Asymmetric Synthesis of Chiral Organofluorine Compounds: Use of Nonracemic Fluoroiodoacetic Acid as a Practical Electrophile and Its Application to the Synthesis of Monofluoro Hydroxyethylene Dipeptide Isosteres within a Novel Series of HIV Protease Inhibitors

Andrew G. Myers,* Joseph K. Barbay, and Boyu Zhong

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

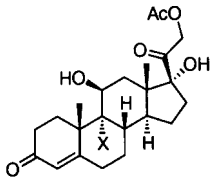
Received January 12, 2001. Revised Manuscript Received March 21, 2001

Abstract: Two stereoselective routes to a series of diastereomeric inhibitors of HIV protease, monofluorinated analogues of the Merck HIV protease inhibitor indinavir, are described. The two routes feature stereoselective construction of the fluorinated core subunits by asymmetric alkylation reactions. The first-generation syntheses were based on the conjugate addition of the lithium enolate derived from pseudoephedrine α-fluoroacetamide to nitroalkene **12**, a modestly diastereoselective transformation. A more practical second-generation synthetic route was developed that is based on a novel method for the asymmetric synthesis of organofluorine compounds, by enolate alkylation using optically active fluoroiodoacetic acid as the electrophile in combination with a chiral amide enolate. Resolution of fluoroiodoacetic acid with ephedrine provides either enantiomeric form of the electrophile in ≥96% ee. Alkylation reactions with this stable and storable chiral fluorinated precursor are shown to proceed in a highly stereospecific manner. With the development of substrate-controlled syn- or anti-selective reductions of α-fluoro ketones **44** and **45** (diastereomeric ratios 12:1−84:1), efficient and stereoselective routes to each of the four targeted inhibitors were achieved. The optimized synthetic route to the most potent inhibitor (**syn,syn-4**, K_i = 2.0 nM) proceeded in seven steps (87% average yield per step) from aminoindanol hydrocinnamide **40** and (*S*)-fluoroiodoacetic acid, and allowed for the preparation of more than 1 g of this compound. The inhibition of HIV-1 protease by each of the fluorinated inhibitors was evaluated in vitro, and the variation of potency as a function of inhibitor stereochemistry is discussed.

Introduction

The identification of potassium fluoroacetate as the toxic principle of the South African plant *Dichapetalum cymosum* in 1943 by Marais is often regarded as an important early discovery that directed attention to the potential of fluorine substitution to profoundly influence the biological activity of organic molecules.[1] Shortly thereafter, Fried reported the synthesis of 9α-fluorohydrocortisone acetate (**1**) and showed that it exhibited glucocorticoid activity 11 times greater than that of the corresponding hydrocarbon (cortisol acetate, **2**).[2] The enhanced activity has been attributed to the lower pK_a of the 11β-hydroxyl group and its increased ability to donate a hydrogen bond, as well as its increased resistance to metabolic inactivation by oxidation. Fried's discovery led to the development of at least six commercial antiinflammatory agents. More importantly, his demonstration of the extraordinary potential of fluorine substitution to alter and enhance the pharmacological properties of organic molecules became the basis of a powerful strategy for lead development in the pharmaceutical industry.

Because of the small size of the fluorine atom (van der Waals radius 1.47 Å versus 1.20 Å for hydrogen), replacement of a carbon−hydrogen bond with a carbon−fluorine bond does not typically present a major steric perturbation in a molecule. As a consequence of the unique physicochemical properties of fluorine (Pauling electronegativity 3.98 versus 2.20 for hydrogen), however, fluorine substitution can alter the metabolic stability, hydrogen-bonding capacity, lipophilicity, solubility, conformation, and even the fundamental structure of a molecule (e.g., the propensity of fluorinated ketones to hydrate), variations that can profoundly influence biological activity.[3] The importance of fluorine substitution in pharmaceutical development is evident in the large number of fluorinated compounds that have been approved by the FDA as drugs; fluorinated anticancer, antiviral, antibacterial, antidiabetic, antimalarial, antifungal, antidepressant, antipyschotic, antiinflammatory, and anesthetic agents, among others, are represented.[4]



1 X = F
2 X = H

Analysis of an electronic database of patented pharmaceutical substances reveals a surprising lack of structural diversity among

(1) Marais, J. S. C. *Onderstepoort J. Vet. Sci. Anim. Ind.* **1943**, *18*, 203.
(2) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455−1456.
(3) For reviews on the physical properties of fluorinated compounds, see: (a) Smart, B. E. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 979−1010. (b) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corporation: New York, 1994; pp 57−88.

10.1021/ja010113y CCC: $20.00
Published on Web 07/07/2001

the fluorinated pharmaceutical agents that have been developed in the 47 years since Fried's synthesis of 9α-fluorohydrocortisone acetate (**1**).[5] Among marketed fluorine-containing drugs (107 compounds), only eight contain a stereogenic (sp^3-hybridized) carbon atom bearing fluorine. Of these, six are 9α-fluorinated steroids, and the remaining two compounds, desflurane and enflurane, are fluorinated inhalation anesthetics marketed as racemic mixtures. It is likely that a major factor contributing to this lack of structural diversity is that there are few practical methods for the asymmetric synthesis of chiral organofluorine compounds. In particular, there are few methods to form carbon−carbon bonds to fluorinated, stereogenic carbon centers.[6]

Organofluorine compounds have been of particular importance in the development of inhibitors of carboxylic ester and peptide hydrolases.[7] Brodbeck first described the use of fluorinated aldehydes and ketones as inhibitors of hydrolases, demonstrating inhibition of acetylcholinesterase.[8] Subsequently, Abeles and co-workers showed that fluoroketones inhibited proteases operating by widely varying mechanisms; aspartyl proteases, zinc metalloproteases, and serine proteases were all inhibited.[9] They demonstrated that the fluoroketone inhibitors form stable tetrahedral intermediates by the addition of active-site nucleophiles to the electrophilic carbonyl and proposed that these adducts mimic the transition state for peptide hydrolysis.[10]

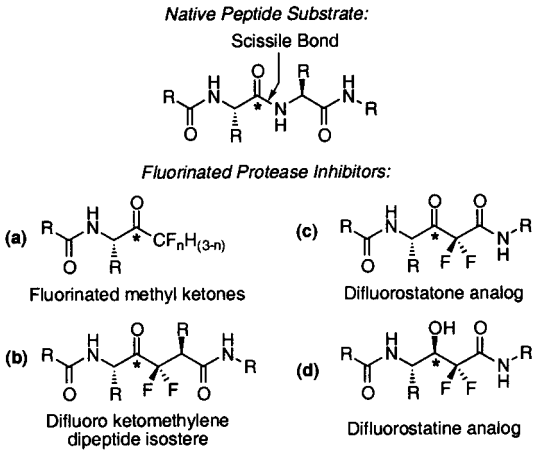


Figure 1. Examples of fluorinated peptidomimetic protease inhibitors.

Fluorinated methyl ketones, inhibitors containing the difluoroketomethylene dipeptide isostere, and difluorostatone and difluorostatine analogues are the most commonly studied classes of fluorine-containing protease inhibitors today (Figure 1). Protease inhibitors containing a fluorine-substituted stereogenic carbon atom have been less frequently studied.[11−14]

In an extension of our recent efforts to develop new methodology for the asymmetric synthesis of organofluorine compounds using fluorocarbon−carbon bond-forming reactions,[15,16] we sought to apply our methodology in the synthesis of a new class of structurally complex, fluorinated protease inhibitors, specifically, inhibitors of HIV protease. HIV protease is perhaps the most significant protease target in antiinfective therapy today. Its inhibition has been shown to extend the length and improve the quality of life of AIDS patients. The development and large-scale production of the stereochemically complex HIV protease inhibitor indinavir (Crixivan) by a team of Merck scientists is one of the great recent achievements in the pharmaceutical industry.[17] Fluorine substitution of the hydroxyethylene dipeptide isostere of indinavir is a logical consideration in the search for inhibitors with improved potencies and properties, but the indinavir structural platform illustrates well

(4) (a) Edwards, P. N. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corporation: New York, 1994; pp 501−541. (b) Ojima, I., McCarthy, J. R., Welch, J. T., Eds. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, 1996. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991. (d) Filler, R. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; pp 1−20. (e) For a review focusing on marketed pharmaceuticals, see: Elliott, A. J. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1119−1125. (f) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645−652.

(5) The ISIS/Base MDL Drug Data Report (MDDR-3D) database was searched for compounds containing a carbon−fluorine bond whose developmental phase was "Launched". ISIS/Base, Version 2.2; Molecular Design Ltd.; San Leandro, CA.

(6) For reviews and monographs on the asymmetric synthesis of chiral organofluorine compounds, see (a) Soloshonok, V. A., Ed. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; John Wiley and Sons Ltd.: New York, 1999. (b) Ramachandran, P. V., Ed. *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (c) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science Publishers: Amsterdam, 1998. (d) Percy, J. M. *Contemp. Org. Synth.* **1995**, *2*, 251−268. (e) Iseki, K.; Kobayashi, Y. In *Reviews on Heteroatom Chemistry*; Oae, S., Ohno, A., Okuyama, T., Eds.; MYU: Tokyo, 1995; Vol. 12, pp 211−237. (f) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (g) Percy, J. M. In *Organofluorine Chemistry: Techniques and Synthons*; Chambers, R. D., Ed.; Topics in Current Chemistry, Volume 193; Springer-Verlag: Berlin, 1997; pp 131−195. (h) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381−436. (i) Hayashi, T.; Soloshonok, V, A. (Guest Editors). Enantiocontrolled Synthesis of Fluoro-organic Compounds. *Tetrahedron: Asymmetry* **1994**, *5*, 955−1126. (j) Resnati, G. *Tetrahedron* **1993**, *49*, 9385−9445. (k) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661−692.

(7) A general review on protease inhibitors: (a) Rich, D. H. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, U. K., 1990; pp 391−441. (b) For a specific review on fluorinated inhibitors of aspartyl proteases, see: Sham, H. L. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; pp 184−195.

(8) Brodbeck, U.; Schweikert, K.; Gentinetta, R.; Rottenberg, M. *Biochim. Biophys. Acta* **1979**, *567*, 357−369.

(9) (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. (b) Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760−3767.

(10) (a) Liang, T.-Y.; Abeles, R. H. *Biochemistry* **1987**, *26*, 7603−7608. (b) Brady, K.; Wei, A.; Ringe, D.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7600−7607.

(11) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823−4826.

