



Stereocontrolled approaches to (+)- and (–)- γ -trifluoromethyl-GABOB, a new hydroxymethylene (statine) dipeptide isostere

Pierfrancesco Bravo,^a Eleonora Corradi,^b Cristina Pesenti,^b Barbara Vergani,^b Fiorenza Viani,^a
Alessandro Volonterio^b and Matteo Zanda^{b,*}

^aC.N.R. - Centro di Studio sulle Sostanze Organiche Naturali, via Mancinelli 7, I-20131 Milano, Italy

^bDipartimento di Chimica del Politecnico, via Mancinelli 7, I-20131 Milano, Italy

Received 14 September 1998; accepted 29 September 1998

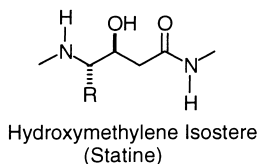
Abstract

Two efficient approaches to both enantiomers of *syn*- γ -trifluoromethyl γ -amino β -hydroxy butyric acid (γ -Tfm-GABOB) (**10**), a new hydroxymethylene (statine) dipeptide isostere, are described. One exploits the recently disclosed ‘non-oxidative’ Pummerer reaction, by means of which α -lithium alkyl sulfoxides are used as chiral α -hydroxyalkyl anion equivalents in the synthesis of β -amino alcohols. Trifluoropyruvaldehyde-*N,S*-ketal (*R*)-**11**, a novel stereochemically stable synthetic equivalent of α -amino trifluoropropanal, is used in the second approach. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Peptide isosteres are structural motifs in which a scissile amide bond has been replaced by a functional group that mimics the peptide bond, but is incapable of hydrolytic cleavage. Many of them have found important applications as efficient protease inhibitors, for example in the regulation of blood pressure (renin inhibitors) and in AIDS therapy (HIV-protease inhibitors).¹ Stereochemically defined β -fluoroalkyl β -amino alcohols feature a great potential for the preparation of new lipophilic peptide mimics, having improved properties as drugs, but the overwhelming difficulties connected with their preparation have strongly limited their application in biomedical chemistry.² In this paper we describe two efficient approaches to both enantiomers of the orthogonally protected *syn*- γ -trifluoromethyl γ -amino β -hydroxy butyric acid (γ -Tfm-GABOB) (**10**), a new hydroxymethylene (statine) dipeptide isostere.

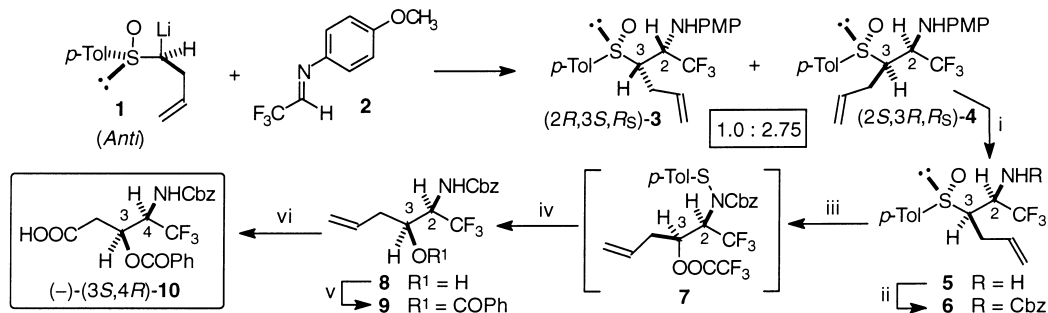
* Corresponding author. E-mail: zanda@dept.chem.polimi.it



2. Results and discussion

2.1. (–)- γ -Tfm-GABOB **10**: α -lithium sulfoxide (*R*)-**1** as a chiral α -hydroxy γ -butenyl anion equivalent

The first approach to γ -Tfm-GABOB **10** (Scheme 1) takes advantage of a synergistic combination of two methodologies we have developed recently: (1) the chiral sulfoxide stereocontrolled additions of nucleophiles to fluorinated imines³ and (2) the ‘non-oxidative’ Pummerer reaction,⁴ that allows for a one-pot S_N2 -type displacement of the sulfinyl auxiliary by a hydroxyl. Thus, easily available α -lithium sulfoxides can be used as chiral α -hydroxyalkyl anion equivalents for preparing β -amino alcohols. In this work, lithiated (*R*)-*p*-tolyl γ -butenyl sulfoxide **1** is used as a chiral α -hydroxy- γ -butenyl anion equivalent with the *N*-*p*-methoxyphenyl (*N*-PMP) imine of fluoral **2**, to achieve the synthesis of a *syn* β -Tfm γ -amino β -hydroxy butyric acid unit.



