Straightforward synthesis of enantiopure (*R*)- and (*S*)-trifluoroalaninol†‡

Julien Pytkowicz, Olivier Stéphany, Sinisa Marinkovic, Sébastien Inagaki and Thierry Brigaud*

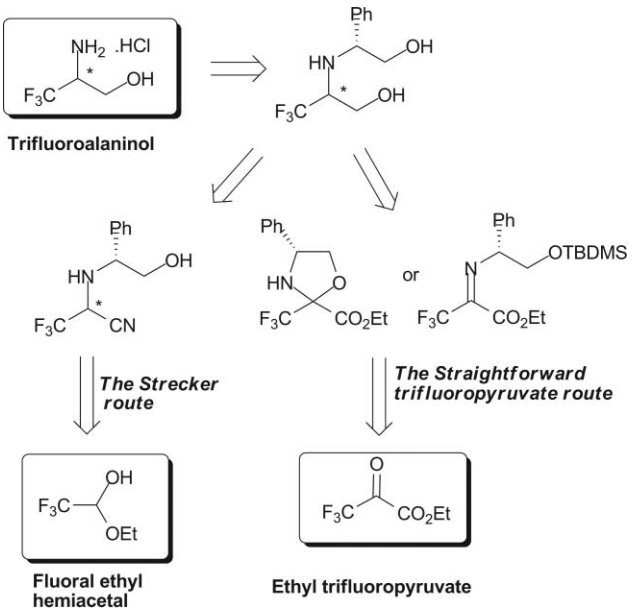
Received 14th July 2010, Accepted 11th August 2010
DOI: 10.1039/c0ob00424c

Two efficient routes are reported for the synthesis of both enantiomers of trifluoroalaninol in enantiopure form. The first pathway involves a Strecker-type reaction performed from a chiral trifluoromethyloxazolidine (Fox). The second route, which is more direct, involves, as a key step, the reduction of chiral oxazolidines or imines derived from ethyl trifluoropyruvate.

Enantiopure β-amino alcohols are very important natural or synthetic pharmacologically active molecules.[1] In addition 1,2-amino alcohols and their derivatives are extensively used as chiral ligands or auxiliaries.[2] These compounds are very conveniently obtained through the reduction of naturally occurring enantiopure amino acids and several synthetic methods are reported in the literature for their preparation.

It is now well documented that the introduction of trifluoromethyl groups into molecules significantly modifies their chemical and biological properties and a growing number of synthetic methods are reported for the synthesis of fluorinated compounds.[3] β-Trifluoromethyl β-amino alcohols are very attractive molecules as biologically active compounds[4] and peptidomimetic units.[5] As the large scale synthesis of enantiopure Tfm-amino acids is still a challenge,[6] there are very few reports on the synthesis of enantiopure β-trifluoromethyl β-amino alcohols resulting from the reduction of the corresponding amino acids.[7] For this reason several strategies were adopted for the stereoselective elaboration of the β-trifluoromethyl β-amino alcohol unit.[8] Intriguingly despite its interest and its apparent structural simplicity, to our knowledge there are very few reports on the synthesis of chiral trifluoroalaninol. Enantiopure (*R*)-trifluoroalaninol was prepared from a multistep procedure involving the reduction of a chiral α-trifluoromethyl-β-sulfinyl enamine followed by a nonoxidative Pummerer rearrangement as key steps.[9,10] However, this procedure does not appear to be easily scalable. Enantioenriched (*R*)-trifluoroalaninol has also been obtained by enantioselective reduction of an ethyl trifluoropyruvate oxime ether.[11]

In order to develop scalable methodologies for the synthesis of both enantiomers of trifluoroalaninol in enantiopure form we report here two diastereoselective strategies involving (*R*)-phenylglycinol-based imines and oxazolidines (Scheme 1). We chose as fluorinated starting materials the commonly available fluoral ethyl hemiacetal and ethyl trifluoropyruvate. Both strategies involve the same aminodiol as a key intermediate giving the target enantiopure trifluoroalaninols after removal of the (*R*)-phenylglycinol side chain.



Scheme 1 Retrosynthetic pathways for the synthesis of (*R*)- and (*S*)-trifluoroalaninol.