(12) (a) Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, *38*, 8469−8472. (b) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 4195−4198. (c) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126−132. (d) Hoffman, R. V.; Tao, J. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed. ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; pp 52−59.

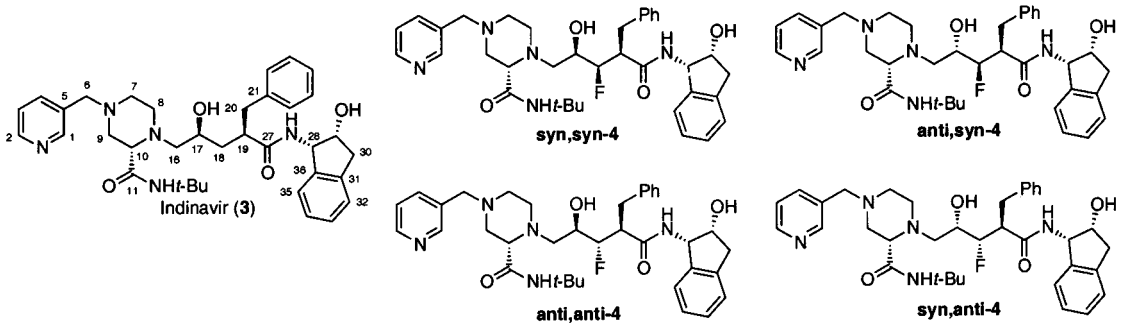
(13) (a) Welch, J. T.; Abudellah, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1005−1013. (b) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454−2462.

(14) (a) De Lucca, G. V.; Liang, J.; De Lucca, I. *J. Med. Chem.* **1999**, *42*, 135−152. (b) De Lucca, G. V.; Qi, H.; Jadhav, P. K.; Kassir, J. M.; Lam, P. Y.-S.; McHugh, R. J., Jr. Substituted Cyclic Ureas and Derivatives Thereof Useful as Retroviral Protease Inhibitors. Int. Pat. App. 97/08150, March 6, 1997.

(15) (a) Myers, A. G.; McKinstry, L.; Barbay, J. K.; Gleason, J. L. *Tetrahedron Lett.* **1998**, *39*, 1335−1338. (b) Myers, A. G.; McKinstry, L.; Gleason, J. L. *Tetrahedron Lett.* **1997**, *38*, 7037−7040. For the use of pseudoephedrine as a chiral auxiliary in asymmetric alkylation reactions, see: (c) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361−9362. (d) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(16) For other asymmetric fluorocarbon−carbon bond-forming reactions, see: (a) Less, S. L.; Handa, S.; Millburn, K.; Leadlay, P. F.; Dutton, C. J.; Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3515−3518. (b) Reference 13.

Chart 1



the difficulty inherent in the stereospecific introduction of single fluorine atoms within a complex target molecule: four diastereomeric monofluoro hydroxyethylene dipeptide isosteres are possible, and each represents a formidable and distinct synthetic problem (structures **4**, Chart 1).[18] We recognized the challenge that the synthesis of these targets represented and elected to develop asymmetric routes to each of the four monofluorinated indinavir analogues with the expectation that any viable solutions that emerged would hold promise for application in a more general sense.[19]

The proposed structures (**4**) raised interesting questions about the influence of the stereochemistry of the fluorinated center upon enzyme binding. In a first-order analysis, fluorine substitution of the hydroxyethylene dipeptide isostere of indinavir is expected to lower the pK_a of the hydroxyl group and thereby perhaps create a better mimic of the hydrated amide that is implicated in peptide bond cleavage.[20,21] The analysis quickly becomes complex, however, when factors are considered such as the differential solvation of free and enzyme-complexed inhibitors, the influence of fluorination upon conformational populations, potential steric and electronic interactions of the enzyme and fluorine atom, and the variation of these factors as a function of stereochemical changes at the fluorinated center. Ultimately, it was clear that the only meaningful analysis would be one based upon experimental findings.

In this work, we describe two successful approaches to the synthesis of each of the four targeted monofluorinated HIV protease inhibitors. These integrate two new methods for the asymmetric synthesis of fluorocarbon−carbon bonds, reported here for the first time. This methodology was used to prepare each of the diastereomeric indinavir analogues **4** in optically pure form, on a gram scale in the case of the most potent inhibitor, **syn,syn-4**. The variation of inhibitor potency as a function of inhibitor stereochemistry was evaluated and proved not to be straightforward, as discussed in detail.

Results and Discussion

Retrosynthetic Analysis. In analyzing routes to the targeted inhibitors **4** it was considered that the fluorinated stereogenic center, when coupled with the adjacent branched alkyl center of asymmetry, presented the most challenging aspect of the synthesis. The remainder of the molecule can be regarded as a largely solved problem in light of synthetic studies that have enabled the annual production of indinavir on the multi-ton scale,[22] work that has defined practical solutions for the asymmetric synthesis of (*S*)-2-*tert*-butylcarboxamide-4-*tert*-butoxycarbonyl-piperazine (**6**)[23] and (1*S*,2*R*)-1-aminoindan-2-ol (**8**)[24] and that has established the carbon−nitrogen bonds shown in Scheme 1 as convenient points of fragment assembly. By this analysis, the synthesis of the inhibitor **anti,anti-4**, for example, is reduced to the stereoselective construction of the fluorinated core structure **anti,anti-7**, or its synthetic equivalent. In retrosynthetic analysis of each of the core structures **7**, disconnection of the σ-bond that links the central stereogenic centers was an appealing and powerfully simplifying strategy. A primary synthetic goal, therefore, became the development of a method for the construction of this carbon−carbon bond, one that would allow for the simultaneous and selective formation of both stereogenic centers. In evaluating σ-bond-forming strategies for the formation of this strategic carbon−carbon bond, we considered applying asymmetric alkylation methodology. In theory, either half of the targets **7** can be viewed as evolving from enolate- or electrophile-derived

(17) (a) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096−4100. (b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443−3451.

(18) The stereochemical descriptors given in compound labels in this document refer to the stereochemical relationships in the central, variable stereochemical triad. The first descriptor indicates the relative configuration of the hydroxyl and fluorine substituents, while the second descriptor depicts the relationship of the fluorine and benzyl substituents.

(19) Analogues of indinavir containing the monofluoro ketomethylene dipeptide isostere were also targeted, see: Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425−428.

(20) For a review on the mechanism of peptide hydrolysis catalyzed by HIV protease, see: Meek, T. D.; Rodriguez, E. J.; Angeles, T. S. In *Retroviral Proteases*; Kuo, L. C., Shafer, J. A., Eds.; Methods in Enzymology, Volume 241; Academic Press: New York, 1994; pp 127−156.

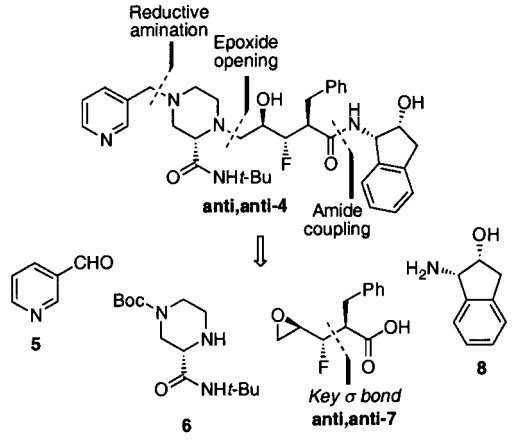
(21) For reviews on X-ray structures of HIV protease−inhibitor complexes, see: (a) Wlodawer, A.; Erikson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543−585. (b) Ringe, D. In *Retroviral Proteases*; Kuo, L. C., Shafer, J. A., Eds.; Methods in Enzymology, Volume 241; Academic Press: New York, 1994; pp 157−177. (c) Appelt, K. *Perspect. Drug Discovery Des.* **1993**, *1*, 23−48. (d) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472.

(22) For a discussion on the industrial process for the asymmetric synthesis of indinavir, see: Reider, P. J. *Chimia* **1997**, *51*, 306−308.

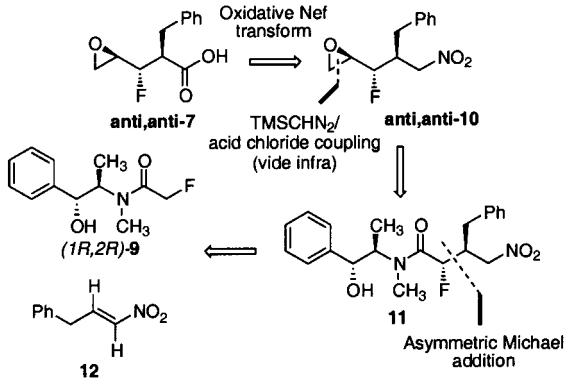
(23) (a) Askin, D.; Reider, P.; Rossen, K.; Varsolona, R. J.; Volante, R. P.; Wells, K. M. Process for Making HIV Protease Inhibitors. U.S. Patent 5,618,939, April 8, 1997. (b) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673−676. (c) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419−6422. (d) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823−6826.

(24) (a) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Frendenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993−3996. (b) Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; Fedenburgh, L. E.; Liu, J.; Roberts, F. E.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 3271−3274. (c) Larrow, J. F.; Roberts, E.; Verhoeven, T. R.; Ryan, K. M.; Senanayke, C. H.; Reider, P. J.; Jacobsen, E. N. *Org. Synth.* **1999**, *76*, 46−56.

Scheme 1



Scheme 2



components and, in practice, both strategies were pursued with success, this representing the fundamental distinction between the two routes described herein.

Synthesis of the Targeted Protease Inhibitors Based on Alkylation of Pseudoephedrine Fluoroacetamide. Initial investigations focused on construction of the vicinal stereocenters of the fluorinated core structure by the alkylation of pseudoephedrine α-fluoroacetamide (**9**)[15a,25] with a variety of electrophiles. The most direct route to the target structures using this chiral fluoroacetamide enolate would involve alkylation with a chiral, nonracemic secondary electrophile. A number of secondary electrophiles bearing α-activating groups were explored as potential alkylation substrates; unfortunately, in no circumstance were alkylation products isolated in yields greater than 6%, as a consequence of the poor reactivity of secondary electrophiles and the limited stability of this enolate above −40 °C. As an alternative strategy, an asymmetric Michael addition reaction was considered for the formation of the key *σ*-bond. The nitro compound **anti,anti-10** was envisioned as a potential precursor to the core structure **anti,anti-7** by application of an oxidative Nef transform (converting the carboxylic acid into a nitro group in the retrosynthetic direction, Scheme 2). The nitro compound **anti,anti-10** was considered to arise, ultimately, from the conjugate addition of the enolate derived from pseudoephedrine α-fluoroacetamide to the nitroalkene **12**.

