(*R*)-Trifluoro- and Difluoropyruvaldehyde *N,S*-Ketals: Chiral Synthetic Equivalents of *β*-Trifluoro and *β*-Difluoro α-Amino Aldehydes†

Alessandro Volonterio, Barbara Vergani, Marcello Crucianelli, and Matteo Zanda*

Dipartimento di Chimica del Politecnico, Via Mancinelli 7, I-20131 Milano, Italy

Pierfrancesco Bravo*

C.N.R.-Centro di Studio per le Sostanze Organiche Naturali, Via Mancinelli 7, I-20131 Milano, Italy

Received April 1, 1998

A new, efficient, and stereoselective two-step approach to stereochemically defined chiral nonracemic *γ*-tri- and *γ*-difluoro *β*-amino alcohols (70% to >95% ee) is described, using tri- and difluoropyruvaldehyde *N,S*-ketals (*R*)-**1a,b** as starting materials. Addition of Grignard reagents to (*R*)-**1** occurs with moderate to excellent *anti*-stereocontrol, depending on the nature of the organomagnesium halides, providing the *β*-*p*-tolylthio *β*-benzyloxycarbonylamino secondary carbinols **5**. The stereochemical outcome of these reactions can be rationalized by means of a chelated Cram's cyclic model, where the NCbz group is the chelating ligand and the *p*-tolylthio residue acts as the stereocontrolling "large" group. Reductive displacement of the 2-*p*-tolylthio substituent of **5** efficiently takes places by means of the $NaBH_4$/pyridine system, probably via the corresponding intermediate transient imines **13**, providing sulfur-free *γ*-tri- and *γ*-difluorinated *β*-amino alcohols **7** with high levels of *anti*-stereoselectivity. A considerable shift toward *syn*-stereoselectivity was obtained performing the reaction on the corresponding phenylacetates **8**. Cleavage and reduction of the NHCbz moiety of **7** provided tri- and difluoro analogues of, respectively, norephedrine (**11**) and ephedrine (**12**).

Introduction

Selective introduction of one or more fluorine atoms in natural or synthetic organic molecules can lead to a profound modification of their chemical and physical properties, as well as a dramatic change in biological activity.[1] Nowadays, a number of efficient methods are available to the chemist for the synthesis of fluorinated molecules, thanks to the impressive development of new mild and chemoselective fluorinating agents, to the increasing commercial availability of novel fluorinated building blocks, and to the disclosure of new synthetic approaches to easily accessible fluorinated templates.[2] On the other hand, despite the great impact of the "stereochemical factor" in modern medicinal chemistry[3] and the preminent position of fluorinated molecules in the biomedicinal and pharmaceutical field,[4] asymmetric synthesis in the area of fluoroorganic chemistry is still poorly developed.[5] This is true both for the classical diastereoselective synthesis via chiral auxiliaries as well as for the enantioselective approach via chiral catalysts, enzymes, or living microorganisms, including the use of fluorinating agents, which are barely stereospecific.[6]

Because of their biological importance, a huge number of well-established methods have been developed for the synthesis of stereochemically defined chiral *β*-amino alcohols, according to two distinct general strategies: (1) the introduction of amino alcohol entities without altering the molecular carbon framework;[7] (2) the construction of the amino alcohol array by C−C bond interconnection between two building blocks.[8] One of the most direct retrosynthetic analyses of the problem, belonging to the second group of methods, leads to a chiral α-amino aldehyde and an appropriate nucleophile R^- (retrosynthetic scheme).

Since chiral nonracemic α-amino aldehydes feature a reasonable configurational stability when treated with nucleophiles and can be readily prepared from the corresponding α-amino acids, this approach meets with

* To whom correspondence should be addressed. Fax: (39-2) 2399 3080. E-mail: zanda@dept.chem.polimi.it.

† Presented in part at the 15th International Symposium on Fluorine Chemistry, Vancouver, Canada, August 2−7, 1997.

(1) (a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645.

(2) (a) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards;* Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print no. 58; *Tetrahedron* **1996**, *52*, 1−330. (b) *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994.

(3) Casy, A. F. *The Steric Factor in Medicinal Chemistry. Dissymmetric Probes of Pharmacological Receptors*; Plenum Press: New York, 1993.

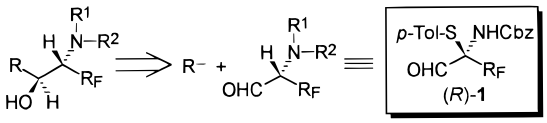
(4) (a) Welch, J. T.; Eswarakrischnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha: Tokyo, 1982. (c) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (d) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, D.C., 1996.

(5) (a) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (b) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, *Tetrahedron: Asymmetry Special Issue*, Guest Editors: T. Hayashi and V. A. Soloshonok, *Tetrahedron: Asymmetry*, **1994**, *5*, 955−1126. (c) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, scheduled to appear in 1998.

(6) For some recent successful stereoselective fluorinations: (a) Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2362. (b) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546. For a review: (c) Davis, F. A.; Qi, H.; Sundarababu, G. in the book of ref 5c, 1st Chapter.

S0022-3263(98)00602-1 CCC: $15.00
Published on Web 09/19/1998

Retrosynthetic Scheme



great success in asymmetric synthesis.[9,10] In contrast, the same strategy has never been successfully applied in the field of organofluorine chemistry for the stereoselective synthesis of γ-fluoro β-amino alcohols, a poorly developed class of molecules with great potential in biomedicinal chemistry.[11] In fact, β-fluoro α-amino aldehydes are expected to have high proclivity toward racemization even in a very weakly basic environment, the α-proton being strongly acidic due to the presence of fluorine.[12] Furthermore, the preparation of β-fluoro α-amino aldehydes is very troublesome, given the lack of readily available precursors and appropriate synthetic methodologies. Trifluoro-, difluoro-, and chlorodifluoropyruvaldehyde *N*,*S*-ketals (*R*)-**1a**−**c** (Retrosynthetic Scheme) represent a new class of readily available, versatile and stereochemically stable equivalents of chiral nonracemic β-fluoro α-amino aldehydes, recently synthesized in our laboratories. Substrates (*R*)-**1** are nonenolizable, and therefore optically stable, since the *p*-tolylthio substituent creates a quaternary α-stereogenic center. In a later stage of the synthetic sequence, the *p*-tolylthio residue can be stereoselectively substituted by a hydrogen atom, providing the targeted γ-fluoro β-amino alcohol frameworks. The *p*-tolylthio group plays the key-role of a removable auxiliary function which acts as the main stereocontrolling group as well.[13]

In this paper we describe in detail the use of tri- and difluoropyruvaldehyde *N*,*S*-ketals (*R*)-**1a,b**, for the stereoselective approach to biologically interesting fluoro-

(7) Catalytic asymmetric aminohydroxylation: (a) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207 and references therein. Ring opening of epoxides with nitrogen-centered nucleophiles: (b) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970 and references therein. (c) Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389. (d) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1996**, *118*, 3584. (e) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557. Reduction of α-hydroxy/alkoxy imines or oximes: (f) Meunier, N.; Veith, U.; Jäger, V. *J. Chem. Soc., Chem. Commun.* **1996**, 331 and references therein. (g) Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 5193. (h) Kreutz, O. C.; Moran, P. J. S.; Rodrigues, J. A. R. *Tetrahedron: Asymmetry* **1997**, *8*, 2649. Reduction of α-amino ketones: (i) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292. (j) Paleo, M. R.; Sardina, F. J. *Tetrahedron Lett.* **1996**, *37*, 3403. Hydroboration/oxidation of enamines: (k) Fisher, B. G.; Goralski, C. T.; Nicholson, L. W.; Hasha, D. L.; Zakett, D.; Singaram, B. *J. Org. Chem.* **1995**, *60*, 2026 and references therein. Azide opening of cyclic diol-derived carbonates: (l) Chang, H.-T.; Sharpless, K. B. *Tetrahedron Lett.* **1996**, *37*, 3219. Coniugate addition of *O*-nucleophiles to nitroalkenes: (m) Lucet, D.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 2682 and references therein. (n) Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2388.

