JOC*Note*

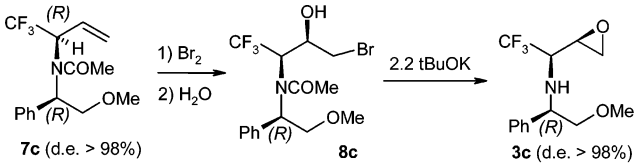
Analogues of Key Precursors of Aspartyl Protease Inhibitors: Synthesis of Trifluoromethyl Amino Epoxides

Nguyen Thi Ngoc Tam, Guillaume Magueur, Michèle Ourévitch, Benoit Crousse, Jean-Pierre Bégué, and Danièle Bonnet-Delpon*

BioCIS-CNRS, Centre d'Etudes Pharmaceutiques, rue J.B. Clément, Châtenay-Malabry 92296 Cedex, France

daniele.bonnet-delpon@cep.u-psud.fr

Received August 23, 2004



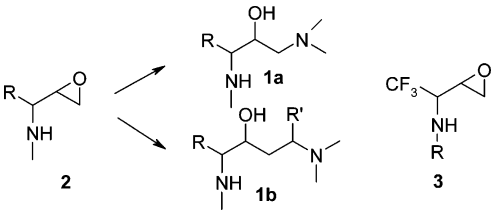
The synthesis of the title compound is described through original and tailored synthetic protocols. The addition of vinylmagnesium bromide to CF_3-*N*-aryl and *N*-alkyl aldimines was efficient and did not require an activating *N*-substituent. The resultant CF_3-allylamines were converted in an efficient and completely stereoselective route to syn CF_3-epoxides **3** via formation of bromhydrins **8**. The same sequence performed from the aldimine substituted with the methyl ether of the (*R*)-phenylglycinol provided the homochiral (*R*,*R*)-amino epoxide (de >98%). This study has allowed access to the novel racemic and homochiral trifluoromethyl β-amino epoxides, analogues of key precursors of various HIV protease inhibitors.

Introduction

Peptidomimetic binding units **1a** or **1b** where R is a benzyl or an isopropyl group are present in most HIV-1 protease inhibitors used in advanced clinical trials or in tritherapies[1] and in inhibitors of other proteases such as cathepsin D[2] and plasmepsins.[3]

Both types of diamino alcohols **1** can be easily accessed from a common precursor, the amino epoxides **2**, which

SCHEME 1. Access to Diamino Alcohols 1



are versatile intermediates for the synthesis of a variety of highly functionalized compounds (Scheme 1).[4]

The need still exists to find new protease inhibitors to improve selectivity toward homologous proteases, fight against problems associated with the development of drug-resistant strains, and limit secondary effects.

While structural diversity can be easily introduced through combinatorial libraries based on core units **1**, a modulation of the central unit has still to be explored.

Considering that strategies using specific properties of fluorine have resulted in the production of effective biomedical tools or drugs for numerous therapeutic targets,[5] the design of new inhibitors based upon a fluorinated hydroxyethylamine scaffold could be of benefit. Fluorinated amino acids[6] and peptidomimetic units[5b,7] can exhibit attractive features: a higher resistance to oxidative[8] and proteolytic degradation,[9] a better bioavailability, conformational restrictions on the peptide chain, and modification of binding properties through modulation of the pK_a of adjacent functionalities.[10] These specific properties have been largely exploited for the design of fluorine-containing protease inhibitors.[11]

(1) (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305−341. (b) James, M. N. G., Ed. *Advances in Experimental Medicine and Biology*; 1998; Vol. 436. (c) Takahashi, K., Ed. *Advances in Experimental Medicine and Biology*; 1995; Vol. 362.

(2) (a) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472. (b) Seife, C. *Science* **1997**, *277*, 1602−1603. (c) Craik, M. S.; Debouck, C. *Perspect. Drug Discovery Des.* **1995**, *2*, 1−125. (d) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543−585.