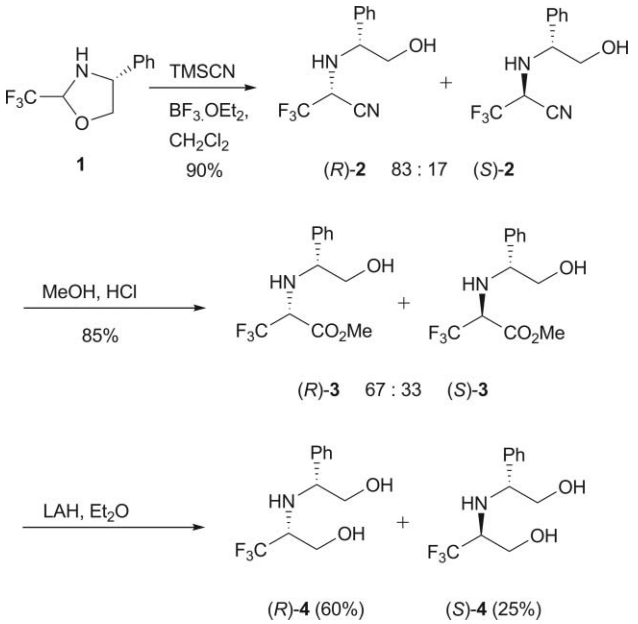
In a first approach the amino alcohols (*R*)-**4** and (*S*)-**4** were conveniently obtained through a multistep procedure involving a Strecker-type reaction on the oxazolidines **1**, followed by the methanolysis of the corresponding amino nitriles **2** and the reduction of the amino esters **3** (Scheme 2). According to our previous reports,[12] the Lewis acid mediated Strecker-type reaction performed on chiral Tfm-oxazolidines **1** gave the amino nitriles (*R*)-**2** and (*S*)-**2** as a diastereomeric mixture. As the separation of these two diastereomers was quite difficult, the following methanolysis step was achieved from the diastereomeric mixture to give the (*R*)-**3** and (*S*)-**3** methyl esters in 85% yield. A partial epimerization of the C-2 centre of **3** occurred during this transformation to give (*R*)-**3** and (*S*)-**3** as a 67 : 33 diastereomeric mixture. The epimerization of a similar trifluoroalanine ester through its enol form due to the high C–H acidity has already been reported in the literature.[13] In order to save a tedious separation,[14] the diastereomeric (*R*)-**3** and (*S*)-**3** mixture was engaged in the lithium aluminium hydride reduction step. At this stage the expected amino diols **4** were conveniently separated by silica gel chromatography to give (*R*)-**4** and (*S*)-**4** in 60% and 25% isolated yield respectively.

Although the Strecker pathway was efficient for the preparation of diastereomerically pure amino alcohols **4**, which are precursors of the target enantiopure trifluoroalaninols, we investigated a more direct route involving the reduction of imine and oxazolidines. The chiral imine **5** and the diastereomeric mixture of oxazolidines **6**

Université de Cergy-Pontoise, Laboratoire SOSCO, F-95000, Cergy-Pontoise, France. E-mail: thierry.brigaud@u-cergy.fr; Fax: +33 (0)1 34 25 70 71; Tel: +33 (0)1 34 25 70 66

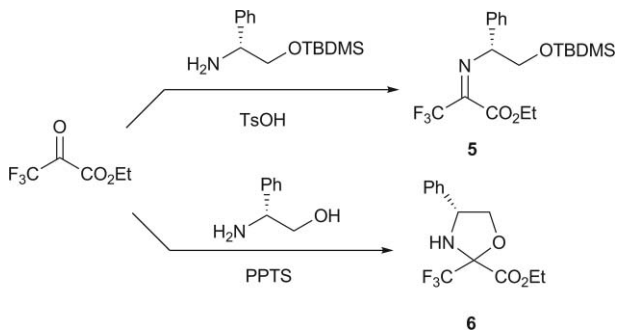
† This publication is part of the web themed issue on fluorine chemistry

‡ Electronic supplementary information (ESI) available: Procedures, synthesis and characterization data of products **2–7**, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of compounds **3**, **4** and **7**. See DOI: 10.1039/c0ob00424c



Scheme 2 The Strecker pathway for the synthesis of the amino diols (*R*)-**4** and (*S*)-**4**.

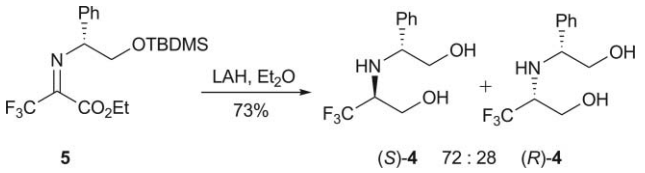
were conveniently prepared from ethyltrifluoropyruvate and (*R*)-phenylglycinol according to our previously reported procedures (Scheme 3).[7,15–17] The main advantage of these intermediates is that they already include the three carbon atoms of the target trifluoroalaninols.[18] It should be noticed that the imine **5** was obtained in high yield (92%) without formation of haloform type decomposition products frequently observed during the reaction of trifluoropyruvate esters and amines.[19]



Scheme 3 Synthesis of ethyl trifluoropyruvate-based imine **5** and oxazolidines **6**.