(25) **CAUTION:** Fluoroacetyl chloride, fluoroacetic acid, and derivatives of fluoroacetic acid are exceedingly toxic, causing convulsions and ventricular fibrillation upon inhalation and should be used only under adequate supervision and in an appropriate fume hood. Although the specific toxicities of **9** and other fluoroacetate derivatives described herein are unknown, we urge that extreme caution be exercised in their preparation and handling.

Addition of the nitroalkene **12**[26] (1.2 equiv) to a cold (−78 °C) solution of the lithium enolate derived from either enantiomer of pseudoephedrine α-fluoroacetamide resulted in the rapid formation of conjugate addition products (Scheme 3). Spectroscopic analysis (^{1}H, ^{19}F NMR) of the crude reaction mixtures showed that just two stereoisomers had been formed in each reaction. It was later established that these isomers differed only in the configuration of the *β*-center (ratio anti:syn = 1.7:1); the α-center had been formed with a single configuration, with the same stereochemical preference as that found in pseudoephedrine enolate alkylation reactions using alkyl halides as electrophiles.[15d] The nitroalkene that was recovered from the product mixtures had undergone complete isomerization to the corresponding styrene, indicating that deprotonation of the electrophile competed with Michael addition. Nevertheless, the reaction was amenable to relatively large-scale implementation; on a 60-mmol scale, 15 g (65%) of the mixture of diastereomeric adducts **11** and **13** was obtained. Synthetically useful quantities of diastereomerically pure adduct **11** were obtained by recrystallization of the mixture of diastereomeric products, typically in 5-g batches (23% isolated yield).[27]

Hydrolysis of the amide **11** occurred smoothly at 75 °C in a mixture of 2 N aqueous sodium hydroxide, *tert*-butyl alcohol, and methanol (Scheme 4). Following protonation of the intermediate nitronate anion by the addition of glacial acetic acid,[28] the acid **14** was obtained in 98% yield (unpurified), without detectable epimerization of the fluorinated center. Conversion of the carboxylic acid **14** to the bromomethyl ketone **16** was accomplished in a two-step sequence involving formation of the diazomethyl ketone **15** (oxalyl chloride, catalytic DMF, CH_2Cl_2; trimethylsilyldiazomethane, THF), followed by treatment of this intermediate with hydrobromic acid.

Reduction of bromo ketone **16** with sodium borohydride (EtOH, −78 °C) afforded the anti-fluorohydrin **anti,anti-17** selectively, in 75% yield after chromatographic isolation (diastereoselectivity 9.4:1). The stereoselectivity of the reduction is interesting and merits brief comment. The Anh−Eisenstein model for nucleophilic addition to carbonyl compounds with an adjacent polar group would have predicted the opposite stereochemical outcome; this model invokes a Felkin-type transition structure[29] with the strongest acceptor ligand (in this case fluorine) oriented antiperiplanar to the forming bond (Scheme 4).[30,31] Thus, in the case of α-fluoro ketones, this model predicts preferential formation of syn-fluorohydrins, which was not observed. A careful examination of reductions of α-fluoro ketones reported in the literature,[32] as well as of the data presented herein, fails to reveal any compelling evidence to support the dominance of an Anh−Eisenstein transition structure in the reduction of α-fluoro ketones and suggests that the stereochemical outcome is strongly dependent upon the reductant used and upon subtle features of the substrate. In practice,

(26) (a) Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929−1935. (b) Hass, H. B.; Susie, A. G.; Heider, R. L. *J. Org. Chem.* **1950**, *15*, 8−14.

(27) The stereochemistry of *ent*-**11** was established by X-ray crystallographic analysis—see the Supporting Information.

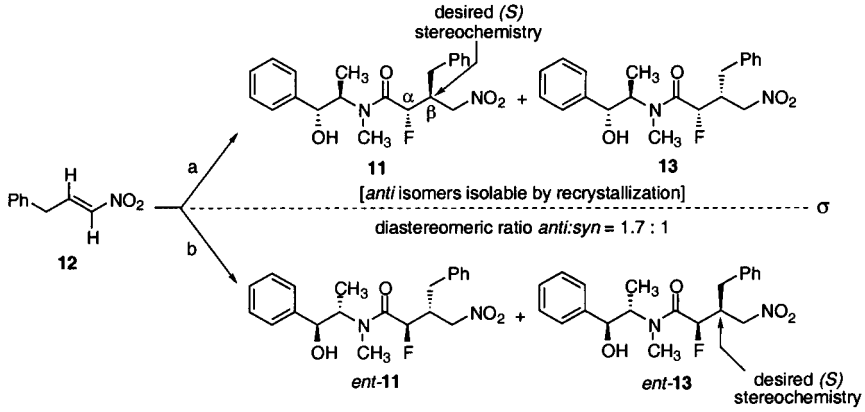
(28) Acetic acid has been demonstrated to be an effective reagent for the regeneration of nitroalkanes from their nitronate salts without significant competing Nef reaction: Kornblum, N.; Graham, G. E. *J. Am. Chem. Soc.* **1951**, *73*, 4041−4043.

(29) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199−2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205−2208.

(30) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61−70.

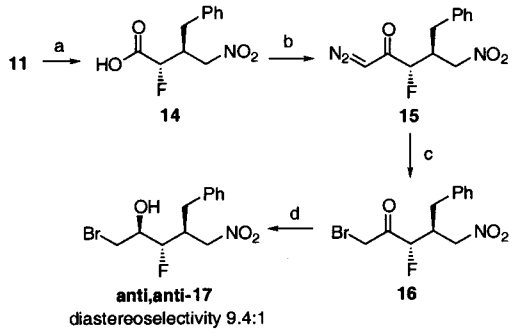
(31) For computational studies on the diastereoselectivity of the addition of nucleophiles to α-fluoro ketones, see: (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456−458. (b) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327−330.

Scheme 3



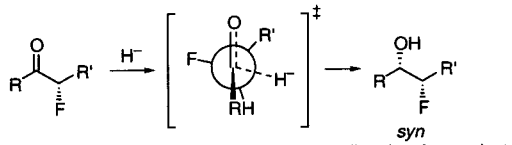
a. *(1R,2R)*-**9**, LHMDS, LiCl, THF, −78 °C; **12**, THF, −78 °C; recrystallization, 23% (stereoisomerically pure **11**).
b. *(1S,2S)*-**9**, LHMDS, LiCl, THF, −78 °C; **12**, THF, −78 °C, 47% (1.7:1 mixture of *ent*-**11**:*ent*-**13**).

Scheme 4

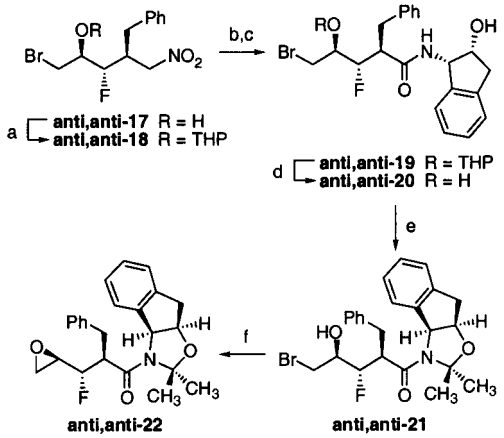


a. 2 N aq NaOH, *t*-BuOH, MeOH, 75 °C, 98%. b. $(COCl)_2$, DMF (0.1 equiv), CH_2Cl_2, 0 → 23 °C; $TMSCHN_2$, THF, 0 → 23 °C, 69%. c. 48% aq HBr, AcOH, 93%. d. $NaBH_4$, EtOH, −78 °C, 75%.

The Anh-Eisenstein model predicts the opposite stereochemical outcome:



Scheme 5



a. DHP, *p*-TsOH•H_2O (0.1 equiv), CH_2Cl_2, 23 °C, 93% (one recycle of starting material). b. *t*-BuOK, *t*-BuOH, 23 °C; $KMnO_4$, $Na_2B_4O_7$, H_2O, 23 °C. c. **8**, EDC•HCl, HOBt, Et_3N, CH_2Cl_2, 0 → 23 °C, 89% (two steps). d. *p*-TsOH•H_2O, MeOH, 23 °C, 91%. e. 2-methoxypropene, CH_3SO_3H, EtOAc, 23 °C, 93%. f. *t*-BuOK, THF, 0 °C, 94%.

conditions for the selective reduction of a variety of α-fluoro ketone substrates to either syn- or anti-configured fluorohydrin products have been found by rapidly screening a variety of simple, achiral reductants. A complete summary of diastereoselectivities observed in the reduction of α-fluoro ketones in the course of this work is presented in graphical form in the Supporting Information.

Protection of fluorohydrin **anti,anti-17** as the corresponding tetrahydropyranyl ether set the stage for application of the oxidative Nef reaction (Scheme 5). Conversion of nitroalkane **anti,anti-18** to the corresponding carboxylic acid occurred smoothly upon sequential treatment with potassium *tert*-butoxide and potassium permanganate in a buffered mixture of *tert*-butanol and water.[33] The crude acid was coupled with (1*S*,2*R*)-1-aminoindan-2-ol (**8**), affording amide **anti,anti-19** in 89% yield for the two-step sequence. Following cleavage of the tetrahydropyranyl ether, the hydroxyamide within the resultant diol was protected selectively in 93% yield by treatment with 2-methoxypropene and catalytic methanesulfonic acid. Rapid and efficient epoxide formation then occurred upon treatment of bromohydrin **anti,anti-21** with potassium *tert*-butoxide in THF at 0 °C.