(3) (a) Haque, T. S.; Skillman, A. G.; Lee, C. E.; Habashita, H.; Gluzman, I. Y.; Ewing, T. J. A.; Goldberg, D. E.; Kuntz, I. D.; Ellman, J. A. *J. Med. Chem.* **1999**, *42*, 1428−1440. (b) Mineno, T.; Avery, M. A. *Chemstracts—Org. Chem.* **2001**, *14*, 518−523. (c) Dahlgren, A.; Kvarnström, I.; Vrang, L.; Hamelink, E.; Hallberg, A.; Rosenquist, A.; Samuelsson, B. *Bioorg. Med. Chem.* **2003**, *11*, 827−841. (d) Nöteberg, D.; Hamelink, E.; Hultén, J.; Wahlgren, M.; Vrang, L.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **2003**, *46*, 734−746.

(4) See for example: (a) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merret, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656−3664. (b) Brånalt, J.; Kvarnström, I.; Classon, B.; Samuelsson, B.; Nillroth, U.; Helena Danielson, U.; Karlén, A.; Hallberg, A. *Tetrahedron Lett.* **1997**, *38*, 3483−3486. (c) Beaulieu, P. L.; Wernic D. *J. Org. Chem.* **1996**, *61*, 3635−3645. (d) Ghosh, A. K.; Hussain, K. A.; Fidanze, S. *J. Org. Chem.* **1997**, *62*, 6080−6082. (e) Ma, D.; Zou, B.; Zhu, W.; Xu H. *Tetrahedron Lett.* **2002**, *43*, 8511−8513. (f) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2002**, *58*, 341−354.

(5) (a) *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L., Eds.; Elsevier: Amsterdam, 1993. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996. (c) Edwards, P. N. In *Use of Fluorine in Chemotherapy. In Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; p 501.

(6) (a) *Fluorine-Containing Amino Acids, Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (b) *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000.

(7) Abouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Kornilov, A.; Rodrigues, I.; Than Nga, T. T. In *Asymmetric Fluoroorganic Chemistry*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; Chapter 7.

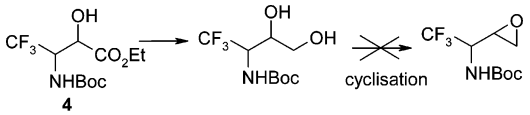
(8) (a) Park, B. K.; Kitteringham, N. R. *Drug Metabolism Rev.* **1994**, *26*, 605−643. (b) Irurre, J.; Casas, J.; Messeguer, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 179−182. (c) Miller, J. A.; Coleman, M. C.; Matthews, R. S. *J. Org. Chem.* **1993**, *58*, 2637−2639.

(9) Ojima, I.; Kato, K.; Jameison, F. A.; Conway, J.; Nakahashi, K.; Hagiwara, M.; Miyama, T. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 219−222.

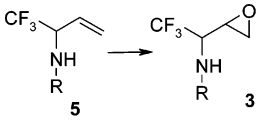
(10) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W., Jr. *J. Med. Chem.* **1993**, *36*, 2431−2447.

10.1021/jo0485233 CCC: $30.25 © 2005 American Chemical Society
Published on Web 12/10/2004

SCHEME 2



SCHEME 3. Trifluoromethyl Diamino Alcohol



Furthermore, fluoroalkyl groups can mimic the side chain (phenyl, benzyl, or isopropyl) of hydrophobic amino acids,[12] and this can be a powerful tool for optimizing the binding properties with proteases that exhibit a preference for a large hydrophobic P^1-residue. Difficulty in this case resides in the synthesis of a novel class of peptidomimetics containing a fluoroalkyl stereogenic center.

Our efforts have thus been focused on the preparation of trifluoromethyl epoxides **3**, which could undergo ring opening leading to various central units based on trifluoromethyl amino alcohols, analogues of **1**.