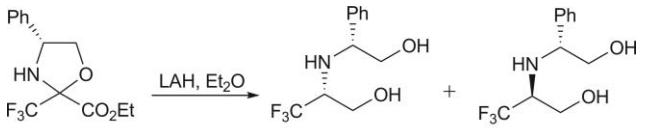
The treatment of the imine **5** with lithium aluminium hydride afforded the aminodiols (*S*)-**4** and (*R*)-**4** as a 72 : 28 diastereomeric mixture in 73% yield. Under these conditions both the imine and the ester function are reduced and we observe a complete desilylation to yield (*S*)-**4** as the major diastereomer (Scheme 4). In contrast to the Strecker pathway giving the major (*R*) diastereomer (Scheme 2), the major aminodiols obtained by reduction of the imine **5** was the (*S*) one. This result is consistent with a major *re* face attack of the imine **5**.

In a similar manner, the treatment of oxazolidine **6** with lithium aluminium hydride yielded the two amino diols (*R*)-**4** and (*S*)-**4**. The diastereomeric ratio of (*R*)-**4** and (*S*)-**4** were dependant of the starting oxazolidines **6** diastereomeric ratio. Starting from



Scheme 4 The imine **5** reduction pathway for the synthesis of the amino diols (*S*)-**4** and (*R*)-**4**.

Table 1 The oxazolidine **6** reduction pathway for the synthesis of the amino diols (*R*)-**4** and (*S*)-**4**



Entry	Starting material	Yield of **4**[a]	(*R*)-**4**/(*S*)-**4** dr[b]
1	$\mathbf{6}_{maj}$	95	72 : 28
2	$\mathbf{6}_{min}$	79	50 : 50
3	$\mathbf{6}_{maj}/\mathbf{6}_{min}$ (83 : 17 dr)	84[c]	69 : 31

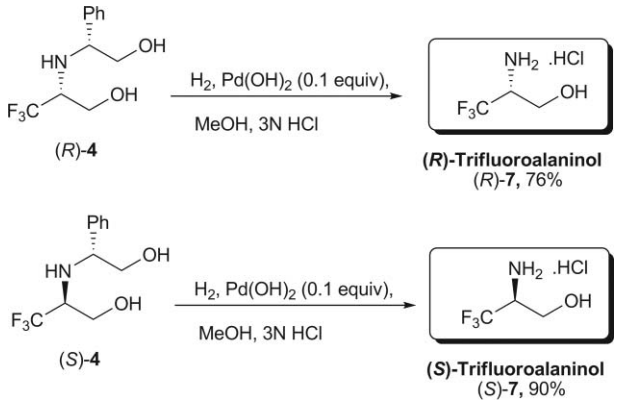
[a] Isolated yield. [b] Measured by ^{19}F and ^{1}H NMR. [c] After silica gel separation, (*R*)-**4** was isolated in 60% yield and (*S*)-**4** was isolated in 24% yield.

the diastereomerically pure **6** major diastereomer, (*R*)-**4** and (*S*)-**4** were obtained in 95% yield as a 72 : 28 diastereomeric mixture (Table 1, entry 1). Starting from the minor **6** diastereomer, (*R*)-**4** and (*S*)-**4** were obtained in 79% yield with a 50 : 50 diastereomeric ratio (Table 1, entry 2). These results suggest that the reductions of the oxazolidines **6** are not stereoselective. It is thus useless to isolate both oxazolines **6** before the LAH reduction. Therefore the reduction was performed on a 83 : 17 distereomeric mixture of **6** to give the amino diols (*R*)-**4** and (*S*)-**4** in 84% yield as a 69 : 31 diastereomeric mixture (Table 1, entry 3). The two diastereomers were easily separated by silica gel chromatography and diastereomerically pure (*R*)-**4** and (*S*)-**4** were obtained in 60% and 24% isolated yield respectively. As for the Strecker pathway and in contrast to the imine **5** reduction, the (*R*)-**4** diastereomer was the major.