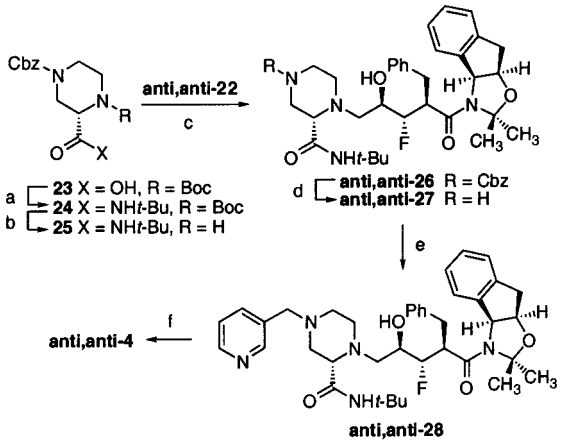
Epoxide **anti,anti-22** proved to be a convenient precursor to two of the targeted indinavir analogues. Piperazine **25** (1.2 equiv, prepared in two steps from (*S*)-1,2,4-piperazine tricarboxylic acid, 1-*tert*-butyl-4-benzyl ester (**23**)[34] as shown in Scheme 6) reacted smoothly with this epoxide (1 equiv) upon heating at 80 °C in 2-propanol, in analogy with the commercial synthesis of indinavir. Transfer hydrogenolysis of the benzyl carbamate (1,4-cyclohexadiene, 10% Pd/C, EtOH) afforded the secondary

(32) For reductions of α-fluoro ketones in which the only stereogenic center is the fluorinated carbon, see: (a) Barnett, J. E. G.; Kent, P. W. *J. Chem. Soc.* **1963**, 2743−2747. (b) Salon, M. C.; Hamman, S.; Beguin, C. G. *J. Fluorine Chem.* **1985**, *27*, 361−370. (c) Brandange, S.; Dahlman, O.; Olund, J. *Acta Chem. Scand., Ser. B* **1983**, *37*, 141−145. (d) Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem.* **1987**, *52*, 3218−3223. For reductions of α-fluoro ketones containing more than one stereogenic center, see: (e) Bravo, P.; Piovosi, E.; Resnati, G. *J. Chem. Res. (S)* **1989**, 134−135; *(M)*, 1115−1147. (f) Bravo, P.; Resnati, G. *Tetrahedron Lett.* **1987**, *28*, 4865−4866. (g) Bravo, P.; Ganazzoli, F.; Resnati, G.; De Munari, S.; Albinati, A. *J. Chem. Res (S)* **1988**, 1701; *(M)*, 1701−1736. (h) Ishihara, T.; Yamaguchi, K.; Kuroboshi, M.; Utimoto, K. *Tetrahedron Lett.* **1994**, *35*, 5263−5266.

(33) (a) Shechter, H.; Williams, F. T., Jr. *J. Org. Chem.* **1962**, *27*, 3699−3701. (b) Saville-Stones, E. A.; Lindell, S. D. *Synlett* **1991**, 591−592. (c) Görlitzer, K.; Bömeke, M. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 983−987.

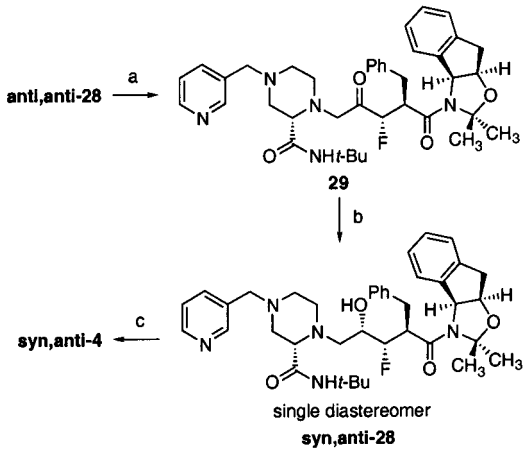
(34) Warshawsky, A. M.; Patel, M. V.; Chen, T.-M. *J. Org. Chem.* **1997**, *62*, 6439−6440.

Scheme 6



a. *t*-BuNH$_2$, EDC•HCl, HOBt, Et$_3$N, DMF, 0 → 23 °C. b. TFA, Et$_3$SiH, CH$_2$Cl$_2$, 85%. c. *i*-PrOH, 80 °C, 24 h, 91%. d. 1,4-cyclohexadiene, 10% Pd/C, EtOH, 23 °C, 94%. e. 3-picolyl chloride hydrochloride, Et$_3$N, DMF, 23 °C, 80%. f. *p*-TsOH•H$_2$O, MeOH, 23 °C, 92%.

Scheme 7

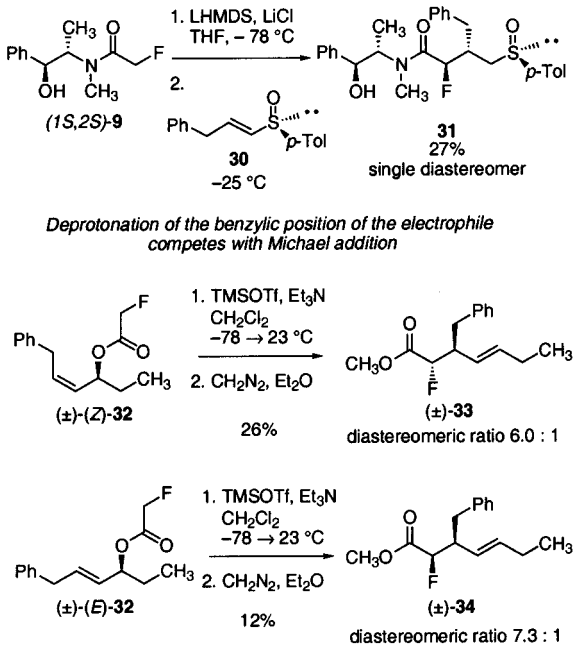


a. DMSO, (COCl)$_2$, −78 °C; Et$_3$N, −78 → 0 °C. b. LiBH(*s*-Bu)$_3$, THF, −78 °C, 78% (two steps). c. *p*-TsOH•H$_2$O, MeOH, 23 °C, 58%.

amine **anti,anti-27** in 94% yield. Finally, alkylation of the secondary amine with 3-picolyl chloride hydrochloride and acidic methanolysis of the acetonide protecting group furnished **anti,anti-4**, the first of the targeted protease inhibitors to be prepared.

An oxidation−reduction strategy was employed to prepare small quantities of inhibitor **syn,anti-4** for determination of its potential as an inhibitor of HIV protease (Scheme 7).[35] Swern oxidation of alcohol **anti,anti-28** cleanly afforded ketone **29**.[36] Unexpectedly, ketone **29** was found to be unstable; decomposition of this compound occurred upon storage in solution (CH_2Cl_2) or during chromatography. We have found that α-amino α′-fluoro ketones are generally unstable and, in a separate study, have proposed and presented evidence for the facile formation of a reactive oxyvinyliminium ion intermediate during their decomposition.[19] Ketone **29** was therefore reduced immediately (LiBH(*s*-Bu)$_3$, THF, −78 °C) without purification or storage. Analysis of the crude reduction product by ^{19}F NMR indicated formation of syn-fluorohydrin **syn,anti-28** without detectable contamination by the anti diastereomer; the diastereomerically pure fluorohydrin was isolated in 78% yield for the two-step oxidation−reduction sequence. Acetonide deprotection afforded fluorinated C$_{17}$-*epi*-indinavir analogue **syn,anti-4**.

Scheme 8



Having completed the synthesis of two of the targeted HIV protease inhibitors, the problem of accessing compounds **syn,-syn-4** and **anti,syn-4**, having (*R*)-configuration at the fluorinated center, remained to be addressed. These compounds were prepared from Michael adduct *ent*-**13** by synthetic sequences closely related to those described above, for which complete details are provided in the Supporting Information. Thus, asymmetric alkylation of pseudoephedrine fluoroacetamide enolate with a nitroalkene electrophile was successful in providing access to the four stereoisomeric targets. However, the moderate yield of the key Michael addition reaction encouraged us to investigate alternative strategies for construction of the fluorinated core structures.

Two alternative, and ultimately unsuccessful, approaches toward the key bond formation are summarized in Scheme 8, with complete details provided in the Supporting Information. The Michael addition of the lithium enolate derived from pseudoephedrine fluoroacetamide to vinyl sulfoxide **30** produced a single stereoisomeric adduct, but the efficiency of the reaction was reduced by competing deprotonation of the electrophile. Attempted Claisen rearrangement of secondary fluoroacetates **32** revealed complications due to elimination of fluoroacetic acid from these substrates.[37] These efforts were abandoned upon discovery of an efficient and stereoselective means of synthesizing the fluorinated core subunit, based on an asymmetric alkylation reaction employing nonracemic fluoroiodoacetic acid as the electrophile, as described in detail below.

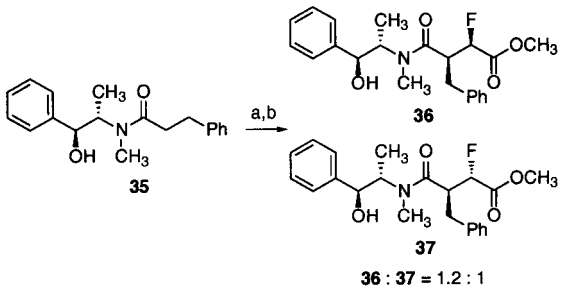
Synthesis of the Targeted Protease Inhibitors Using Nonracemic Fluoroiodoacetic Acid. Having encountered difficulties in the stereoselective construction of the fluorinated core subunits by alkylation of a chiral fluoroacetamide enolate or by fluoroacetate Claisen rearrangement, we became interested in exploring an alternative asymmetric alkylation strategy involving reversal of the polarity of the reaction components,

(35) Attempted inversion of alcohol **anti,anti-28** under Mitsunobu conditions (4-nitrobenzoic acid, Ph$_3$P, DEAD, THF) failed due to a lack of reactivity of this substrate.

(36) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(37) Araki, K.; Welch, J. T. *Tetrahedron Lett.* **1993**, *34*, 2251−2254.

Scheme 9



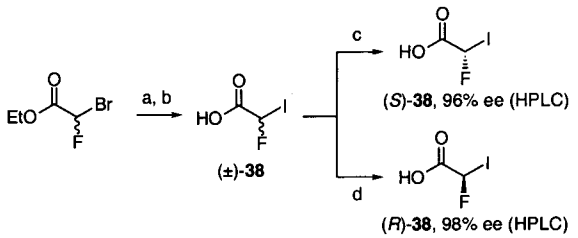
a. **35** (2.05 equiv), LDA, LiCl, THF, −78 → 23 °C; (±)-IFHCO$_2$H (1 equiv), −78 → 0 °C. b. TMSCHN$_2$, PhH, MeOH, 80% (two steps, **36**:**37** = 1.2:1).

transferring the fluorine atom to the electrophilic partner. Specifically, we proposed to use a chiral, nonracemic geminal fluoroiodide as the electrophilic component. Issues that would need to be addressed for the successful implementation of this proposal included the identification of a suitably reactive, yet stereochemically stable, electrophile that would undergo stereospecific S_N2 displacement, and the development of a practical method for the asymmetric synthesis of such a species. With regard to the issue of reactivity, kinetic studies have demonstrated that α-fluorine substitution retards the rate of S_N2 displacement of alkyl halides.[38] The scarcity of methodology for the asymmetric synthesis of geminal fluoroiodides presented perhaps a greater obstacle. To the best of our knowledge, Bailey and co-workers have reported the only previous syntheses of optically pure α-fluorinated iodides, by chromatographic separation of the diastereomeric fluoroiodoacetamides derived from α-methylbenzylamine.[39] Importantly, displacement of iodide in these compounds with nitrogen nucleophiles was demonstrated to occur stereospecifically, with 85−100% inversion of stereochemistry, providing precedent for the use of optically pure geminal fluorohalides as reagents for the asymmetric synthesis of organofluorine compounds.