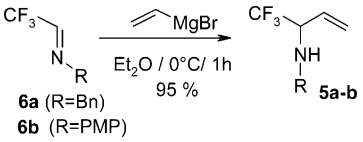
Results and Discussion

Extensive literature has been devoted to the synthesis of non-fluorinated α-amino epoxides **2**. Among them, the ring closure of diols is a versatile method to provide different stereomers of epoxides **2**.[1] However, these classical approaches could not be applied to dihydroxyl trifluoromethylamines, which are easily accessible from the known ethyl 3-trifluoromethyl-isoserinates **4**.[13] For example, intramolecular mesylate displacement, or Mitsunobu reaction, led to mixtures of products, which we were unable to elucidate (Scheme 2).[14]

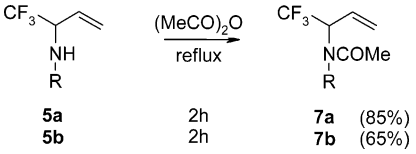
We thus turned to a direct epoxidation of double bond, which first required an easy access to allylamines **5** (Scheme 3).

Allylamines were previously prepared by reaction of vinylmagnesium bromide with the activated *N*-acyl-1-chloro-2,2,2-trifluoro ethylamine.[15] Recently, a similar approach involving the addition of a vinyl trifluoroborate to a trifluoromethyl iminium salt was reported.[16] An alternative approach is the trifluoromethylation of unsaturated *N*-sulfinimines or *N*-tosyl imines.[17] Otherwise,

SCHEME 4. Allylation Reaction on Trifluoroaldimines 6a,b



SCHEME 5. Protection of Allyl Amines 5a,b



the unsaturation could also be indirectly introduced from fluorinated β-amino sulfones by a desulfonylation reaction.[18] Our objective was to perform a direct addition of an organometallic agent, a process that, so far, has not been explored for nonactivated trifluoromethyl aldimines **6**.

The reaction of vinylmagnesium bromide (1.2 equiv) was investigated with the trifluoromethyl aldimines **6a** (*N*-benzyl) and **6b** (*N*-*para*-methoxyphenyl) (Scheme 4).

As already observed with non-fluorinated imines,[19] diethyl ether was found to be the best solvent for this reaction: with 1.2 equiv of the vinyl Grignard, in ether at 0 °C, the allylamines **5a** and **5b** were isolated in 95% yield. In toluene, the reaction rate was slower, and in THF, the reaction was incomplete. The next step involved protection of the nitrogen in order to attempt epoxidation reaction with *m*CPBA.[20] The usual protection conditions with Boc_2O or CbzCl failed with amines **5**. Finally, *N*-acylamines **7a**,**b** could be obtained in good yield after treatment of **5a**,**b** with acetic anhydride at reflux (Scheme 5).

However, trifluoromethyl allyl amides **7** were found to be completely unreactive toward epoxidation with *m*CPBA in CH_2Cl_2 at 0 °C, even at reflux. This poor reactivity of the double bond can be explained by the presence of the amide group and the β effect of the electron-withdrawing CF_3 group.

At this stage, we had to explore again indirect formation of epoxides, through ring closure of bromhydrins. Treatment of the allylamine **7a** with Br_2 in CH_2Cl_2, followed by hydrolysis, resulted in a clean reaction, providing remarkably only one bromhydrin **8a** as a single regio- and stereoisomer (^{19}F NMR analysis) in an excellent yield (98%). ^1H NMR and ^{13}C NMR data indicated that bromine was located at the terminal position, which corresponds to the ring opening of the bromonium ion **A** at the more hindered center (Scheme 6), expected in a S_N1-type reaction. However, such a process was assumed to be unfavorable because of β-electron-withdrawing substituents. Furthermore, an S_N1 reaction may proceed

(11) Sham, H. L.; Schirlin, D. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996.

(12) (a) Ojima, I.; Kuduk, S. D.; Chakravarty, S.; Ourévitch, M.; Bégué, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 5519−5527. (b) Ojima, I.; Slater, J. C.; Veith, J. P.; Abouabdellah, A.; Bégué, J. P.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 133−138. (c) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207−7219. (d) Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760. (e) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volontario, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063. (f) Pesenti, C.; Arnone, A.; Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Frigerio, M.; Meille, S. V.; Monetti, M.; Panzeri, W.; Viani, F.; Venturini, R.; Zanda, M. *Tetrahedron* **2001**, *57*, 6511−6522.

(13) Abouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826−8833.

(14) Bégué, J. P.; Bonnet-Delpon, D.; Allain, L.; Thanh Nga, T. T. Unpublished results.

