, G. B. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 219.
11. Aebischer, B.; Bieri, J. H.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2251.
12. ElAmin, B.; Ananthramaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.
13. IR stretches for the carbonyls in ε-caprolactam and pyrrolidinone appear at ~1730 and ~1700 $cm^{-1}$, respectively. Compound **5** showed an IR stretch at ~1705 $cm^{-1}$ suggesting that γ- (and not ε) lactamization had taken place. For recent examples of γ-lactamization accompanying reduction of nitro groups, see (a) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Toke, L. *Tetrahedron Lett.* **1994**, *35*, 4413. (b) Chittari, P.; Thomas, A.; Rajappa, S. *Tetrahedron Lett.* **1994**, *35*, 3793.
14. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
15. Ono, N.; Fujii, M.; Kaji, A. *Synthesis* **1987**, 532.
16. Reetz, M. T.; Drewes, M. W.; Mathews, B. R.; Lennick, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1474.
17. Morelock, M. M.; Pargellis, C. A.; Graham, E. T.; Lamarre, D.; Jung, G. *J. Med. Chem.* **1995**, *38*, 1751.
18. Kempf, D. J.; Marsh, K. C.; Paul, D. A; Knigge, M. F.; Norbeck, D. W.; Kohlbrenner, W. E.; Codacovi, L.; Vasavanonda, S.; Bryant, P.; Wang, X. C.; Wideburg, N. E.; Clement, J. J.; Plattner, J. J.; Erickson, J. *Antimicrob. Agents Chemother.* **1991**, *35*, 2209; see also: Kempf, D. J.; Marsh, K. C.; Fino, L. C.; Bryant, P.; Craig-Kennard, A.; Sham, H. L.; Zhao, C.; Vasavanonda, S.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Green, B. E.; Herrin, T.; Norbeck, D. W. *Bioorg. Med. Chem.* **1994**, *2*, 847.
19. Randad, R. S.; Lubkowska, L.; Bujacz, A.; Naik, R. H.; Gulnik, S. V.; Yu, B.; Silva, A.; Munshi, S.; Lynch, T. M.; Clanton, D. J.; Bhat, T. N.; Erickson, J. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2557.
20. Hanessian, S.; Kagotani, M.; Koumaglo, K. *Heterocycles* **1989**, *28*, 1115.

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