Fluoroiodoacetic acid was ultimately selected as the electrophile in the proposed alkylation reaction after preliminary studies with the alternative electrophiles 1,1-bromofluoro-2-*tert*-butyldimethylsilyloxyethane and *tert*-butyl fluoroiodoacetate had shown the former to be unreactive and the latter to suffer from competitive addition of nucleophiles to the ester carbonyl group. These difficulties were avoided with fluoroiodoacetic acid, as demonstrated by the alkylation of the enolate derived from pseudoephedrine hydrocinnamide (**35**).[15d] Using racemic fluoroiodoacetic acid, the diastereomeric alkylation products **36** and **37** were formed in 80% yield (**36**:**37** = 1.2:1, Scheme 9). The efficiency of this carbon−carbon bond-forming process encouraged us to develop a procedure for the resolution of fluoroiodoacetic acid, with the goal of obtaining a practical solution for the preparation of either enantiomer on a multigram scale.

Fluoroiodoacetic acid can be readily prepared by basic hydrolysis of ethyl fluoroiodoacetate.[40] Although ethyl fluoroiodoacetate is now commercially available,[41] in practice we have typically prepared this compound from the cheaper reagent ethyl bromofluoroacetate by means of a Finkelstein reaction. Crude ethyl fluoroiodoacetate produced in this manner was subjected to basic hydrolysis (2 N aq LiOH, 0 °C) followed by an acidic workup to provide fluoroiodoacetic acid in 86% overall yield. This simple procedure required no chromatographic purification and could be implemented without difficulty to prepare >20 g of racemic fluoroiodoacetic acid in a single batch.

Scheme 10



a. NaI, acetone, 23 °C. b. 2 N aq LiOH, 0 °C, 30 min, 86% (two steps). c. Resolution with (+)-ephedrine hemihydrate; 3 N aq H_2SO_4, 43%. d. Resolution with (−)-ephedrine; 3 N aq H_2SO_4, 39%.

Screening a variety of chiral bases for the resolution of fluoroiodoacetic acid led to the identification of ephedrine as the optimal resolving agent.[42] Using this readily available and inexpensive chiral reagent, either enantiomer of fluoroiodoacetic acid can be prepared in ≥96% ee (Scheme 10). The optimized procedure for the resolution involves heating a mixture of racemic fluoroiodoacetic acid and (+)-ephedrine (hemihydrate) or (−)-ephedrine in 2-propanol-methyl *tert*-butyl ether (9:1 v/v) to reflux for 2 h.[43] Epimerization of the fluorinated center occurs under these conditions, allowing for dynamic resolution. Thus, in theory, it is possible to obtain a quantitative yield of diastereomerically pure product using racemic starting material. In practice, the yields of crystalline material (80 and 84% de) were 71 and 70% in resolutions using (−)-ephedrine and (+)-ephedrine hemihydrate, respectively. Further diastereomeric enrichment was achieved by successive recrystallizations from ether−MeOH (10:1 v/v). Typically, four successive recrystallization steps were required to obtain salt of ≥96% de. From a practical standpoint, it is noteworthy that precipitation of the salt was invariably rapid, allowing each recrystallization to be conducted within 30 min; the entire resolution procedure can be completed in a period of 7 h. From the diastereomerically pure salt, enantiomerically enriched fluoroiodoacetic acid was obtained in nearly quantitative yield and with ≤1% loss of stereochemical purity by protonation with aqueous sulfuric acid. The yields of enantiomerically enriched (*R*)- and (*S*)-fluoroiodoacetic acid were 43 and 39%, respectively, based on racemic fluoroiodoacetic acid.[44] This resolution procedure has proven to be highly reproducible, routinely providing access to highly enantiomerically enriched (≥96% ee) fluoroiodoacetic acid on scales up to 4.5 g. The enantiomerically enriched acid is a fine, white powder that does not measurably epimerize upon

(38) (a) McBee, E. T.; Christman, D. L.; Johnson, R. W.; Roberts, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 4595−4596. (b) Hine, J.; Thomas, C. H.; Ehrenson, S. J. *J. Am. Chem. Soc.* **1955**, *77*, 3886−3887.

(39) (a) Bailey, P. D.; Boa, A. N.; Crofts, G. A.; van Diepen, M.; Helliwell, M.; Gammon, R. E.; Harrison, M. J. *Tetrahedron Lett.* **1989**, *30*, 7457−7460. (b) Bailey, P. D.; Baker, S. R.; Boa, A. N.; Clayson, J.; Rosair, G. M. *Tetrahedron Lett.* **1998**, *39*, 7755−7758.

(40) (a) Takeuchi, Y.; Takagi, K.; Yamaba, T.; Nabetani, M.; Koizumi, T. *J. Fluorine Chem.* **1994**, *68*, 149−154. (b) Barth, F.; O−Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121−1124.

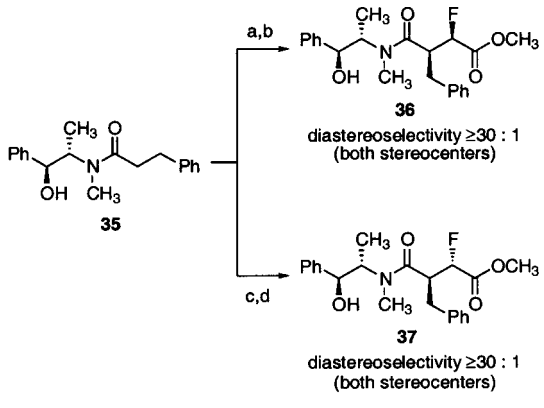
(41) Apollo Scientific Ltd., Derbyshire, UK.

(42) Other bases screened for the resolution included brucine, cinchonidine, cinchonine, dehydroabietylamine, norephedrine, α-methylbenzylamine, pseudoephedrine, quinidine, quinine, strychnine, and tyrosine ethyl ester.

(43) The use of enantiomeric resolving agents in different hydration states (i.e., anhydrous (−)-ephedrine versus (+)-ephedrine hemihydrate) is a result of commercial availability and did not cause significant differences in the resolutions.

(44) The absolute stereochemistry of the enantiomers of fluoroiodoacetic acid was determined by separate carbodiimide-mediated coupling reactions of (*R*)-fluoroiodoacetic acid with each enantiomer of α-methylbenzylamine, forming diastereomeric amides displaying physical properties (^{1}H NMR, ^{19}F NMR, melting point, TLC R_f values) in agreement with the values reported in ref 39b.

Scheme 11



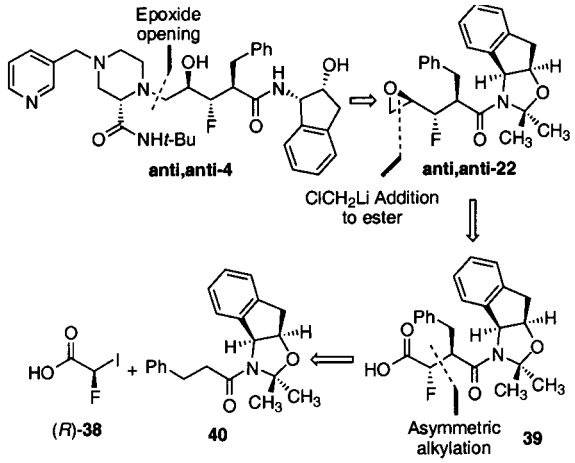
a. LDA, LiCl, THF, −78 → 23 °C; *(S)*-**38**, −78 → 0 °C. b. CH_2N_2, Et_2O, 23 °C, 89% (two steps). c. LDA, LiCl, THF, −78 → 23 °C; *(R)*-**38**, −78 → 0 °C. d. CH_2N_2, Et_2O, 23 °C, 91% (two steps).

prolonged storage at −20 °C in the dark.[45,46] The chemical and stereochemical stability of this compound significantly enhance its potential as a useful two-carbon building block for the asymmetric synthesis of organofluorine compounds.

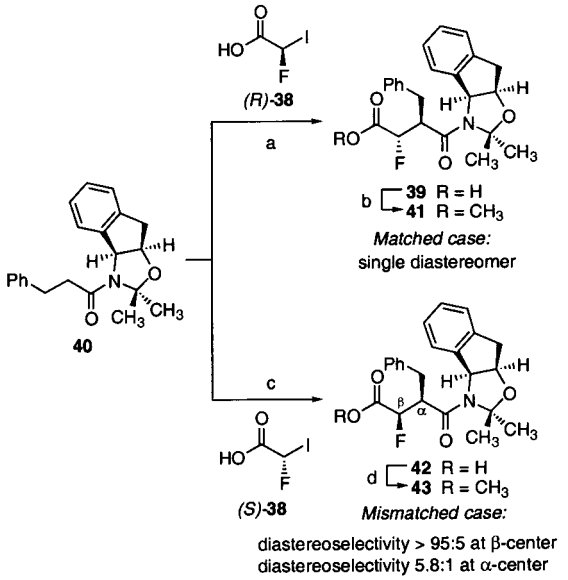
Alkylations of pseudoephedrine hydrocinnamide (**35**) with either enantiomer of fluoroiodoacetic acid proceeded in approximately 90% yield, with a high level of stereocontrol (Scheme 11). In each alkylation reaction, each of the two newly formed stereogenic centers was formed with >95% selectivity, indicative of a high degree of stereospecificity in the displacement reaction, as well as a high degree of diastereofacial selectivity by the enolate, a characteristic of pseudoephedrine amide enolate alkylations. These reactions provided an efficient process for the formation of each of the diastereomeric fluorinated core structures with high levels of stereocontrol and could, in principle, form the basis of a synthetic route to the targeted inhibitors. However, the availability of optically pure fluoroiodoacetic acid and its now demonstrated participation in stereospecific displacement reactions with amide enolate nucleophiles, coupled with literature precedent for highly diastereoselective alkylations of the enolate of aminoindanol hydrocinnamide **40**,[47] raised the possibility of an even more rapid and efficient route for the synthesis of inhibitors **4**. This strategy is depicted retrosynthetically in Scheme 12.