Scheme 1. (i) CAN, CH₃CN, H₂O (66%). (ii) ClCOOCH₂Ph, K₂CO₃ 50%, dioxane (>98%). (iii) (CF₃CO)₂O, *sym*-collidine, CH₃CN. (iv) a. K₂CO₃/H₂O up to pH 7; b. NaBH₄, THF/H₂O, 0°C (94%). (v) PhCOOH, DCC, DMAP (cat.), CH₂Cl₂ (92%). (vi) KMnO₄, H₂SO₄ 3 N, acetone/H₂O (89%)

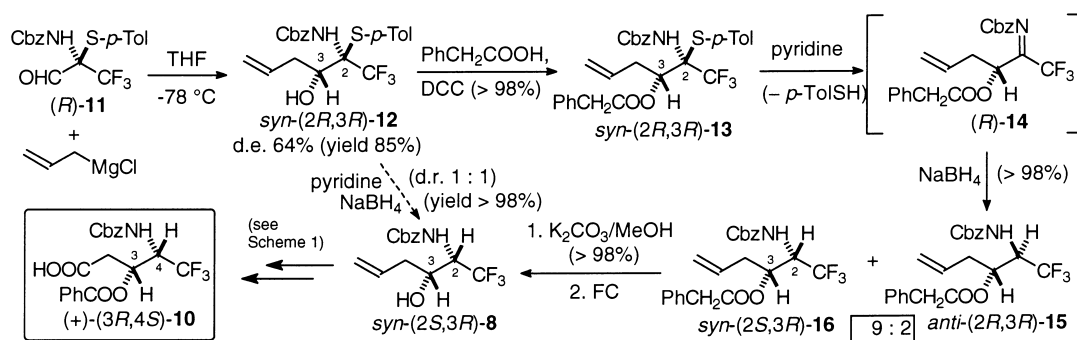
A THF solution of lithium sulfoxide **1** (Scheme 1), prepared from (*R*)-*p*-tolyl γ -butenyl sulfoxide with 1.2 equiv. of LDA,^{5a–h} was treated with a THF solution of trifluoro imine **2** at –70°C. The reaction afforded two diastereomeric *N*-PMP β -amino sulfoxides (2*R*,3*S*,*R_S*)-**3** and (2*S*,3*R*,*R_S*)-**4** out of four possible, in 1.0/2.75 d.r. and quantitative overall isolated yields.⁵ⁱ The preferential formation of the diastereomer **4** might be explained by the fact that the lithiated butenyl sulfoxide **1** reacts mainly in the *anti*-geometry, having *p*-tolyl and allyl groups *trans* with respect to the plane defined by the O–S–C–Li bonds,^{5j} through a Zimmerman–Traxler (aldol-type) transition state.^{5k,b}

The mixture of diastereomeric sulfoxides **3** and **4** was treated with ceric ammonium nitrate (CAN) (5 equiv.) in acetonitrile/water to cleave the *N*-PMP group, providing the free amino sulfoxide **5** in diastereomerically pure form after flash chromatography (FC) (66%). The absolute stereochemistry of **5** was determined by X-ray diffraction.⁶ Compound **5** was reprotected as *N*-Cbz derivative **6** (quantitative), then submitted to the ‘non-oxidative’ Pummerer reaction protocol.⁴ As expected, treatment of **6** with trifluoroacetic anhydride (5 equiv.) and *sym*-collidine (3 equiv.) triggered an S_N2 displacement of the sulfinyl by a trifluoroacetoxy group, leading to the intermediate sulfenamide **7**. One-pot treatment with aqueous K₂CO₃ up to pH 7 and finally with an excess of NaBH₄, provided the β -amino alcohol (2*R*,3*S*)-**8**

(Scheme 1) in a very clean manner (94%),⁷ with overall stereoselectivity >98/2 (the other diastereomer was not detected). Conversion of (2*R*,3*S*)-**8** into the corresponding *O*-benzoate **9** (92%), and oxidative cleavage of the double bond with KMnO₄ (89%) delivered the targeted enantiopure γ -Tfm-GABOB (–)-(3*S*,4*R*)-**10**, orthogonally protected and suitable for preparing new potential protease inhibitors via coupling to other amino acids.