(8) For a general review on the addition of nucleophiles to C=N bonds: (a) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. See also: (b) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1723. Henry (nitroaldol) reaction: (c) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. Condensation of allylamino-boranes with aldehydes: (d) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. (e) Alkylation of glycol aldehyde hydrazones: Enders, D.; Reinhold: U. *Liebigs Ann.* **1996**, 11.

(9) For a general review on α-amino aldehydes: (a) Devant, R. M.; Radunz, H.-E. In *Houben-Weyl: Methods in Organic Synthesis*; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1995; Vol. E21b, pp 1236−1248. For a review on *N*-monoprotected α-amino aldehydes: (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. For recent papers: (c) Curran, T. T. *J. Org. Chem.* **1993**, *58*, 6360. (d) Jurczak, J.; Prokopowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107. (e) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739. (f) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021. (g) Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286. (h) Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913. (i) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607. (j) 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.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656. (k) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958. (l) Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. (m) Ciapetti, P.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183. (n) Niel, G.; Roux, F.; Maisonnasse, Y.; Maugras, I.; Poncet, J.; Jouin, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1275. (o) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074. (p) Palomo, C.; Miranda, J. C.; Cuevas, C.; Odriozola, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1735. (q) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602. (r) Ciapetti, P.; Falorni, M.; Taddei, M. *Tetrahedron* **1996**, *52*, 7379. (s) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Chem. Eur. J.* **1996**, *2*, 1001. (t) Ambroise, L.; Jackson, R. F. W. *Tetrahedron Lett.* **1996**, *37*, 2311. (u) Bastiaans, H. M. M.; van der Baan, J. L.; Ottenheijm, H. C. J. *J. Org. Chem.* **1997**, *62*, 3880. (v) Panek, J. S.; Liu, P. *Tetrahedron Lett.* **1997**, *38*, 5127. (w) Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223. (x) Gryko, D.; Urbanczyk-Lipkowska Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 4059. (y) Rübsam, F.; Seck, S.; Giannis, A. *Tetrahedron* **1997**, *53*, 2823. (z) Braun, M.; Opdenbusch, K. *Liebigs Ann.* **1997**, 141. See also ref 12c and ref 13f.

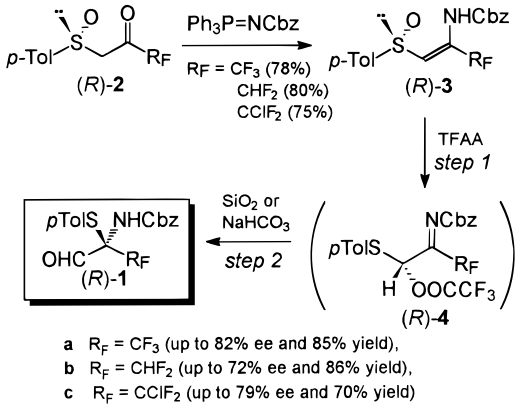
(10) For a review on *N*,*N*-diprotected α-amino aldehydes: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. For other examples: (b) Bubert, C.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 4985. (c) Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97. (d) O'Brien, P.; Powell, H. R.; Raithby, P. R.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1031. (e) Gryko, D.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron* **1997**, *53*, 13373. (f) Shimizu, M.; Wakioka, I.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 6027. (g) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 353 and references therein. (h) Laïb, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1771. (i) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1997**, *62*, 999. (j) Gryko, D.; Jurczak, J. *Tetrahedron Lett.* **1997**, *38*, 8275. (k) D'Aniello, F.; Falorni, M.; Mann, A.; Taddei, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1217. (l) Dinh, T. Q.; Du, X.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606. (m) Andrés, J. M.; Barrio, R.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210. (n) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673. (o) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248. (p) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139. (q) Garner, P.; Park, J.-M. *Org. Synth.* **1991**, *70*, 18.

(11) (a) Bégué, J.-P.; Bonnet-Delpon, D. in the book of ref 4d; Chapter 4, pp 59−72. (b) Ojima, I.; Kuduk, S. D.; Slater, J. C.; Gimi, R. H.; Sun, C. M.; Chakravarty, S.; Ourevitch, M.; Abouabdellah, A.; Bonnet-Delpon, D.; Bégué, J.-P.; Veith, J. M.; Pera, P.; Bernacki, R. J. in the book of ref 4d; Chapter 17, pp 228−243. (c) Marti, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann.* **1995**, 1193. (d) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897. (e) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826. (f) Ojima, I.; Slater, J. C.; Pera, P.; Veith, J. M.; Abouabdellah, A.; Bégué, J.-P.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 133. (g) Bravo, P.; Farina, A.; Kukhar, V. P.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M.; Zappalà, C. *J. Org. Chem.* **1997**, *62*, 3424. (h) Uneyama, K.; Hao, J.; Amii, H. *Tetrahedron Lett.* **1998**, *39*, 4079.

(12) (a) Konno, T.; Yamazaki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 199. (b) Hedhli, A.; Baklouti, A.; Cambon, A. *Tetrahedron Lett.* **1994**, *35*, 6877. (c) Angert, H.; Czerwonka, R.; Reissig, H.-U. *Liebigs Ann.* **1997**, 2215.

(13) For some examples on the use of α-thio aldehydes in asymmetric synthesis: (a) Eames, J.; de las Heras, M. A.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4077 and references therein. (b) Eames, J.; Jones, R. V. H.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4823. (c) Sato, T.; Otera, J. *Synlett* **1995**, 351. (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456. (e) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775 (f) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293. (g) Enders D.; Piva, O.; Burkamp, F. *Tetrahedron* **1996**, *52*, 2893. (h) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484. (i) Annunziata, R.; Cinquini, M.; Cozzi, F.; Fuchicello, A. *Tetrahedron* **1991**, *47*, 3853. (j) Antolini, L.; Bellesia, F.; Ghelfi, F.; Pagnoni, U. M.; Pinetti, A. *Gazz. Chim. Ital.* **1997**, *127*, 11. (k) Watanabe, M.; Komota, M.; Nishimura, M.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2193; corrigenda: *J. Chem. Soc., Perkin Trans. 1* **1993**, 3177. (l) Brown, M. D.; Witham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 817. (m) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1980**, *21*, 4883. (n) Shimagaki, M.; Takubo, H.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6235.

Scheme 1. Preparation of Fluoropyruvaldehyde *N,S*-Ketals (*R*)-1



organic molecules having a γ-tri- and γ-difluoro β-amino alcohol unit, for example analogues of *Ephedra* alkaloids.[14] As a further matter of interest, the peculiar reactivity of tri- and difluoropyruvaldehyde *N,S*-ketals (*R*)-**1a,b** toward Grignard reagents allowed us to compare directly, for the first time, the relative stereodirecting properties of an arylthio group, a monoprotected amino group, and a fluoroalkyl group.