(15) Weygand, F.; Steglich, W.; Pietta, P. *Chem. Ber.* **1967**, *100*, 3841−3849.

(16) Langlois, B. R.; Billard, T. *Synthesis* **2003**, *2*, 185−194.

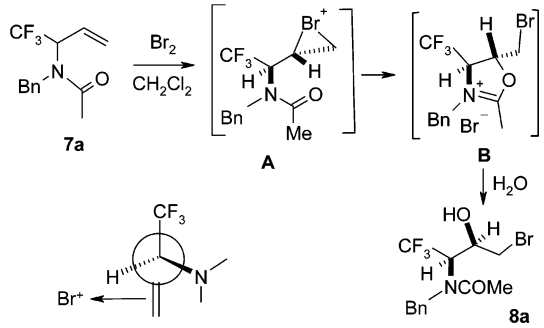
(17) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847−2850. (b) Kumadaki, I.; Jonoshita, S.; Harada, A.; Omote, M.; Ando, A. *J. Fluorine Chem.* **1999**, *97*, 61−63. (c) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572−2582.

(18) Fustero, S.; Garcia Soler, J.; Bartolomé, A.; Sanchez Rosello, M. *Org. Lett.* **2003**, *5*, 2707−2710.

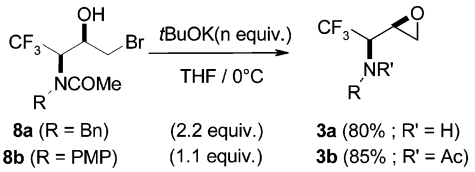
(19) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2003**, 2268−2275.

(20) Epoxidation reaction from nonprotected amine **5a** with *m*CPBA was attempted but afforded a mixture of products.

SCHEME 6. Stereoselective Access to Bromhydrin 8a



SCHEME 7. Cyclization of Bromhydrins with *t*BuOK



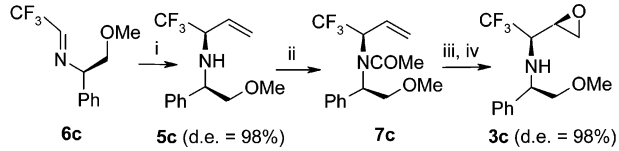
without a high level of stereoselectivity. An alternative S_N2-type ring opening would occur at the least hindered carbon. The opposite regioselectivity suggests an intermediate that involves the intramolecular ring opening of the bromonium ion by the *N*-acyl group. Under hydrolysis, it is likely that an addition to the iminium salt occurred, rather than substitution. Similar halolactonizations are known for *N*-Cbz and *N*-Boc groups[21] and, to a lesser extent, for amides.[22] In these reactions, the trans isomer is preferentially formed. It is assumed that the unsuccessful preparation of epoxides **3** from the corresponding diols (Scheme 2) was the result of a similar side reaction, among others. This mechanism easily explains the regioselectivity, with the formation of a five-member ring intermediate **B** (5-*exo-tet*), more favored than that of a six-member ring (6-*endo-tet*). The generation of a single stereomer is the result of a stereoselective formation of the initial bromonium ion, which was not anticipated, and a stereoselective bromonium ring opening, by an anti addition of the acyl group. A concerted process generating directly the intermediate **B** from the amine **7a** cannot be ruled out.

Further experiments allowed us to assign the syn configuration to **8a** (vide infra). It can thus be assumed that the initial bromine attack to **7a** occurred opposite to the hindered amide substituent (Newman's view in Scheme 6). The same reaction performed with the allylamine **7b** also provided the bromhydrin **8b** in good yield and with an excellent regio- and stereoselectivity.

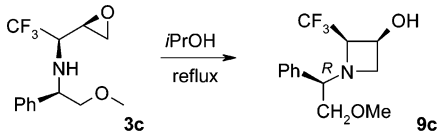
The cyclization of bromhydrins **8a**,**b** into epoxides was performed under basic conditions, with *t*BuOK in THF at 0 °C offering the best conditions. With **8a**, a partial deacetylation occurred, and 2.2 equiv of base was used to achieve a complete deprotection leading to the CF_3-epoxide **3a**, which was isolated in 80% yield. From **8b**, the epoxide was obtained without any deacetylation (Scheme 7).