The last step towards the synthesis of the enantiopure trifluoroalaninol was the removal of the (*R*)-phenylglycinol side chain of (*R*)-**4** and (*S*)-**4** using the palladium catalyzed hydrogenolysis. This reaction was performed in acidic medium in order to avoid the deactivation of the Pearlman's catalyst. Finally, the two enantiomers of the targeted trifluoroalaninol **7** were conveniently isolated in good yields as their hydrochloride salts (Scheme 5). As the hydrogenolysis reactions were carried out from diastereomerically pure isolated amino diols (*R*)-**4** and (*S*)-**4**, the corresponding trifluoroalaninols were likely to be enantiomerically pure.[20] This was confirmed by comparison of their optical rotations with literature data.[21]

Conclusions

In conclusion, we developed two routes for the synthesis of both enantiomers of trifluoroalaninol in enantiopure form starting from (*R*)-phenylglycinol derived fluorinated oxazolidines (Fox) or



Scheme 5 The synthesis of enantiopure (*R*)- and (*S*)-trifluoroalaninols.

imines. The first route relies on a Strecker type reaction whereas the more straightforward second one uses ethyl trifluoropyruvate as fluorinated starting material. The convenient separation of the two diastereomers of the common intermediate amino diol **4** ensures the achievement of trifluoroalaninols in enantiopure form. These two routes use common and cheap reactants and can be scaled up to gram quantities.

Acknowledgements

We thank Central Glass Co. for financial support and the gift of trifluoroacetaldehyde hemiacetal and ethyl trifluoropyruvate.

Notes and references

1 (*a*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561–2576; (*b*) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367–1376; (*c*) H.-S. Lee and S. H. Kang, *Synlett*, 2004, 1673–1685.

2 (*a*) F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159–2231; (*b*) C. H. Senanayake, *Aldrichim. Acta*, 1998, **31**, 3–15; (*c*) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835–875; (*d*) H. A. McManus and P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151–4202; (*e*) A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1–45; (*f*) D. Rechavi and M. Lemaire, *Chem. Rev.*, 2002, **102**, 3467–3494; (*g*) C. Anaya, de Parrodi and E. Juaristi, *Synlett*, 2006, 2699–2715; (*h*) J. L. Vicario, D. Badia, L. Carrillo, E. Reyes and J. Etxebarria, *Curr. Org. Chem.*, 2005, **9**, 219–235.

3 (*a*) J.-P. Begue and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008; (*b*) I. Ojima, *Fluorine In Medicinal Chemistry And Chemical Biology*, Wiley-Blackwell, 2009; (*c*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2004; (*d*) K. Uneyama, *Organofluorine chemistry*, Blackwell Publishing, Oxford, 2006; (*e*) V. A. Soloshonok, *Fluorine-Containing Synthons*, American Chemical Society, Washington, DC, 2005; (*f*) J.-A. Ma and D. Cahard, *J. Fluorine Chem.*, 2007, **128**, 975–996; (*g*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119–6146; (*h*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1–PR43.

4 (*a*) P. Bravo, M. Crucianelli, T. Ono and M. Zanda, *J. Fluorine Chem.*, 1999, **97**, 27–49; (*b*) L. V. Kuznetsova, A. Pepe, I. M. Ungureanu, P. Pera, R. J. Bernacki and I. Ojima, *J. Fluorine Chem.*, 2008, **129**, 817–828; (*c*) C. Binkert, M. Frigerio, A. Jones, S. Meyer, C. Pesenti, L. Prade, F. Viani and M. Zanda, *ChemBioChem*, 2006, **7**, 181–186; (*d*) C. Pesenti, A. Arnone, S. Bellosta, P. Bravo, M. Canavesi, E. Corradi, M. Frigerio, S. V. Meille, M. Monetti, W. Panzeri, F. Viani, R. Venturini and M. Zanda, *Tetrahedron*, 2001, **57**, 6511–6522.

5 (*a*) M. Molteni, C. Pesenti, M. Sani, A. Volonterio and M. Zanda, *J. Fluorine Chem.*, 2004, **125**, 1735–1743; (*b*) C. Philippe, T. Milcent, T. N. T. Nguyen, B. Crousse and D. Bonnet-Delpon, *Eur. J. Org. Chem.*, 2009, 5215–5223.

6 (*a*) R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727–1739 and references therein; (*b*) T. Brigaud, G. Chaume, J. Pytkowicz and F. Huguenot, *Chim. Oggi*, 2007, **25**, 8–10; (*c*) X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711–6745.