Results

Preparation of Fluoropyruvaldehyde *N,S*-Ketals. Fluoropyruvaldehyde *N,S*-ketals (*R*)-**1a**−**c** (Scheme 1) can be prepared in three steps from fluoroacetic esters, which are commercially available and cheap fluorine sources, and (*R*)-methyl *p*-tolyl sulfoxide, which is also an easily available chiral building-block.[15]

Condensation of lithiated (*R*)-methyl *p*-tolyl sulfoxide and fluoroacetic esters afforded high yields of the corresponding α-fluoro α′-sulfinyl ketones (*R*)-**2a**−**c**,[16] which were transformed in good yields into geometrically homogeneous *cis*-α-(fluoroalkyl)-β-sulfinyl enamines (*R*)-**3a**−**c** by reaction with *N*-Cbz iminotriphenylphosphorane.[17] A highly enantioselective tandem Pummerer reaction/1,2-migration of the *p*-tolylthio group, which produced in *one-pot* the target fluoropyruvaldehyde *N,S*-ketals (*R*)-**1a**−**c** from the enamines (*R*)-**3a**−**c**, through the intermediate imine (*R*)-**4a**−**c**, is the last step of the sequence.[18] This tandem reaction is operatively simple, fast, and requires nonexotic and inexpensive reagents, namely 1 equiv of trifluoroacetic anhydride, which promotes the Pummerer rearrangement (step 1), and silica gel or aqueous $NaHCO_3$, which trigger the suprafacial migration of the *p*-tolylthio residue to give the desired fluoropyruvaldehyde *N,S*-ketals (*R*)-**1a**−**c** (step 2). Very recently the enantioselectivity of the process has been further improved and optimized by means of chemometric methods.[19] Fluoropyruvaldehyde *N,S*-ketals (*R*)-**1a**−**c** are now available with ee ranging from 82% (the trifluoro derivative (*R*)-**1a**) to 72% (the difluoropyruvaldehyde (*R*)-**1b**).

Scheme 2. Reaction of Fluoropyruvaldehyde *N,S*-Ketals (*R*)-1 with Grignard Reagents

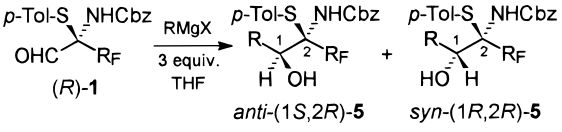


Table 1. Reaction of Fluoropyruvaldehyde *N,S*-ketals (*R*)-1 with Grignard Reagents

entry	product	X	R	R_F	*anti*/*syn*[a]	yields (%)[b]
1	**5a**	Cl	CH_3	CF_3	17:1	72
2	**5b**	Br	CH_2CH_3	CF_3	4:1	72
3	**5c**	Br	$CH{=}CH_2$	CF_3	36:1	94
4	**5d**	Cl	Ph	CF_3	7:1	90
5	**5e**	Cl	CH_3	CHF_2	8:1	75
6	**5f**	Cl	Ph	CHF_2	10:1	90

[a] Determined by ^1H and ^{19}F NMR. [b] Isolated overall yields of the diastereoisomers *anti*- and *syn*-**5**.

Reaction with Grignard reagents. Trifluoro Derivatives. Addition of a THF solution of methylmagnesium chloride (3.0 equiv) to a solution of trifluoropyruvaldehyde *N,S*-ketal (*R*)-**1a**, in the same solvent at −78 °C, gave rise to a fast reaction, affording with high diastereoselectivity (17:1) and good yields (72%) the corresponding carbinol *anti*-**5a** (Scheme 2 and Table 1, entry 1).[20] Ethyl, vinyl-, and phenylmagnesium halides (Scheme 2 and Table 1, entries 2−4) efficiently added to the aldehyde (*R*)-**1a**, upon slow addition of a THF solution of (*R*)-**1a** to the solution of Grignard reagent (3.0 equiv) in the same solvent,[21] producing the corresponding carbinols *anti*-**5** as major diastereomers. Ethylmagnesium bromide (Table 1, entry 2) added with moderate facial diastereoselectivity, producing a 4:1 mixture of isomers *anti*/*syn* **5b**. Vinylmagnesium bromide (Table 1, entry 3) produced the highest discrimination between the two carbonylic diastereofaces of (*R*)-**1a**, leading to the formation of the allylic alcohol *anti*-**5c** with ca. 95% de, in almost quantitative yield. The reaction of (*R*)-**1a** with phenylmagnesium chloride was of particular interest, as the benzyl carbinols **5d** are precursors of trifluoro analogues of *Ephedra* alkaloids, molecules of remarkable biological and pharmaceutical interest.[11c,d] Satisfactorily, the reaction (Table 1, entry 4) occurred smoothly, as usual, affording the desired products **5d** in *anti*/*syn* 7:1 ratio and 90% yield.

The ee's of the major *anti* β-amino alcohols **5a,c** were checked by esterification with both enantiomers of α-phenylpropionic acid (PPA), producing the corresponding diastereomeric α-PPA esters (**6a,c**).[22] Careful examina-

(14) Volonterio, A.; Bravo, P.; Capelli, S.; Meille, S. V.; Zanda, M. *Tetrahedron Lett.* **1997**, *38*, 1847.

(15) Bravo, P.; Crucianelli, M.; Fronza, G.; Zanda, M. *Synlett* **1996**, 249.

(16) (a) Bravo, P.; Piovosi, E.; Resnati, G. *Synthesis* **1986**, 579. (b) Bravo, P.; Zanda, M. "Asymmetric Synthesis of Fluoro-Organic Compounds via Chiral Sulfoxide Chemistry" in the book of ref 5c, Chapt. 4.

(17) (a) Bravo, P.; Crucianelli, M.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 3043. (b) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375; corrigenda: *J. Org. Chem.* **1996**, *61*, 9635.

(18) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, *62*, 8031.

(19) Bjørsvik, H.-R.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2817.

(20) In this paper, *syn* and anti descriptors refer to the relative position of the amino and the hydroxy groups with respect to the molecular carbon backbone.

(21) Inverse addition of THF solutions of ethyl, vinyl, and phenyl Grignard reagents to (*R*)-**1a** in the same solvent invariably produced low amounts of the corresponding carbinols **5b**−**d** together with partially racemized, unreacted starting pyruvaldehyde (*R*)-**1a**, even after prolonged reaction time and heating to room temperature.

(22) (a) Helmchen, G.; Nill, G.; Flockerzi, D.; Schuhle W.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 62−63. (b) Bravo, P.; Ganazzoli, F.; Resnati, G.; De Munari, S.; Albinati, A. *J. Chem. Res.* **1988**, (S) 216, (M) 1701.

tion of the corresponding crude reaction mixtures by ^{1}H and ^{19}F NMR allowed us to assess that no loss of enantiomeric purity had occurred during the addition of methyl and vinyl Grignard reagents to (*R*)-**1a**. In fact, the de of **6a,c** were almost identical to the ee of the starting (*R*)-**1a**.

Absolute and relative stereochemistry of the major methyl carbinol *anti*-**5a** was determined by X-ray diffraction of its (+)-(*S*)-PPA ester **6a**.[14] Absolute (*S*)-stereochemistry of the carbinolic center C-1 of the major derivative *anti*-**5c** was determined by NMR analysis of its (*R*)- and (*S*)-PPA esters **6c**.[22,23] *Anti*-(1*S*,2*R*) stereochemistry was confidently assigned to the major diastereoisomer of ethyl and phenyl derivatives **5b,d** on the basis of their ^{19}F NMR spectra (stereochemistry of **5d** was later confirmed by chemical correlation, as shown below). In fact, the ^{19}F NMR signals of the trifluoromethyl groups of the major diastereoisomers **5a**−**d** were always observed at lower fields than those of the minor diastereomers (see Experimental Section and Supporting Information). A similar trend has been already described for the ^{19}F NMR spectra of a closely related series of *anti*- and *syn*-γ-trifluoro β-amino alcohols.[11c,d]

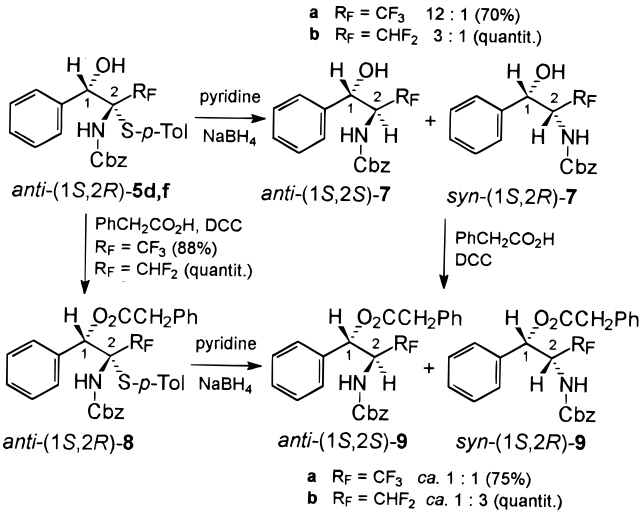
3,3,3-Trifluoro-2-NHCbz-2-*p*-tolylthio alcohols **5a**−**d** are stable compounds, both chemically and optically: no deterioration was detected after several months of storage at 4 °C, as well as after a prolonged stay in chloroform or AcOEt solution at room temperature.