2.2. (+)- γ -Tfm-GABOB **10** from (*R*)-trifluoropyruvaldehyde *N,S*-ketal **11**

The second approach to γ -Tfm-GABOB **10** exploits trifluoropyruvaldehyde *N,S*-ketal (*R*)-**11**, recently prepared in our laboratories, as a new chiral and stereochemically stable synthetic equivalent of α -amino trifluoropropanal (Scheme 2).⁸ Slow addition of a THF solution of (*R*)-**11** (ee ca. 70%) to allylmagnesium chloride in THF (3 equiv., –78°C, 1 min) produced the corresponding homoallylic alcohol *syn*-**12** in 9/2 d.r. (85% overall isolated yield). The absolute stereochemistry of **12** was determined by X-ray diffraction of an enantiomerically pure analytical sample obtained by crystallization from *n*-hexane.^{6a} Next, the thio derivative **12** was submitted to reductive desulfenylation with NaBH₄/pyridine (0°C, 60 min),^{8b,c} but disappointingly the diastereomeric β -amino alcohols (2*S*,3*R*)-**8** and its (2*R*,3*R*)-epimer were produced without stereocontrol (yield >98%). In order to improve the diastereoselectivity, **12** was transformed into the corresponding phenylacetic ester **13** (yield >98%),^{8c,d} which was submitted to reductive desulfenylation affording the desired *syn*-derivative (2*S*,3*R*)-**16** with good diastereoselectivity, in a mixture with the diastereomer *anti*-(2*R*,3*R*)-**15** (15:16=2:9, yield >98%). Compound **16** might be directly transformed into the corresponding *O*-phenylacetoxyl *N*-Cbz γ -Tfm-GABOB by oxidative cleavage of the double bond. However, in order to confirm the stereochemistry at C-2 and to perform a formal synthesis of the (+)- γ -Tfm-GABOB **10**, the phenylacetate **16** was transformed into the β -amino alcohol (2*S*,3*R*)-**8**, that is the enantiomer of (2*R*,3*S*)-**8** prepared from the sulfoxide (*R*)-**1** (see Section 2.1, Scheme 1). Thus, methanolysis of the mixture of esters **15**,**16** afforded in quantitative yields the corresponding diastereomeric β -amino alcohols, from which (2*S*,3*R*)-**8** was obtained in pure form by FC, without loss of enantiomeric purity with respect to the starting material (*R*)-**11**.



Scheme 2.

The protocol shown in Scheme 2 involves two fairly stereoselective asymmetric transformations: (1) formation of the C-3 carbinolic centre of **12** by addition of allylmagnesium chloride to (*R*)-**11**, that might be rationalized by the *syn*-selective chair-like transition state **A** (Fig. 1), involving sterically controlled approach of the allylic nucleophile to the *Re* face of the carbonyl (Felkin–Anh);^{9,10} (2) reductive desulfenylation of the thio derivative **13**, which involves two steps:^{8b,c} (a) generation of the transient imine **14** (Scheme 2) by pyridine promoted elimination of *p*-thiocresol, (b) reduction of **14** by

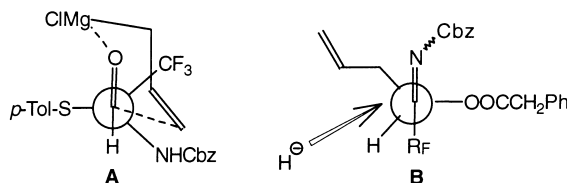


Figure 1.

NaBH₄, that might be explained by the Felkin–Anh model **B** (Fig. 1), in which the phenylacetoxo group plays the role of electronegative, ‘large’ substituent.⁹

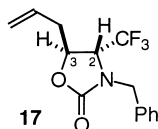
In summary, we have described two alternative stereocontrolled entries to both enantiomers of the orthogonally protected γ -Tfm-GABOB **10**, a new hydroxymethylene (statine) dipeptide isostere now available in gram-quantities. The synthesis of new potential protease inhibitors incorporating γ -Tfm-GABOB is currently in progress.¹¹

Acknowledgements

C.P., E.C. and B.V. thank Politecnico for a scholarship.