The crystalline amide **40** was prepared from commercial (1*S*,2*R*)-1-aminoindan-2-ol (**8**) in 93% yield and without chromatographic purification, following the literature procedure.[48] Conditions for the stereoselective alkylation of the enolate derived from amide **40** with optically pure fluoroiodoacetic acid were developed. The optimized alkylation procedure involved initial enolate formation (2.2 equiv amide **40**, 2.3 equiv *n*-BuLi, THF, −78 °C) followed by addition of (*R*)- or (*S*)-fluoroiodoacetic acid (1 equiv) and incubation at −60 °C. Excess base was quenched by the addition of water; extractive isolation then provided the alkylation products **39** or **42** in >90% yield (see Scheme 13). The alkylation reaction employing (*R*)-fluoroiodoacetic acid is a "matched" case; the product **39** was obtained as a single diastereomer, within the limits of detection by ^{19}F NMR spectroscopy. The crude product was typically converted directly to the methyl ester by treatment with ethereal diazomethane, affording **41** in 82% yield for the two-step sequence. "Mismatched" alkylation of **40**, using (*S*)-fluoroiodoacetic acid as the electrophile, afforded a 5.8:1 mixture of epimers at the amide-derived center. A single recrystallization of the crude reaction mixture from benzene afforded the stereoisomerically pure alkylation product **42** in 70% yield. No compounds epimeric at the fluorinated stereogenic center were detected in either alkylation reaction, indicating that each displacement reaction occurred with a high degree of stereospecificity. The stereochemistry of the alkylation products **39** and **42** was determined unambiguously (see Supporting Information), demonstrating that the displacement reactions occur with inversion of stereochemistry at the fluorinated stereogenic center. The inefficiency associated with the use of an extra equivalent of the amide enolate to neutralize the acidic proton of fluoroiodoacetic acid is to some degree offset by the fact that the excess starting amide is recoverable (69−79% of theory) and by the simplicity of the alkylation procedure. We have used this method to prepare multigram quantities of

Scheme 12



Scheme 13



a. *n*-BuLi, THF, −78 °C; *(R)*-**38**, THF, −78 → −60 °C, 5 h. b. CH_2N_2, Et_2O, 23 °C, 82% (two steps). c. *n*-BuLi, THF, −78 °C; *(S)*-**38**, THF, −78 → −60 °C, 17 h; recrystallization, 70% (isolated **42**). d. $TMSCHN_2$, PhH, MeOH, 23 °C, 83%.

(45) A sample of acid (*S*)-**38** having an enantiomeric excess of 99.8% was stored in the dark at −20 °C for six months with no detectable loss of stereochemical purity and without detectable decomposition.

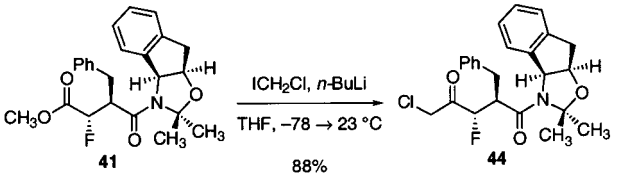
(46) Fluoroiodoacetic acid is hygroscopic and was therefore weighed under an inert atmosphere.

(47) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771−2773.

(48) Askin, D.; Eng, K. K.; Maligres, P. E.; Reider, P. J.; Rossen, K.; Volante, R. P.; Upadhyay, V.; Weissman, S. A. Process for Making an Epoxide. U.S. Patent 5,728,840, March 17, 1998.

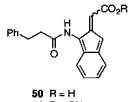
diastereomerically pure acids **39** and **42** (the largest reactions to date have produced 5.7 g of **39** and 3.6 g of **42**).[49]

Preliminary evidence suggested that activated acyl donors derived from acids **39** and **42** were unstable, undergoing intramolecular cyclization by attack of the amide carbonyl group, raising doubts about the prospects of methods involving carboxylic acid activation to transform the alkylation products to chloromethyl ketones. This potential obstacle was overcome by the development of a direct transformation of the methyl esters **41** and **43** to the chloromethyl ketones **44** and **45** using chloromethyllithium.[50,51] In the optimized procedure, *n*-BuLi (1.2 equiv) was added to a rapidly stirring mixture of the methyl ester (**41** or **43**, 1 equiv) and chloroiodomethane (1.25 equiv) in THF at −78 °C, followed by warming to 23 °C for 10 min prior to an acidic quench. The chloromethyl ketones **44** and **45** were obtained in 88 and 89% yields, respectively, after column chromatography. Spectroscopic analysis of the crude products (^{19}F NMR) showed no evidence of epimerization of the fluorinated stereogenic center during the course of these transformations.



Elaboration of intermediates **44** and **45** to the targeted inhibitors involved conversion of the chloromethyl ketones to the corresponding epoxides. Toward this end, the reduction of these ketones with a number of simple, achiral reducing agents was investigated, resulting in the development of conditions for the stereoselective synthesis of each of the four targeted fluorohydrin products **46** with diastereoselectivities of 12:1 or greater (Scheme 14). The diastereomeric products were in all cases separable by chromatography on silica gel, allowing the isolation of products that were diastereomerically pure within the limits of detection by ^{19}F NMR.

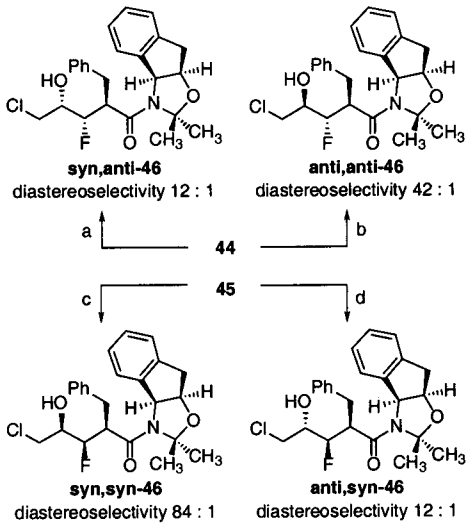
(49) Alkylation products **39** and **42** are invariably contaminated with a bright yellow-colored impurity, ascribed to the formation of trace amounts (≤3%) of isobenzofulvene **50** in the alkylation reactions. This assignment is based on the isolation of the methyl ester **51** in 3% yield (trimethylsilyldiazomethane, benzene, MeOH, 23 °C). Formation of the isobenzofulvene impurity is proposed to occur as a result of benzylic deprotonation of amide **40**, followed by elimination of acetone, alkylation of the resulting lithiated enamide, tautomerization, and elimination of hydrofluoric acid. The isobenzofulvene impurity can be chromatographically separated; therefore, its formation does not significantly detract from the utility of this alkylation protocol.



(50) In situ generation of $ClCH_2Li$ in the presence of carbonyl compounds: Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795−798.

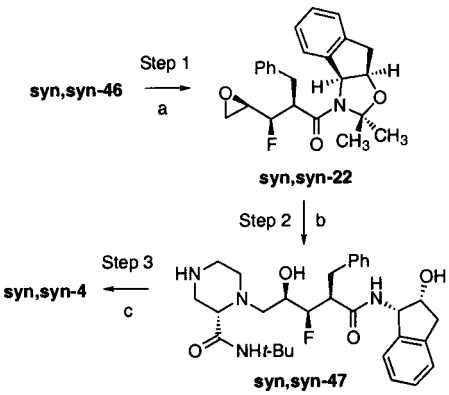
(51) Application of $ClCH_2Li$ to the synthesis of α,α′-dihalogenated ketones: (a) Barluenga, J.; Llavona, L.; Concellón, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 417. (b) Barluenga, J.; Llavona, L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 297−300.

Scheme 14



a. $LiAlH(Ot\text{-}Bu)_3$, THF, −78 °C, 77%. b. DIBAL, toluene, CH_2Cl_2, −78 °C, 74%. c. DIBAL, toluene, −78 → 0 °C, 81%. d. $NaBH_4$, EtOH, −78 → 0 °C, 84%.

Scheme 15



a. *t*-BuOK, THF, 0 °C. b. **6**, *i*-PrOH, reflux; 6 N aq HCl, 0 → 23 °C. c. 3-pyridinecarboxaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane, 23 °C.

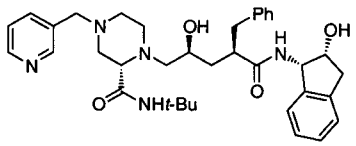
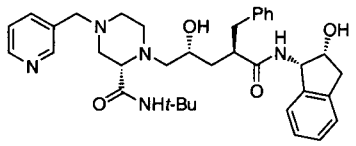
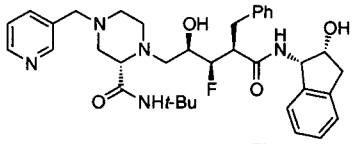
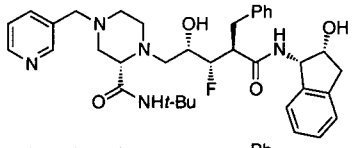
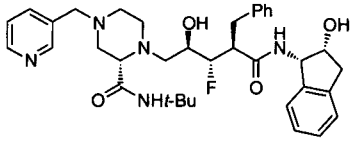
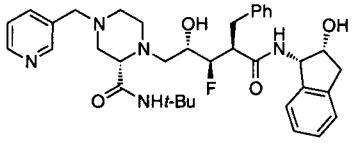
Diastereomeric Series	Yield (%)		
	Step 1	Step 2	Step 3
syn,syn	85[a]	96	84
anti,anti	88	81	82
anti,syn	83	70	73
syn,anti	89	87	83

[a] Yield over two steps from ketone **45**.

The conversion of alcohols **46** to the targeted protease inhibitors was accomplished in three steps, following literature precedent (Scheme 15).[23b] Thus, addition of potassium *tert*-butoxide to solutions of each diastereomeric alcohol **46** in THF led to rapid and clean formation of the corresponding epoxide. The epoxides (1 equiv) were individually heated with (*S*)-2-*tert*-butylcarboxamide-4-*tert*-butoxycarbonylpiperazine[23] (**6**, 1.05 equiv, ≥99% ee) in 2-propanol at 75 °C. Following epoxide opening, 6 N aqueous HCl was added, to deprotect the carbamate- and acetonide-protective groups, simultaneously. The secondary amines **47** were each obtained in good yield (70−96%) for the two-step sequence. Finally, reductive alkylation of amines **47** with 3-pyridinecarboxaldehyde using sodium triacetoxyborohydride as reductant afforded the targeted compounds in good yields.