Difluoro Derivatives. Next, we examined the reactivity of the difluoropyruvaldehyde *N,S*-ketal (*R*)-**1b** toward Grignard reagents (Scheme 2, Table 1), to extend the methodology to the synthesis of chiral nonracemic γ-difluoro β-amino alcohols. Addition of a THF solution of difluoropyruvaldehyde (*R*)-**1b** to a solution of methylmagnesium chloride (3.0 equiv) (Table 1, entry 5), in the same solvent, at −78 °C, provided the corresponding difluoro carbinol *anti*-**5e**, in 75% yield and 8:1 dr.

The reaction of difluoro pyruvaldehyde (*R*)-**1b** with phenylmagnesium chloride (3.0 equiv) (Table 1, entry 6) was of particular synthetic interest, since the product **5f** could be used as a synthetic intermediate for the synthesis of difluoro analogues of *Ephedra* alkaloids. Satisfactorily, the reaction proved to be a high yielding (90%) and remarkably stereoselective process (10:1 *anti*/*syn*). In contrast with the trifluoro derivatives (entries 1−4, Table 1), a partial loss of enantiomeric purity with respect to the starting difluoro aldehyde (*R*)-**1b** was evidenced by NMR analysis of *anti*-**5f** with the chiral shift reagent Eu(hfc)$_3$. Starting from a sample of difluoro aldehyde (*R*)-**1b** with 61% ee, we obtained mixtures of diastereomeric **5f** having 50% ee, independently of the reaction time. This must be necessarily explained in terms of a partial racemization occurring at the level of the starting difluoropyruvaldehyde (*R*)-**1b**, catalyzed by the Grignard reagents, in competition with the desired 1,2-addition reaction.[24,25]

In analogy with the corresponding trifluoro derivatives **5a**−**d**, 3,3-difluoro-2-NHCbz-2-*p*-tolylthio alcohols **5e,f** are stable compounds, when stored in chemically pure state, but, surprisingly, *N,S*-ketalic centers C-2 of **5e,f**, were found to be configurationally unstable in solution of HPLC grade AcOEt at room temperature. For example, in these conditions an *anti*/*syn* 10:1 mixture of **5f** epimerized completely overnight, producing a 1:1 mixture of diastereomers. In contrast, no epimerization took place either in $CHCl_3$ solution even after several days at room temperature, or under reaction conditions in the presence of the Grignard reagent. The latter point was checked by performing two parallel reactions between (*R*)-**1b** and phenylmagnesium chloride, lasting, respectively, 5 and 30 min, which produced the same 10:1 ratio of *anti* and *syn* diastereomers **5f** (see Table 1, entry 6).

Scheme 3. Stereoselective Reductive Desulfenylation



Stereoselective Reductive Desulfenylation. Pursuing the goal to obtain stereoselectively sulfur-free γ-fluoro β-amino alcohols from the adducts **5d,f**, we turned our attention to the problem of the stereocontrolled replacement of the *p*-tolylthio group with a hydrogen atom.[26] Inspection of the literature revealed a report by Tsuchihashi and Ogura (1975) on the reductive removal of a SCH_3 group from racemic *N,S*-ketals by means of a $NaBH_4$/pyridine system.[27] We therefore decided to submit *anti*-**5d** to the same conditions. The substrate was dissolved in pyridine, and 5 equiv of $NaBH_4$ were added portionwise at 0 °C during 3 h, producing a 12:1 mixture of *anti*/*syn* diastereomeric *N*-Cbz γ-trifluoro β-amino alcohols **7a**,[28] in 70% yield (Scheme 3). With this excellent result in hand, we repeated the protocol on the difluoro derivative *anti*-**5f**. The reaction was very smooth, reaching completion in a few minutes, delivering the desired *N*-Cbz γ-difluoro

(23) The δ_H of the C*H*=CH_2 of (1*S*,2*R*,2′*R*)-**6c** resonates at higher fields (5.76−5.95 ppm) with respect to the corresponding signal of (1*S*,2*R*,2′*S*)-**6c** (5.84−6.03 ppm), because of the shielding effect exerted by the phenyl ring of the PPA residue (see Supporting Information).

(24) Such racemization should occur by addition−elimination of *p*-thiocresol from **1b**, through the transient *N*-Cbz ketimine of difluoropyruvaldehyde.

(25) The higher configurational and chemical stability featured by the sp^3 *N,S*-ketalic stereocenters C-2 of all trifluoro derivatives studied in this work, with respect to the corresponding difluoro derivatives, should be due to the stronger electron-withdrawing effect of the trifluoromethyl group. For other examples of stable acyclic α-trifluoromethyl *N,S*-ketals see: Laduron, F.; Ates, C.; Viehe, H. G. *Tetrahedron Lett.* **1996**, *37*, 5515.

(26) Initial attempts to accomplish this transformation on the trifluorobenzyl alcohol *anti*-**5d** by means of the classical hydrogenolysis catalyzed by Raney-Ni produced very low yields of an almost equimolar mixture of the corresponding sulfur-free diastereomeric *N*-Cbz β-amino alcohols **7a**.

(27) Ogura, K.; Yoshimura, I.; Katoh, N.; Tsuchihashi, G. *Chem. Lett.* **1975**, 803.

(28) *anti*-**7a** is a known compound: see ref 11 g.

β-amino alcohols **7b** in *anti*/*syn* 3:1 ratio and quantitative yield.

To examine the effect of the hydroxyl on the diastereoselectivity of the reductive desulfenylation, as well as the possibility of achieving inversion as the stereochemical outcome of the process, for preparing γ-fluoro β-amino alcohols of the *syn* series, we addressed the preparation of the phenylacetic esters **8a,b**. High yields of these compounds were obtained by treatment of the carbinols *anti*-**5d,f** with DCC/phenylacetic acid (Scheme 3). In contrast, attempts to prepare the corresponding benzoates, under the same conditions, were surprisingly unsuccessful, the reaction being very slow.

Trifluoro ester *anti*-**8a** underwent desulfenylation with $NaBH_4$/pyridine under the conditions described for the corresponding carbinol *anti*-**5d**, producing the desired transformation with slightly higher yields, but with a dramatic drop of diastereoselectivity. In fact, the diastereomeric phenylacetoxy γ-trifluoro β-amino derivatives **9a** were formed in 75% yield, as an almost equimolar *anti*/*syn* mixture. The same procedure, applied on the difluoro ester *anti*-**8b** (Scheme 3), led to a clear-cut inversion of diastereoselectivity, with respect to the desulfenylation of the corresponding carbinol *anti*-**5f**. Thus, the desired *syn* phenylacetoxy γ-difluoro β-NHCbz derivative **9b** was produced with 50% de, in quantitative overall yield.