References

- (a) Huff, J. R.; Darke, P. L. Inhibition of HIV protease: a strategy for the treatment of AIDS. In *Anti-AIDS Drug Development: Challenges, Strategies and Prospects*; Mohan, P.; Baba, M., Eds; Harwood Academic Publishers, 1995; pp. 93–116. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720. (c) Tao, J.; Hoffman, R. V. *J. Org. Chem.* **1997**, *62*, 6240–6244 and references cited therein. (d) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 4195–4198. (e) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419–10433.
- (a) Bégué, J.-P.; Bonnet-Delpon, D. Trifluoromethylated amino alcohols: new synthetic approaches and medicinal targets. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds; ACS Books, American Chemical Society: Washington, DC, 1996; pp. 59–72. (b) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826–8833. (c) Ojima, I.; Slater, J. C.; Pera, P.; Veith, J. M.; Abouabdellah, A.; Bégué, J.-P.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 133–138. (d) Marti, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann.* **1995**, 1193–1215. (e) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897–2911.
- 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*, 3424–3425.
- Bravo, P.; Zanda, M.; Zappalà, C. *Tetrahedron Lett.* **1996**, *37*, 6005–6006.
- (a) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961–998. (b) Pyne, S. G.; Boche, G. *J. Org. Chem.* **1989**, *54*, 2663–2667. (c) Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.* **1978**, *19*, 471–474. (d) Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1974**, *15*, 2915–2918. (e) Williams, D. R.; Phillips, J. G.; White, F. H.; Huffman, J. C. *Tetrahedron* **1986**, *42*, 3003–3011. (f) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277–297. (g) Tsuchihashi, G.; Iriuchijima, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, *14*, 3389–3392. (h) Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 6101–6104. (i) Attempts to improve the stereocontrol were made, however, changing the temperature of lithiation, the use of more bulky bases such as lithium tetramethylpiperidide, or the use of toluene as solvent produced little or no changes of diastereoselectivity. (j) This is in agreement with the few existing reports on additions of metallated alkyl sulfoxides across the C–N double bonds of imines (see above, Refs. 5a–h), but in sharp contrast with the peculiar behaviour of α -lithium benzyl *p*-tolyl sulfoxide, which was found to react with the imine **2** almost exclusively via the *syn*-geometry (Ref. 3). (k) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
- (a) Full data will be reported in a full paper. (b) The stereochemistry of the minor diastereomer **3** was determined as follows. A mixture of sulfoxides **4** (having known stereochemistry) and **3** were deoxygenated with Me₃SiCl/NaI providing the corresponding sulfides, which proved to be enantiomers by NMR analysis (a single set of signals was detected). This allowed us to assess that **3** has (2*R*,3*S*,*R*_S)-stereochemistry.



7. In order to confirm the stereochemistry of (2*R*,3*S*)-**8**, this compound was treated with NaH and PhCH₂Br affording the oxazolidinone **17** (93%), whose J_{2-3} =3.6 Hz strongly suggests a *trans* pseudo-equatorial configuration, in full agreement with the expected configuration.
8. (a) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, 62, 8031–8040. (b) Volonterio, A.; Bravo, P.; Capelli, S.; Meille, S. V.; Zanda, M. *Tetrahedron Lett.* **1997**, 38, 1847–1850. (c) Volonterio, A.; Vergani, B.; Crucianelli, M.; Zanda, M.; Bravo, P. *J. Org. Chem.* **1998**, in press. (d) Transformation of *N,S*-ketals, like **12**, into the corresponding phenylacetates followed by treatment with NaBH₄/pyridine is an efficient strategy for obtaining the corresponding desulfonylated derivatives, like **16**, with *syn*-stereoselectivity: see Ref. 8c.
9. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 9, 2199–2202. (b) Anh, N. G.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 17, 155–158.
10. The stereoselectivity of this reaction is quite surprising, since all the reactions of (*R*)-**11** with alkyl, vinyl and phenyl Grignard reagents showed opposite stereocontrol, producing the corresponding *anti*-products, possibly originated from a highly effective ‘chelation control’ (Ref. 8b,c). An opposite stereochemical outcome (chelation control) was also reported for a wide range of reactions between *N*-monoprotected α-amino aldehydes and Grignard reagents, including allylic ones. See for example: (a) Devant, R. M.; Radunz, H.-E. In *Houben-Weyl: Methods in Organic Synthesis*; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1995; Vol. E21b, pp. 1236–1239. (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, 89, 149–164. (c) Roush, W. R. In *Comprehensive Organic Synthesis Vol. 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; pp. 1–54. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 93, 2207–2293. For recent examples see: (e) Veerasha, G.; Datta, A. *Tetrahedron Lett.* **1997**, 38, 5223–5224. (f) Gryko, D.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, 8, 4059–4067. (g) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, 56, 6939–6942. (h) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, 31, 1803–1806. (i) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, 49, 8739–8756. (j) Ciapetti, P.; Falorni, M.; Taddei, M. *Tetrahedron* **1996**, 52, 7379–7390. (k) Rübsam, F.; Seck, S.; Giannis, A. *Tetrahedron* **1997**, 53, 2823–2834.
11. All new compounds have been characterized by means of ¹H, ¹⁹F and ¹³C NMR, mass spectrometry and microanalyses.