7 G. Chaume, M.-C. Van Severen, S. Marinkovic and T. Brigaud, *Org. Lett.*, 2006, **8**, 6123–6126.

8 (*a*) P. Bravo, A. Farina, V. P. Kukhar, A. L. Markovsky, S. V. Meille, V. A. Soloshonok, A. E. Sorochinsky, F. Viani, M. Zanda and C. Zappala, *J. Org. Chem.*, 1997, **62**, 3424–3425; (*b*) P. Bravo, M. Guidetti, F. Viani, M. Zanda, A. L. Markovsky, A. E. Sorochinsky, I. V. Soloshonok and V. A. Soloshonok, *Tetrahedron*, 1998, **54**, 12789–12806; (*c*) A. Volonterio, B. Vergani, M. Crucianelli and M. Zanda, *J. Org. Chem.*, 1998, **63**, 7236–7243; (*d*) A. Volonterio, P. Bravo, E. Corradi, G. Fronza, S. V. Meille, B. Vergani and M. Zanda, *J. Fluorine Chem.*, 2001, **108**, 245–252; (*e*) P. Bravo, E. Corradi, C. Pesenti, B. Vergani, F. Viani, A. Volonterio and M. Zanda, *Tetrahedron: Asymmetry*, 1998, **9**, 3731–3735; (*f*) A. E. Sorochinsky and V. A. Soloshonok, *J. Fluorine Chem.*, 2010, **131**, 127–139; (*g*) M. Dos Santos, B. Crousse and D. Bonnet-Delpon, *Tetrahedron Lett.*, 2009, **50**, 857–859; (*h*) K. Uneyama, J. Hao and H. Amii, *Tetrahedron Lett.*, 1998, **39**, 4079–4082; (*i*) A. Abouabdellah, J.-P. Begue, D. Bonnet-Delpon and T. T. T. Nga, *J. Org. Chem.*, 1997, **62**, 8826–8833.

9 A. Arnone, P. Bravo, S. Capelli, G. Fronza, S. V. Meille, M. Zanda, G. Cavicchio and M. Crucianelli, *J. Org. Chem.*, 1996, **61**, 3375–3378, (*J. Org. Chem.*, 1996, **61**, 9635).

10 A. Arnone, P. Bravo, L. Bruche, M. Crucianelli, L. Vichi and M. Zanda, *Tetrahedron Lett.*, 1995, **36**, 7301–7304.

11 T. Sakai, F. Yan, S. Kashino and K. Uneyama, *Tetrahedron*, 1996, **52**, 233–44.

12 (*a*) F. Huguenot and T. Brigaud, *J. Org. Chem.*, 2006, **71**, 7075–7078; (*b*) N. Lebouvier, C. Laroche, F. Huguenot and T. Brigaud, *Tetrahedron Lett.*, 2002, **43**, 2827–2830.

13 V. A. Soloshonok and V. P. Kukhar, *Tetrahedron*, 1997, **53**, 8307–8314.

14 Pure (*R*)-**3** and (*S*)-**3** samples were isolated for analytical studies.

15 C. Caupene, G. Chaume, L. Ricard and T. Brigaud, *Org. Lett.*, 2009, **11**, 209–212.

16 G. Chaume, M.-C. Van Severen, L. Ricard and T. Brigaud, *J. Fluorine Chem.*, 2008, **129**, 1104–1109.

17 G. Chaume, N. Lensen, C. Caupene and T. Brigaud, *Eur. J. Org. Chem.*, 2009, 5717–5724.

18 For pioneer works on the synthesis of chiral derivatives of trifluoropyruvate see: P. Bravo, S. Capelli, S. V. Meille, F. Viani, M. Zanda, V. P. Kukhar and V. A. Soloshonok, *Tetrahedron: Asymmetry*, 1994, **5**, 2009–2018.

19 H. Ohkura, D. O. Berbasov and V. A. Soloshonok, *Tetrahedron*, 2003, **59**, 1647–1656.

20 As no further purification by chromatography or sublimation was achieved, a change in the enantiomeric composition of (*R*)-**7** and (*S*)-**7** through self-disproportionation is not likely to occur. See: (*a*) V. A. Soloshonok, *Angew. Chem., Int. Ed.*, 2006, **45**, 766–769; (*b*) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi and D. A. Singleton, *J. Am. Chem. Soc.*, 2007, **129**, 12112–12113.

21 (*R*)-**7** $[\alpha]_D$ +8.1 (*c* 0.8, EtOH). (*S*)-**7**: $[\alpha]_D$ −8.0 (*c* 0.6, EtOH). Lit. data for (*R*) enantiomer (see ref. 9): $[\alpha]_D$ +7.86 (*c* 0.70, EtOH).