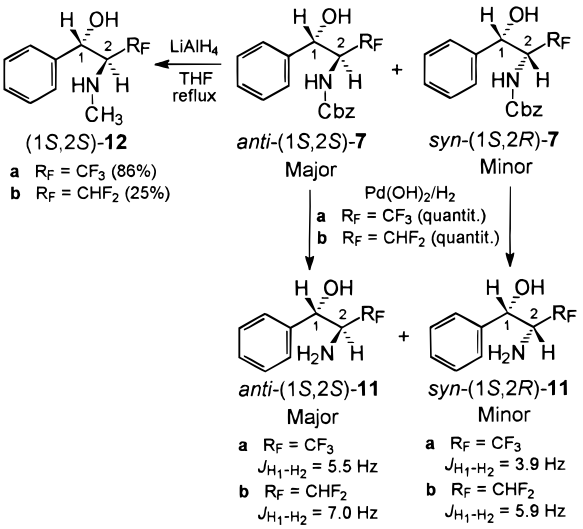
Stereochemistry of the diastereomeric difluorinated phenylacetates **9b** was determined by correlation with the corresponding unprotected derivatives **7b** (Scheme 3). Thus, esterification of *anti*-**7b** with phenylacetic acid/DCC produced the minor diastereomer obtained by desulfenylation of **8b**. Ee's of the major diastereomeric γ-tri- and γ-difluoro β-amino alcohols **7a,b** were checked by esterification with both enantiomers of PPA, leading to the corresponding α-phenylpropionates (**10a,b**), and subsequent analysis of the crude reaction mixtures. Starting from a sample of trifluoropyruvaldehyde (*R*)-**1a** having 70% ee, *N*-Cbz trifluorononorephedrine *anti*-**7a** was obtained with essentially the same degree of enantiomeric purity. Starting from a difluoropyruvaldehyde (*R*)-**1b** with 61% ee, *N*-Cbz difluoro norephedrine *anti*-**7b** was obtained with 50% ee, owing to partial epimerization of (*R*)-**1b** by action of phenylmagnesium chloride (see above). Samples of *N*-Cbz difluorononorephedrine *anti*-**7b** with ee > 95% were obtained easily by fractional crystallization from diisopropyl ether.

Synthesis of Fluorinated *Ephedra*-Alkaloids. The final step of the synthesis of the targeted fluorinated *Ephedra* alkaloids was performed by means of simple manipulations of the *N*-Cbz residue of trifluoro and difluoro *N*-Cbz norephedrines **7a,b** (Scheme 4).

Trifluorononorephedrine *anti*-**11a**, having 70% ee, was obtained from *anti*-**7a** in quantitative yield by hydrogenolysis of the *N*-Cbz group with H_2/$Pd(OH)_2$. Trifluoroephedrine *anti*-**12a** (70% ee) was isolated in 86% yield after reduction of the *N*-Cbz group with $LiAlH_4$ in refluxing THF. The same protocols, applied on enantiopure *N*-Cbz difluorononorephedrine *anti*-**7b** (ee > 95%), produced difluorononorephedrine *anti*-**11b** (quantitative) and difluoroephedrine *anti*-**12b** (25%) in enantiomerically pure form.

The absolute and relative stereochemistry of trifluorononorephedrine *anti*-(1*S*,2*S*)-**11a** was assessed by comparison with a sample of the enantiomer *anti*-(1*R*,2*R*)-**11a**, obtained through a different synthetic strategy, recently reported from these laboratories.[11g] Further evidence was obtained by comparison of the spectral features of *anti*- and *syn*-**11a** with those reported by Seebach for the racemic compounds.[11c,d] Trifluorononorpseudoephedrine *syn*-**11a** was obtained from a pure sample of *syn*-**7a** (Scheme 4). As expected, the spectral properties of both diastereomers *anti*- and *syn*-**11a** were found to match those reported in the literature.

Scheme 4. Synthesis of Fluorinated *Ephedra* Alkaloids



With the hope of confirming the stereochemistry of both diastereomeric difluoro derivatives *anti*- and *syn*-**11b**, a 3:1 mixture of these compounds was obtained by hydrogenolysis of a mixture of anti and *syn N*-Cbz difluoro derivatives **7b**, having the same dr (Scheme 4). Next, we compared the spectral properties of both diastereomers **11b** with the corresponding trifluoro derivatives **11a**, having known stereochemistry. Both the major trifluoro and difluoro diastereomers **11a,b** were found to feature a higher value of J_{H1-H2} with respect to the minor diastereomers (Scheme 4), strongly suggesting that the major diastereomer **11b** should be difluorononorephedrine, having *anti*-(1*S*,2*S*) stereochemistry, whereas the minor diastereomer should be difluorononorpseudoephedrine *syn*-(1*S*,2*R*)-**11b**, in analogy with the trifluorinated derivatives **11a**.

Discussion

Reaction with Grignard Reagents: A Model for the Facial Diastereoselectivity. On considering what factors determine the stereochemical outcome of the addition of Grignard reagents to fluoropyruvaldehydes (*R*)-**1**, it should be noted (Scheme 2) that 3 equiv of Grignard reagents are necessary for obtaining a complete conversion of (*R*)-**1** into the secondary carbinols **5**. This observation is in line with the literature reports on the behavior of *N*-monoprotected α-amino aldehydes, which are known to undergo removal of the acidic aminic proton when submitted to reactions with basic nucleophiles.[9a,b] The resulting salts are proposed to react with an excess of nucleophile through a Cram's cyclic five-membered chelated structure,[29] involving the counterion, the carbonylic oxygen, and the nitrogen in the α-position (Figure 1).

(29) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.

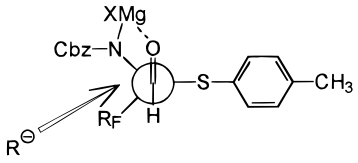
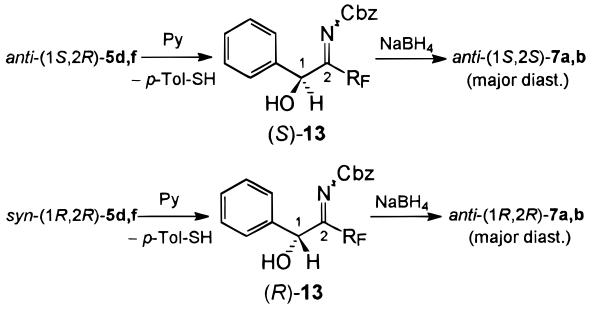


Figure 1. Model for the facial diastereoselectivity of the reaction of (*R*)-**1** with Grignard reagents.

Scheme 5. Mechanism of the Reductive Desulfenylation



Attack of the Grignard reagents to the *Si* face of the carbonyl group of (*R*)-**1** must therefore occur from the R_F group side, with the *p*-tolylthio group behaving as the large substituent, which occupies the staggered position (Figure 1). This hypothesis is also supported by the X-ray diffraction of a single crystal of racemic difluoropyruvaldehyde **1b**.[30] Although it is clear that the situation of **1b** in the solid state cannot be directly transferred to the case of its magnesium salt dissolved in THF, it is worth noting that the conformation of **1b** in a crystal grown from diisopropyl ether is very close to the conformation represented in Figure 1. Finally, this picture is also supported by the quite popular assumption that the trifluoromethyl group should be "similar in size" to the isopropyl group.[31] Since some authors reported that an arylthio residue is remarkably "larger" than the isopropyl group,[13d,e] as a logical consequence, attack of the Grignard reagents from the fluoroalkyl group side (*Si* face) of (*R*)-**1** is expected to be strongly preferred over the attack from the *p*-tolylthio group side (*Re* face), in agreement with the experimental findings.

A Rationale for the Reductive Displacement of the *p*-Tolylthio Group. The mechanism of the displacement of the *p*-tolylthio group by action of $NaBH_4$ in pyridine has been investigated in detail. The first step of the process should be the elimination of *p*-thiocresol from the *N*,*S*-ketalic center C-2 of *anti*-**5d,f**, promoted by pyridine, producing the corresponding transient *N*-Cbz imines (*S*)-**13** (Scheme 5), which, according to this picture, should be the true reactive species toward $NaBH_4$.