Biological Evaluation. Inhibition constants (K_i) for indinavir (**3**), each of the four diastereomeric analogues **4**, and C_{17}-*epi*-

Table 1. Inhibition Constants (K_i) for Inhibition of HIV-1 Protease by Indinavir and Analogues

Compound	Structure	K_i (nM)	Compound	Structure	K_i (nM)
Indinavir (**3**)		1.9	C_{17}-*epi*-Indinavir (**48**)		160
syn,syn-4		2.0	**syn,anti-4**		20
anti,anti-4		27	**anti,syn-4**		5900

indinavir (**48**)[52] were determined with respect to HIV-1 protease using a standard assay wherein the initial rate of enzymatic cleavage of the synthetic substrate Lys-Ala-Arg-Val-Nle-Nph-Glu-Ala-Nle-NH_2 is measured in the presence of varying concentrations of inhibitor.[53,54] Inhibition constants are presented in Table 1. The most potent of the fluorinated inhibitors was the diastereomer **syn,syn-4**; this compound was essentially equipotent to indinavir in this assay. Inhibition constants varied over a range of 3 orders of magnitude among the series of diastereomers **4**.

In an attempt to rationalize the effect of the stereochemistry of the monofluoro hydroxyethylene core on the potency of inhibitors **4**, we examined proton−proton and proton−fluorine coupling constants in these compounds and all fluorohydrin synthetic intermediates employed in this study. A graphical summary of the spectral characteristics of these fluorohydrins is presented in Figure 2. Three patterns are invariant in the series: (1) each anti-fluorohydrin exhibits a greater vicinal C**H**OH−C**H**F proton−proton coupling constant than any of the syn-fluorohydrins (Figure 2a), (2) each anti-fluorohydrin has a smaller vicinal C**H**OH−CH**F** proton−fluorine coupling constant than any of the syn-fluorohydrins (Figure 2b), and (3) within a given structural framework, the anti-fluorohydrins display ^{19}F NMR resonances shifted downfield in comparison to the corresponding syn-fluorohydrins (Figure 2c). All three trends have been observed previously in other acyclic fluorohydrins.[55] The observed trends in coupling constants can be used to gain insight into the conformational preferences of fluorohydrins, as vicinal proton−fluorine coupling constants exhibit a Karplus-type dependence on dihedral angle.[56] The observed vicinal coupling constants for both syn- and anti-fluorohydrins are qualitatively consistent with preferred solution conformations wherein the carbon chain is fully extended (see Newman projections, Figure 2), although it is apparent that the anti-fluorohydrins display a greater degree of conformational variability than their syn counterparts.

Although the data set is small, it is nevertheless apparent that insertion of fluorine into the hydroxyethylene cores of indinavir or C_{17}-*epi*-indinavir to form syn-fluorohydrins has a more favorable impact on potency than the alternative substitutions, producing anti-configured fluorohydrins. Thus, syn-fluorine substitution into the indinavir and *epi*-indinavir frameworks results in an equipotent and an 8-fold more potent inhibitor, respectively, while anti-fluorine substitution results in 14- and 37-fold less potent inhibitors. Qualitative analysis of proton−proton and proton−fluorine coupling constants suggests that the syn-fluorohydrin-containing inhibitors **syn,-syn-4** and **syn,anti-4** maintain a fully extended conformation of the carbon−carbon chain encompassing the fluorohydrin subunit (C_{16}−C_{19}). In contrast, the anti-fluorohydrin-containing inhibitors **anti,anti-4** and **anti,syn-4** exhibit coupling constants indicative of the presence of significant populations of alternative conformers. When bound to HIV protease, the carbon backbone of indinavir assumes an extended conformation in the region of the central hydroxyl (dihedral angles (C_{16}−C_{17})−(C_{18}−C_{19}) = 178.6° and 173.2° when bound to HIV-1 and HIV-2 proteases, respectively).[57] The weaker binding of inhibitors containing anti-fluorohydrin subunits, relative to nonfluorinated or syn-fluorohydrin inhibitors, may be due in part to the larger population of solution conformations of these inhibitors that differ significantly from the enzyme-bound conformation.

The difference in conformational preferences of syn- and anti-fluorohydrin inhibitors may be a consequence of the gauche effect. The gauche effect is a tendency for vicinal electronegative substituents to adopt a gauche conformation.[58,59] The physical

(52) The preparation of C_{17}-*epi*-indinavir (**48**) is described in the Supporting Information.

(53) Abbreviations: Nle, norleucine; Nph, 4-nitrophenylalanine.

(54) (a) Richards, A. D.; Phylip, L. H.; Farmerie, W. G.; Scarborough, P. E.; Alvarez, A.; Dunn, B. M.; Hirel, P.-H.; Konvalinka, J.; Strop, P.; Pavlickova, L.; Kostka, V.; Kay, J. *J. Biol. Chem.* **1990**, *265*, 7733−7736. (b) Phylip, L. H.; Richards, A. D.; Kay, J.; Konvalinka, J.; Strop, P.; Blaha, I.; Velek, J.; Kostka, V.; Ritchie, A. J.; Broadhurst, A. V.; Farmerie, W. G.; Scarborough, P. E.; Dunn, B. M. *Biochem. Biophys. Res. Commun.* **1990**, *171*, 439−444.

(55) Bravo, P.; Piovoisi, E.; Resnati, G. *J. Chem. Res.* (*M*) **1988**, 1115−1147 and references therein.

(56) Caution must be exercised in this analysis, as it has been demonstrated that proton−fluorine coupling constants are more sensitive than proton−proton coupling constants to C−C−H and C−C−F bond angles and to substituent effects, see: (a) Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1998**, *63*, 4967−4984 and references therein. (b) Fabian, J. S.; Guilleme, *J. Chem. Phys.* **1996**, *206*, 325−337 and references therein. (c) Ihrig, A. M.; Smith, S. L. *J. Am. Chem. Soc.* **1970**, *92*, 759−763. (d) Williamson, K. L.; Hsu, Y.-F. L.; Hall, F. H.; Swager, S.; Coulter, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 6717−6722. (e) Williamson, K. L.; Hsu, Y.-F. L.; Hall, F. H.; Swager, S. *J. Am. Chem. Soc.* **1966**, *88*, 5678−5680. (f) Hamman, S.; Beguin, C.; Charlon, C.; Luu-Duc, C. *Org. Magn. Reson.* **1983**, *21*, 361−366.

(57) X-ray structure of indinavir bound to HIV-2 protease: Chen, Z.; Li, Y.; Chen, E.; Hall, D. L.; Darke, P. L.; Culberson, C.; Shafer, J.; Kuo, L. C. *J. Biol. Chem.* **1994**, *269*, 26344−26348. The structure of indinavir bound to HIV-1 protease is available electronically (National Cancer Institute's HIV protease database: www.ncifcrf.gov/CRYS/HIVdb, structure "1hsg").

(58) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102−111.

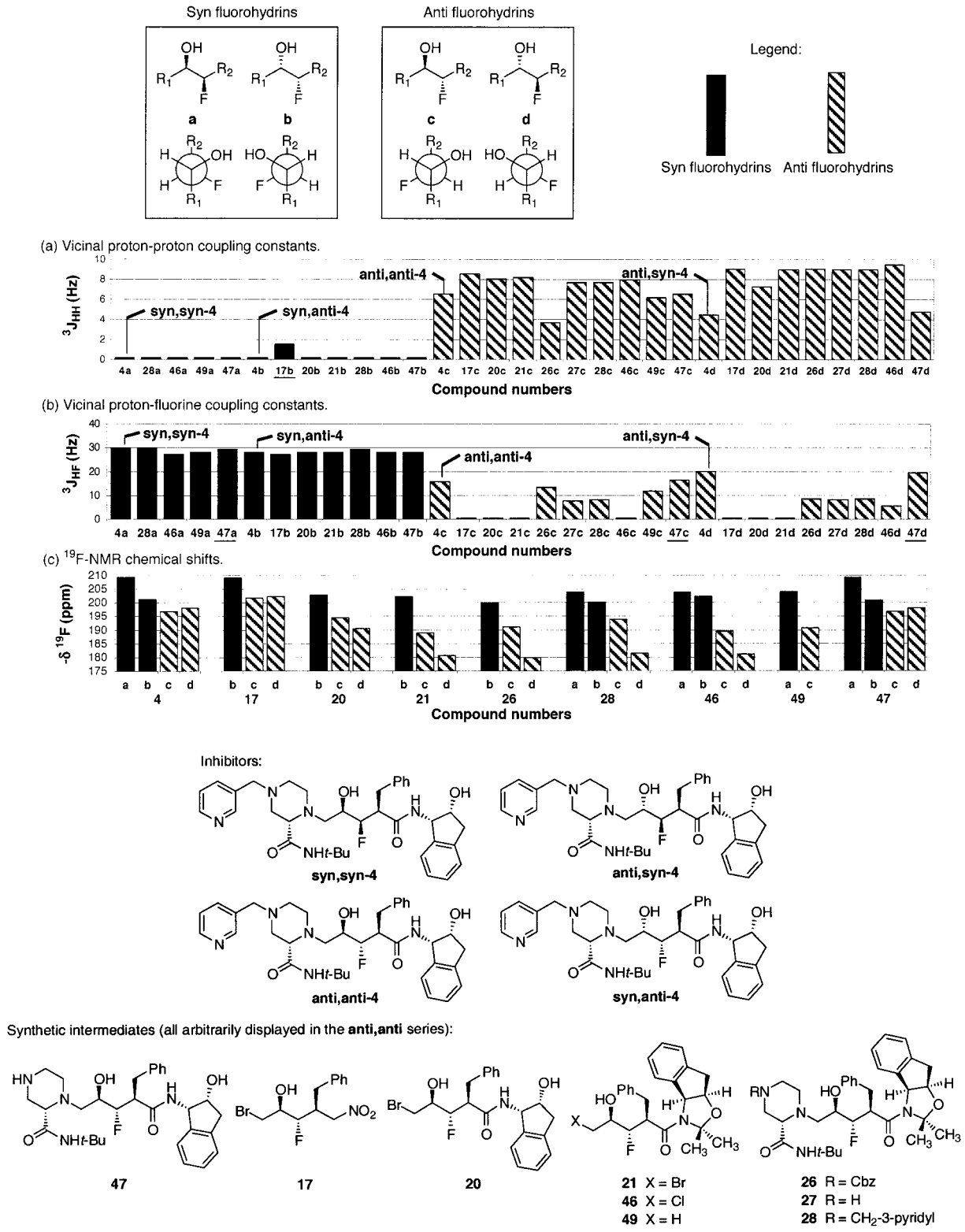


Figure 2. Comparison of NMR spectral characteristics of syn- and anti-fluorohydrins. Underlined compound numbers indicate data from methanol-d_4 solutions. All other data are from chloroform-*d* solutions.