(21) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701−2724.

SCHEME 8. Synthesis of the Chiral Trifluoromethyl Epoxide 3c



SCHEME 9. Synthesis of Azetidonol 9c in 2-Propanol at Reflux



The overall sequence was then applied to the chiral imine **6c**, prepared from the fluoral and the methyl ether of the (*R*)-phenylglycinol. We have recently shown that this chiral *N*-substituent induced high diastereoselectivity in allylation reactions with trifluoromethyl aldimines.[23] The addition of the vinyl reagent to the imine **6c** proceeded smoothly at 0 °C in 1 h and provided the allylamine **5c** in good yield (86%) and with an excellent diastereoselectivity (>98%): only one diastereomer was detected in ^{1}H and ^{19}F NMR spectra of the crude product (Scheme 8).

The *N*-acylamine **7c** was obtained by treatment of **5c** with acetic anhydride and 10% of $InCl_3$, at reflux (52%). Formation of bromhydrin **8c** and its further cyclization were performed under the above-described conditions and led to epoxide **3c** in 65% yield and with high diastereoselectivity (>98%). In this experiment, the intermediate **B** could be observed and characterized by NMR before hydrolysis.

The configuration of chiral compounds could not be established at this stage. Epoxide **3c** was thus converted, by heating, into the azetidinol **9c**, quantitatively obtained as a single diastereomer (one signal in ^{19}F NMR) (Scheme 9). Its crystallization (84% yield) afforded a suitable crystal for X-ray diffraction analysis,[24] which revealed the syn configuration between carbons 2 and 3 (2*R*,3*S*). Hence, the configuration of **3c** is syn *R*,*R*.

The stereochemical course of the vinylation reaction can now be rationalized: from the *cis*-aldimine **6c**, the trifluoromethylamine was obtained with creation of an *R* chiral center, thus confirming that, after coordination of N and O with the metal, the vinyl moiety was delivered from the face opposite to the phenyl group, as already observed in the non-fluorinated series.[25]

(22) (a) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 935−939. (b) Rozners, E.; Liu, Y. *Org. Lett.* **2003**, *5*, 181−184. (c) Blot, V.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2004**, *69*, 1196−1201.

(23) Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. P *J. Org. Chem.* **2003**, *68*, 6444−6446.

(24) See the ORTEP view in Supporting Information. The authors have deposited atomic coordinates for **9c** with the Cambridge Crystallographic Data Centre (CCDC 230713). Copies of data can be obtained via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-(0)223336033, e-mail: deposit@ccdc.cam.ac.uk).

(25) Yanada, R.; Negoro, N.; Okaniwa, M.; Ibuka, T. *Tetrahedron* **1999**, *55*, 13947−13956.

Conclusion

In conclusion, this study has allowed access to the novel racemic and homochiral trifluoromethyl β-amino epoxides, analogues of key precursors of various HIV protease inhibitors. Classical routes giving access to these epoxides in the non-fluorinated series could not be applied to the trifluoromethyl compounds, and new routes had to be developed. We have shown that the addition of vinylmagnesium bromide to CF_3-*N*-aryl and *N*-alkyl aldimines was efficient and did not require an activating *N*-substituent. The resultant CF_3-allylamines were converted in an efficient and stereoselective route to novel *syn*-CF_3-epoxides **3** via formation of bromhydrins **8**. The same sequence performed from the aldimine substituted with the methyl ether of the (*R*)-phenylglycinol provided the homochiral (*R*,*R*)-epoxide (de > 98%). Synthetic applications of this epoxide are under development in our laboratory.

Acknowledgment. We thank CNRS for a fellowship (N.T.N.T.), Central Glass Co., and DSM for a kind gift of fluoral and phenylglycinol. We also thank Mrs. S. Mairesse-Lebrun for elementary analyses and Mr. P. Herson (University Paris VI) for the X-ray structure.

Supporting Information Available: Experimental procedures and full characterization for compounds **3**−**5** and **7**−**9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0485233