This pathway is in agreement with several experimental observations: 1) diastereomerically pure *anti*-ketals **5d,f** dissolved in pyridine, or Hunig's base (see Supporting Information) at room temperature, underwent epimerization of the ketalic center; (2) interconversion between the diastereoisomers anti and *syn*-**5f** was clearly detected by TLC analysis during the reaction, before the irreversible reductive desulfenylation took place; (3) reduction of diastereomerically pure *β*-hydroxy ketals *anti*-**5d,f**, as well as of mixtures of *syn*/*anti* isomers, afforded the same degree of diastereoselectivity, when submitted to the $NaBH_4$/pyridine treatment, independent of the stereochemistry of the starting materials (Scheme 5). By analogy, the same process should be operating in the reductive desulfenylation of phenylacetic esters **8a,b**.

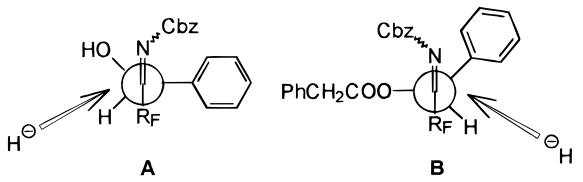


Figure 2. Model for the facial diastereoselectivity of the reduction of the intermediate imines (*S*)-**13**.

The high level of anti selectivity featured by the CF_3-ketal **5d** could be explained by means of the Felkin−Anh model depicted in Figure 2A.[32] The staggered position should be occupied by the phenyl ring, and attack of the hydride should therefore occur from the *Re* face of the imine, with the hydroxyl acting as the "medium" group and, obviously, the hydrogen as the "small" group. Further stabilization of this conformation might derive from hydrogen bonding involving the hydroxyl and the iminic nitrogen, or the carbonyl oxygen of Cbz. The major steric and electronic interactions should involve the incoming hydride reducing species and the R_F groups attached to the azomethine function.[32] This could reasonably explain the fact that the substrate **5d** undergoes reductive desulfenylation with higher anti diastereoselectivity (12:1) than does **5f** (3:1). In fact, the former has $R_F = CF_3$, which is known to be more electron-withdrawing, and more sterically demanding owing to its uniform fluorinated surface, than the residue $R_F = CHF_2$ of the latter.[31]

Transformation of the hydroxyl into a phenylacetoxy residue should result in increasing electron-withdrawing character and steric hindrance of this group, as well as eliminating any hydrogen bonding. For these reasons, the reactive conformation having the phenylacetoxy group in staggered position ("large" residue) (Figure 2B) should become competitive, leading to a considerable increase of *syn* diastereoselectivity. This hypothesis accounts for the observed lack of facial diastereocontrol in the reductive desulfenylation of the phenylacetoxy trifluoro derivative *anti*-**8a** (Scheme 3), and for the *syn* facial diastereoselectivity (3:1) featured by the corresponding difluorinated ester *anti*-**8b**.

Conclusions

The synthetic methodology described in this paper demonstrates that fluoropyruvaldehyde *N*,*S*-ketals (*R*)-**1**

(30) Bravo, P.; Capelli, S.; Meille, S. V.; Zanda, M. Manuscript in preparation.

(31) (a) Smart, B. E. in the book of ref 1a; Chapter 3, pp 80−81, and references therein. See also ref 1b and 12a. For a discussion on the stereolectronic effects of some perfluoroalkyl substituents in asymmetric transformations see: (b) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99. (c) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470. (d) Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 233. (e) Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075 and refs therein.

(32) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Anh, N. G.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *17*, 155. (c) Paddon-Row: M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (d) Wong, S. S.; Paddon-Row: M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (e) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipf, G. *Tetrahedron* **1974**, *30*, 1563. (f) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

are useful chiral nonracemic electrophilic building blocks, which can be used successfully for the stereoselective synthesis of γ-fluoro β-amino alcohols of biological interest. The *N*,*S*-ketalic stereocenter of (*R*)-**1** is a stereogenic masked electrophilic site, which effectively induces stereocontrol in the 1,2-addition of Grignard reagents to the carbonyl moiety. In a later stage of the synthetic sequence the *p*-tolylthio group can be stereoselectively replaced with a hydrogen, affording sulfur-free, stereochemically defined γ-fluoro β-amino alcoholic units. The whole process features high yields, cheap and nonexotic reagents, operationally simple procedures, and mild conditions. These considerations suggest that fluoropyruvaldehyde *N*,*S*-ketals (*R*)-**1** could find many further useful applications in the field of asymmetric organofluorine synthesis.

Experimental Section

General Methods. ^{1}H (400 or 250 MHz), ^{19}F (235 MHz), and ^{13}C (100.6 or 62.8 MHz) NMR samples were prepared as dilute solutions in the appropriate deuterated solvent. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and $\delta_C = 0.00$) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard ($\delta_F = -162.90$) for ^{19}F nuclei. Ee's have been determined by ^{1}H and ^{19}F NMR analysis of pure samples of the appropriate compounds, by using the chiral shift reagent (+)-[Eu(hfc)$_3$] in $CDCl_3$ solution. Anhydrous THF was distilled from sodium and benzophenone. Anhydrous CH_2Cl_2 was distilled from calcium hydride. In all other cases commercially available reagent-grade solvents were employed without purification. Grignard reagents were purchased from Sigma/Aldrich Co. Reactions performed in dry solvents were carried out in nitrogen atmosphere. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230−400 ASTM mesh) was employed as a reagent [for the preparation of (*R*)-**1**] and for flash column chromatography (FC). α-(Fluoroalkyl)-β-sulfinyl enamines (*R*)-**3** were prepared according to the procedure described in the literature.[17]

Fluoropyruvaldehyde *N*,*S*-ketals (*R*)-1. To a stirred 0.15 M solution of (*R*)-(*Z*)-**3a** (0.38 g, 1 mmol) in dry THF, cooled at 0 °C, was added neat TFAA (1 mmol, 0.14 mL) via syringe and left 1 min under stirring. TLC monitoring showed the immediate disappearance of (*R*)-(*Z*)-**3a**, with the formation of a unique spot at much higher R_f (0.45 in *n*-hexane/AcOEt 85:15). Silica gel (ca. 0.4 g) was added in one portion at 0 °C, and the resulting mixture was vigorously stirred for 5 min at the same temperature. Water (ca. 10 mL) was added at 0 °C, and the phases were immediately separated. The aqueous layer was extracted with AcOEt. The collected organic phases were dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure. FC of the crude reaction mixture on a short silica gel column afforded 0.22 g (57%) of (*R*)-**1a**, $[\alpha]^{20}_D$ +138.6 (*c* 0.89, $CHCl_3$) (ee 69%). For an improved procedure (both in terms of yield and enantioselectivity) and a detailed chemometric study on the factors influencing this reaction, see ref 19. Since that study was performed when the present work was already in an advanced stage, the samples of (*R*)-**1a,b** used as starting materials in the present work were usually prepared according to the general procedure described above.

2-[(Benzyloxycarbonyl)amino]-2-[(4-methylphenyl)-sulfenyl]-3,3,3-trifluoropropanal (*R*)-1a: yellowish oil; R_f (85:15 *n*-hexane/AcOEt) 0.45; ^{1}H NMR ($CDCl_3$) δ 9.37 (1H, q, J = 1.7 Hz), 7.43−7.32 (5H, m), 7.20 (2H, d, J = 8 Hz), 7.01 (2H, d, J = 8 Hz), 5.53 (1H, br s), 5.20 (1H, d, J = 12 Hz), 5.07 (1H, d, J = 12 Hz), 2.32 (3H, s); ^{19}F NMR ($CDCl_3$) δ −70.45 (q, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 183.0 (q, J = 1.8 Hz), 153.3, 141.7, 138.1, 135.3, 130.3, 128.8, 128.7, 122.7 (q, J = 287 Hz), 120.7, 72.8 (q, J = 28.9 Hz), 67.9, 21.4; MS (EI, 70 eV) *m*/*z* (%): 383 (M^+, 8), 124 (35), 91 (100). Anal. Calcd for $C_{18}H_{16}NO_3F_3S$: C, 56.39; H, 4.21; N, 3.65. Found: C, 56.49; H, 4.30; N, 3.50.