basis for this conformational preference is thought to be a stabilizing hyperconjugative interaction between a σ-bonding orbital and an adjacent σ^* antibonding orbital that is maximized when σ-bonds having the greatest donor capacity (i.e., C−H) are oriented antiperiplanar to the strongest acceptor σ bonds (in this case, C−F). The gauche effect is expected to stabilize the fully extended conformation of the carbon backbone for syn-fluorohydrins, as this conformation orients C−H bonds antiperiplanar to both electronegative substituents. In contrast, in anti-fluorohydrins the electronegative substituents are oriented

(59) For leading references on the gauche effect, see: (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087. (b) Thatcher, G. R. J., Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993.

in an electronically unfavorable antiperiplanar relationship in the extended conformer.[60]

Considering only the syn-fluorohydrin inhibitors, where fluorination appears to reinforce the extended inhibitor conformation observed in the structure of HIV protease bound to indinavir, it is interesting to note that fluorination of indinavir (**3** → **syn,syn-4**) produces no change in potency, while fluorine substitution in the core of C_{17}-*epi*-indinavir (**48** → **syn,anti-4**) led to an 8-fold increase in potency. Aspartyl proteases display consistently stronger binding to hydroxyethylene-containing inhibitors in which the core hydroxyl has (*S*) absolute configuration (for instance, indinavir) relative to inhibitors epimeric at this stereogenic center; the approximately 90-fold loss in potency observed on inversion of this center in indinavir is consistent with the differences observed in other inhibitors of HIV protease.[61] The central (*S*)-configured hydroxyl in potent inhibitors is typically bound between the two catalytic aspartates, occupying the site taken by the nucleophilic water molecule in the structure of the native enzyme.[21,62] Previous observations showing that difluorostatine-containing inhibitors of the aspartyl proteases renin and pepsin are less potent[63] or essentially equipotent[9a] in comparison to the corresponding nonfluorinated inhibitors suggest that the lack of improved binding of **syn,-syn-4** compared to that of indinavir may be indicative of a general trend. This lack of enhanced potency upon fluorination has been previously suggested to reflect the importance of the central alcohol as a hydrogen-bond acceptor.[63a,b] The tighter binding of the enzyme to **syn,anti-4**, as compared to its nonfluorinated counterpart (C_{17}-*epi*-indinavir, **48**), may be due in part to formation of a stronger hydrogen bond between the catalytic aspartate(s), which are expected to bear a net negative charge,[20] and the β-fluorinated core hydroxyl, due to its increased hydrogen-bond donor ability. The lack of improved potency upon fluorination of indinavir may be the result of a different pattern of hydrogen bonding between the core hydroxyl and the catalytic aspartates in inhibitors varying in the stereochemistry of the central alcohol. Alternatively, it is conceivable that hydrogen bonding to the catalytic aspartates is strengthened for both **syn,syn-4** and **syn,anti-4**, but the effect is diminished by other, unfavorable, consequences of fluorination in the case of **syn,syn-4**. Binding energy is critically dependent upon factors such as solvation, hydrophobic and steric interactions with the enzyme, and populations of alternative inhibitor conformations, each of which may be altered, in poorly defined ways, upon introduction of fluorine.

Table 2. Properties of Indinavir and Analogs

compound	log P^a	inhibition of CYP3A4, IC_{50} (μM)	inhibition of CYP2D6, IC_{50} (μM)
indinavir (**3**)	3.03	1.7	82.6
C_{17}-*epi*-indinavir (**48**)	3.02	no data	no data
syn,syn-4	3.23	1.6	78.9
anti,anti-4	3.01	1.7	57.2
anti,syn-4	3.31	2.4	35.3
syn,anti-4	3.12	7.5	198

[a] Log 1-octanol/water partition coefficient, determined by the shake-flask method.[64]

The lipophilicity and the extent of inhibition of human cytochrome P450 (CYP) by inhibitors **4** and indinavir were determined (Table 2). Each of the fluorinated inhibitors was found to be slightly more lipophilic ($\leq$0.28 log units) than indinavir, with the exception of **anti,anti-4**, which had a measured 1-octanol−water partition coefficient[64] essentially equal to that of the unaltered drug. These results are consistent with the trend that fluorination of carbons adjacent to heteroatom substituents results in increased lipophilicity.[3a] The lipophilicity of drug candidates is an important determinant of pharmokinetic factors such as absorption, cell membrane permeability, plasma protein binding, metabolism, and penetration into the central nervous system.[65] Indinavir and its fluorinated analogues **4** displayed similair inhibition of cytochrome P450 isozymes CYP3A4 and CYP2D6, enzymes responsible for metabolism of indinavir.

Summary

We have developed syntheses of four diastereomeric HIV protease inhibitors (**4**) incorporating the monofluoro hydroxyethylene dipeptide isostere. The two successful routes presented employed asymmetric alkylation reactions for stereoselective construction of the fluorinated core structures. Studies involving the use of a fluorinated nucleophile (pseudoephedrine α-fluoroacetamide) and various nonfluorinated electrophiles in the key carbon−carbon bond-forming reaction revealed complications introduced by the presence of the branched alkyl center of asymmetry in the core structures (lack of reactivity in the case of secondary electrophiles; benzylic deprotonation or lack of diastereoselectivity with Michael acceptors). The alternative carbon−carbon bond construction based on the alkylation of an amide enolate with an α-fluorinated electrophile (enantiomerically enriched fluoroiodoacetic acid) resulted in the development of practical and efficient synthetic routes to the targeted compounds. The optimized synthetic route to the most potent inhibitor (**syn,syn-4**, K_i = 2.0 nM) proceeded in seven steps (87% average yield per step) from aminoindanol hydrocinnamide **40** and (*S*)-fluoroiodoacetic acid. A simple procedure for the resolution of fluoroiodoacetic acid was developed, providing access to either enantiomer in ≥96% ee. The alkylation of the enolate derived from amide **40** with optically active fluor-

(60) For studies on the gauche effect in fluorohydrins, see: (a) Abraham, R. J.; Chambers, E. J.; Thomas, W. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 949−955. (b) Buckley, P.; Giguere, P. A.; Daijiro, Y. *Can. J. Chem.* **1968**, *46*, 2917−2923. (c) Griffith, R. C.; Roberts, J. D. *Tetrahedron Lett.* **1974**, *39*, 3499−3502. (d) Bakke, J. M.; Bjerkeseth, L. H.; Ronnow, T. E. C. L.; Steisvoll, K. *J. Mol. Struct.* **1994**, *321*, 205−214. (e) Huang, J.; Hedberg, K. *J. Am. Chem. Soc.* **1989**, *111*, 6909−6913. (f) Braathen, O.-A.; Marstokk, K.-M.; Mollendal, H. *Acta Chem. Scand.* **1982**, *6*, 173−181. (g) Hagen, K.; Hedberg, K. *J. Am. Chem. Soc.* **1973**, *95*, 8263−8266.

(61) (a) Dreyer, G. B.; Metcalf, B. W.; Tomaszek, T. A.; Carr, T. J.; Chandler, A. C.; Hyland, L.; Fakhoury, S. A.; Magaard, V. W.; Moore, M. L.; Strickler, J. E.; Debouck, C.; Meek, T. D. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 9752−9756. (b) Rich, D. H.; Sun, C.-G.; Prasad, J. V. N.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1222−1228.

(62) For the native structure of HIV-1 protease, see: Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature* **1989**, *337*, 615−620.

(63) (a) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080−2087. (b) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.* **1987**, *30*, 1617−1622. (c) Doherty, A. M.; Kaltenbronn, J. S.; Hudspeth, J. P.; Repine, J. T.; Roark, W. H.; Sircar, I.; Tinney, F. J.; Connolly, C. J.; Hodges, J. C.; Taylor, M. D.; Batley, B. L.; Ryan, M. J.; Essenberg, A. D.; Rapundalo, S. T.; Weishar, R. E.; Humblet, C.; Lunney, E. A. *J. Med. Chem.* **1991**, *34*, 1258−1271.

(64) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525−616.

(65) (a) Navia, M. N.; Chaturvedi, P. R. *Drug Discovery Today* **1996**, *5*, 179−189. For reviews on the pharmacokinetics of anti-HIV agents, see: (b) Williams, G. C.; Sinko, P. J. *Adv. Drug Delivery Rev.* **1999**, *39*, 211−238. (c) Li, X.; Chan, W. K. *Adv. Drug Delivery Rev.* **1999**, *39*, 81−103. (d) Aungst, B. J. *Adv. Drug Delivery Rev.* **1999**, *39*, 105−116. For a review focusing on pharmacokinetic aspects of the development of indinavir, see: (e) Lin, J. H.; Ostovic, D.; Vacca, J. P. In *Integration of Pharmaceutical Discovery and Development: Case Histories*; Borchardt, R. T., Freidinger, R. M., Sawyer, T. K., Smith, P. L., Eds. Pharmaceutical Biotechnology, Volume 11; Plenum Press: New York, 1998; pp 233−255.

oiodoacetic acid proceeded with a high degree of stereospecificity. Coupled with the development of methods for the diastereoselective reduction of α-fluoro ketones **44** and **45**, this route allowed for the efficient and stereoselective synthesis of inhibitors containing each of the four stereoisomeric forms of the monofluoro hydroxyethylene dipeptide isostere, more than one gram in the case of the inhibitor **syn,syn-4**. The inhibitory potency and other relevant biophysical properties of these structurally novel protease inhibitors were determined.

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged. We thank Dr. Michael Day and Dr. Richard Staples for obtaining crystallographic data. We express our appreciation to Dr. Jens Eckstein and Dr. Greg Warner of Enanta Pharmaceuticals for determination of the inhibition of human cytochrome P450 by compounds **4**.

Supporting Information Available: A description of first-generation syntheses of inhibitors **anti,syn-4** and **syn,syn-4**, alternative approaches to the fluorinated core subunits, preparation of C_{17}-*epi*-indinavir, and stereochemical assignments, graphical summaries of diastereoselectivity in the reduction of α-fluoro ketones, synthetic procedures, and characterization data for all new compounds, and X-ray crystal data for compounds *ent*-**11** and **anti,syn-22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010113Y