2-[(Benzyloxycarbonyl)amino]-2-[(4-methylphenyl)-sulfenyl]-3,3-difluoropropanal (*R*)-1b (obtained from (*R*)-(*Z*)-**3b**): yield 58%; $[\alpha]^{20}_D$ +280.8 (*c* 0.64, $CHCl_3$), ee 62%; white solid, the racemate could be crystallized from diisopropyl ether: mp 81−82 °C; R_f (80:20 *n*-hexane/AcOEt) 0.67; ^{1}H NMR ($CDCl_3$) δ 9.49 (1H, s), 7.48−7.32 (5H, m), 7.07 (2H, d, J = 8 Hz), 6.95 (2H, d, J = 8 Hz), 6.90 (1H, t, J = 55 Hz), 5.64 (1H, br s), 5.22 (1H, d, J = 12 Hz), 4.98 (1H, d, J = 12 Hz), 2.30 (3H, s); ^{19}F NMR ($CDCl_3$) δ −132.6 (1F, dd, J = 55 and 290 Hz), −122.1 (1F, dd, J = 55 and 290 Hz); ^{13}C NMR ($CDCl_3$) δ 183.2 (t, J = 4 Hz), 153.7, 141.3, 137.9, 135.5, 130.2, 128.9, 121.2, 113.4 (dd, J = 247.6 and 252.4 Hz), 73.2 (t, J = 23 Hz), 67.6, 21.4; MS (EI, 70 eV) *m*/*z* (%): 365 (M^+, 4), 124 (35), 91 (100); FT IR (cm^{-1}) 3372 (br), 1721 (br), 1494, 1245. Anal. Calcd for $C_{18}H_{17}NO_3F_2S$: C, 59.17; H, 4.69; N, 3.83. Found: C, 59.48; H, 4.85; N, 3.58.

Reaction of (*R*)-1a,b with Grignard Reagents. The synthesis of **5d** is described as an example. To a cooled solution (−78 °C) of phenylmagnesium chloride (993 μL of a 2 M solution in THF, 1.99 mmol) in dry THF (6 mL) was added dropwise a solution of aldehyde (*R*)-**1a** (250 mg, 0.66 mmol) in dry THF (2 mL) under nitrogen atmosphere. After 1 min the reaction was quenched with a saturated aqueous solution of NH_4Cl, heated at room temperature, and extracted with AcOEt. The collected organic phases were dried over anhydrous sodium sulfate and filtered, and the solvent was removed in vacuo. The crude was purified by FC (85:15 hexane/AcOEt), affording 273 mg (90%) of **5d**.

(1*S*,2*R*)-2-[(Benzyloxycarbonyl)amino]-2-[(4-methylphenyl)sulfenyl]-3,3,3-trifluoro-1-phenylpropan-1-ol (5d): R_f (8:2 *n*-hexane/AcOEt) 0.47; $[\alpha]^{20}_D$ −85.8 (*c* 0.3, $CHCl_3$) ee 73%; ^{1}H NMR ($CDCl_3$) δ 7.26−7.49 (12H, m), 7.08 (2H, d, J = 7.8 Hz), 5.50 (1H, br d, J = 3.1 Hz), 5.26 (1H, s), 5.13 (1H, d, J = 12.1 Hz), 5.07 (1H, d, J = 12.1 Hz), 4.77 (1H, br m), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 155.0, 140.9, 138.2, 137.5, 135.3, 129.9, 128.7, 128.66, 128.64, 128.5, 128.4, 127.9, 127.7, 124.4 (q, J = 286.4 Hz), 75.5 (q, J = 25.7 Hz), 74.8, 67.9, 21.3; ^{19}F NMR ($CDCl_3$) δ −69.2 (3F, s); MS (EI, 70 eV) *m*/*z* (%): 584 (M^+ + S-*p*-Tol, 3), 338 (M^+ − S-*p*-Tol, 6), 230 (100), 153 (21); FT IR (cm^{-1}) 3391, 3036, 1710, 1494, 1456.

(1*R*,2*R*)-5d: R_f (8:2 *n*-hexane/AcOEt) 0.37; ^{1}H NMR ($CDCl_3$) δ 7.26−7.49 (14H, m), 5.64 (1H, br d, J = 2.7 Hz), 5.26 (1H, s), 5.16 (1H, d, J = 12.0 Hz), 5.05 (1H, d, J = 12.0 Hz), 4.77 (1H, br m), 2.34 (3H, s); ^{19}F NMR ($CDCl_3$) δ −71.1 (3F, s).

Esterification with Phenylacetic or Phenylpropionic Acid. The synthesis of **8a** is described as an example. To a solution of **5d** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (5 mL) were added neat phenylacetic acid (41 mg, 0.3 mmol) and then DCC (62 mg, 0.3 mmol) and finally a catalytic amount of DMAP. The mixture was kept at room temperature for 1 h. The solution was diluted with Et_2O and filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (8:2 hexane/AcOEt), affording 154 mg (89%) of **8a**.

(1*S*,2*R*)-1-(*O*-Phenylacetyl)-2-[(benzyloxycarbonyl)-amino]-2-[(4-methylphenyl)sulfenyl]-3,3,3-trifluoro-1-phenylpropan-1-ol (8a): R_f (8:2 *n*-hexane/AcOEt) 0.52; $[\alpha]^{20}_D$ −114.0 (*c* 0.65, $CHCl_3$) ee 79%; ^{1}H NMR ($CDCl_3$) δ 7.20−7.50 (17H, m), 7.02 (2H, d, J = 8.0 Hz), 5.02 (1H, d, J = 12.0 Hz), 4.82 (1H, d, J = 12.0 Hz), 4.82 (1H, s), 3.61 (2H, s), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.7, 153.0, 141.2, 138.6, 135.7, 134.3, 133.4, 129.7, 129.6, 128.0, 127.6, 126.9, 124.5 (q, J = 286.7 Hz), 123.0, 73.9, 72.1 (q, J = 27.7 Hz), 67.2, 41.4, 21.3; ^{19}F NMR ($CDCl_3$) δ −68.7 (3F, s); MS (EI, 70 eV) *m*/*z* (%) 456 (M^+ − S-*p*-Tol, 7), 124 (30), 91 (100); FT IR (cm^{-1}) 3391, 3034, 1752 (br), 1496, 1242.

Synthesis of β-Amino Alcohols 7a,b and β-Amino Esters 9a,b. Reaction of **5d** is described as an example. To a cooled solution (0 °C) of **5d** (290 mg, 0.64 mmol) in pyridine (7 mL) was added portionwise $NaBH_4$ (120 mg, 3.2 mmol), and

the mixture was kept under stirring 3 h, at the same temperature. The reaction was quenched with 1 N aqueous solution of HCl and extracted with AcOEt, the collected organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed in vacuo. FC of the crude (9:1 *n*-hexane/AcOEt) afforded 150 mg (70%) of **7a**.

(1*S*,2*S*)-2-[(Benzyloxycarbonyl)amino]-3,3,3-trifluoro-1-phenylpropan-1-ol (7a): R_f (7:3 *n*-hexane/AcOEt) 0.49; $[\alpha]^{20}_D$ +30.6 (*c* 0.67, $CHCl_3$), +2.1 (*c* 0.5, acetone) ee 73.2%; ^{1}H NMR (acetone-d_6) δ 7.10−7.60 (10H, m), 6.79 (1H, d, J = 10.0 Hz), 5.03 (1H, dd, J = 5.1 and 8.1 Hz), 5.00 (1H, d, J = 12.6 Hz), 4.95 (1H, d, J = 5.1 Hz), 4.93 (1H, d, J = 12.6 Hz), 4.60 (1H, m); ^{13}C NMR (acetone-d_6) 157.4, 142.6, 138.5, 129.8, 129.6, 129.5, 129.3, 128.9, 128.7, 127.1 (q, J = 283.5), 73.4, 67.6, 59.2 (q, J = 28.2 Hz); ^{19}F NMR (acetone-d_6) δ −67.4 (3F, d, J = 7.7 Hz); MS (EI, 70 eV) *m*/*z* (%) 340 (M^+, 4), 233 (29), 197 (29), 107 (73), 91 (100); FT IR (cm^{-1}) 3310 (br), 1696, 1549, 1249.

(1*S*,2*R*)-7a: R_f (7:3 *n*-hexane/AcOEt) 0.54; ^{19}F NMR (acetone-d_6) − 67.7 (3F, d, J = 7.7 Hz).

Trifluoro- and Difluoronorephedrine 11a,b. The synthesis of **11a** is described as an example. A solution of **7a** (100 mg, 0.29 mmol) in MeOH (6 mL) was stirred for 15 min in the presence of an excess of $Pd(OH)_2$/C under a dihydrogen atmosphere. The solution was then filtered on a Celite pad, and after evaporation of the solvent, the crude was purified by FC (7:3 *n*-hexane/AcOEt), affording 59 mg (quantitative) of **11a**. The same procedure was applied for the synthesis of **11b** (quantitative).

(1*S*,2*S*)-2-Amino-3,3,3-trifluoro-1-phenylpropan-1-ol (11a): R_f (7:3 *n*-hexane/AcOEt) 0.22; $[\alpha]^{20}_D$ +11.5 (*c* 1.053, $CHCl_3$) ee 70%; mp 196−198 °C dec (hydrochloride); ^{1}H NMR ($CDCl_3$) δ 7.2−7.6 (5H, m), 4.93 (1H, d, J = 5.5 Hz), 3.60 (1H, dq, J = 5.5 and 7.4 Hz), 2.72 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 139.0, 128.62, 128.56, 127.0, 72.1, 58.5 (q, J = 26.4 Hz), the corresponding resonance of the CF_3 group is obscured; ^{19}F NMR ($CDCl_3$) δ −74.7 (3F, d, J = 7.4 Hz); MS (EI, 70 eV) *m*/*z* (%) 206 (M^+ + 1, 10), 185 (30), 107 (76), 79 (100); FT IR (cm^{-1}) 3380 (br), 2924, 1456, 1261.

(1*S*,2*R*)-11a: R_f (7:3 *n*-hexane/AcOEt) 0.22; ^{1}H NMR ($CDCl_3$) δ 7.2−7.45 (5H, m), 4.94 (1H, d, J = 3.9 Hz), 3.35 (1H, dq, J = 7.5 and 3.9 Hz), 2.0 (2H, br s); ^{19}F NMR ($CDCl_3$) δ −75.7 (3F, d, J = 7.5 Hz).

(1*S*,2*S*)-2-Amino-3,3-difluoro-1-phenylpropan-1-ol (11b): R_f (7:3 *n*-hexane/AcOEt) 0.17; $[\alpha]^{20}_D$ +12.4 (*c* 1.00, MeOH) ee > 95%; mp 212−215 °C dec (hydrochloride); ^{1}H NMR ($CDCl_3$) δ 7.3−7.45 (5H, m), 5.82 (1H, dt, J = 56.1 and 3.2 Hz), 4.69 (1H, d, J = 7.0 Hz), 3.25 (1H, dddd, J = 3.2, 6.7, 7.0 and 19.1 Hz); ^{13}C NMR (CD_3OD) δ 139.8, 130.0, 129.9, 127.7, 114.4 (t, J = 243.2 Hz), 71.1, 58.2 (dd, J = 18.5 and 22.2 Hz); ^{19}F NMR ($CDCl_3$) δ −127.7 (1F, ddd, J = 284.5, 56.1 and 6.7 Hz), −135.3 (1F, ddd, J = 284.5, 56.1 and 19.1 Hz); MS (EI, 70 eV) *m*/*z* (%) 188 (M^+ + 1, 10), 118 (19), 79 (55), 61 (100); FT IR (cm^{-1}) 3370 (br), 2957 (br), 1561, 1522, 1385.

(1*S*,2*R*)-11b: R_f (7:3 *n*-hexane/AcOEt) 0.17; ^{1}H NMR ($CDCl_3$) δ 7.3−7.45 (5H, m), 5.59 (1H, ddd, J = 55.8, 56.6 and 3.5 Hz), 4.65 (1H, d, J = 5.9 Hz), 3.08 (1H, dddd, J = 3.5, 5.9, 7.2 and 17.3 Hz); ^{19}F NMR ($CDCl_3$) δ −127.7 (1H, ddd, J = 284.8, 55.8 and 7.2 Hz), −135.3 (1F, ddd, J = 284.8, 56.6 and 17.3 Hz).

Synthesis of trifluoro- and difluoroephedrine 12a,b. The synthesis of **12a** is described as an example. To a solution of **7a** (45 mg, 0.13 mmol) in dry THF (2 mL) $LiAlH_4$ (25 mg, 0.66 mmol) was added portionwise under nitrogen. The mixture was refluxed for 7 h, quenched with water, and extracted with AcOEt, the collected organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed in vacuo. FC of the crude (7:3 *n*-hexane/AcOEt) afforded 25 mg (86%) of **12a**. The same procedure was performed for **12b** (25%).

(1*S*,2*S*)-2-(Methylamino)-3,3,3-trifluoro-1-phenylpropan-1-ol (12a): R_f (6:4 *n*-hexane/AcOEt) 0.44; $[\alpha]^{20}_D$ +9.0 (*c* 0.79, $CHCl_3$) ee 74%; mp 173−177 °C dec (hydrochloride); ^{1}H NMR ($CDCl_3$) δ 7.27−7.44 (5H, m), 4.96 (1H, d, J = 5.1 Hz), 3.36 (1H, dq, J = 5.1 and 7.4 Hz), 2.55 (3H, q, J = 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 128.6, 128.34, 128.32, 126.8, 125.9 (q, J = 285.4 Hz), 71.0 (q, J = 2.0 Hz), 66.2 (q, J = 25.6 Hz), 35.7; ^{19}F NMR ($CDCl_3$) δ −70.7 (3F, d, J = 7.4 Hz); MS (EI, 70 eV) *m*/*z* (%) 220 (M^+ + 1, 100), 202 (22); FT IR (cm^{-1}) 3364 (br), 3019, 2928, 1456, 1261.

(1*S*,2*S*)-2-(Methylamino)-3,3-difluoro-1-phenylpropan-1-ol (12b): R_f (6:4 *n*-hexane/AcOEt) 0.28; $[\alpha]^{20}_D$ +3.9 (*c* 0.70, MeOH), ee > 95%; mp 160−162 °C dec (hydrochloride); ^{1}H NMR ($CDCl_3$) δ 7.27−7.46 (5H, m), 5.68 (1H, dt, J = 3.7 and 55.3 Hz), 4.85 (1H, d, J = 5.5 Hz), 3.03 (1H, m), 2.5 (3H, s); ^{19}F NMR ($CDCl_3$) δ −122.8 (1F, ddd, J = 288.6, 55.3 and 7.0 Hz), −131.0 (1F, ddd, J = 288.6, 55.3 and 16.8 Hz); MS (EI, 70 eV) *m*/*z* (%) 202 (M^+ + 1, 20), 94 (100), 75 (52); FT IR (cm^{-1}) 3423 (broad), 1385.

Acknowledgment. Consiglio Nazionale delle Ricerche is gratefully acknowledged for financial support. Dr. Alessandro Volonterio and Dr. Barbara Vergani thank Politecnico di Milano for a scholarship.

Supporting Information Available: Full list of spectral data of compounds **5a,b,c,e,f**, **6a,c**, **7b**, **8b**, **9a,b**, **10a,b**. Copies of ^{1}H, ^{19}F, ^{13}C NMR spectra of componds **5a**−**f**, **6a**, **7a,b**, **8a,b**, **9a,b**, **11a,b**, **12a,b** (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980602P