Asymmetric Synthesis of (Trifluoromethyl)piperidines: Preparation of Highly Enantioenriched α′-(Trifluoromethyl)pipecolic Acids

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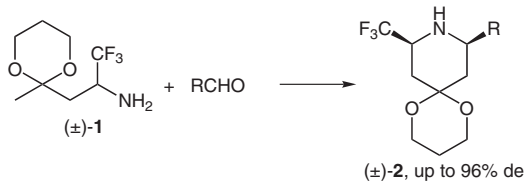
Abstract: The first asymmetric synthesis of (trifluoromethyl)pipecolic acids is reported. The synthetic strategy involves as key step an intramolecular Mannich reaction of a homochiral α-Tfm-β-amino ketal, prepared with a high stereoselectively in four steps from a fluoral hemiacetal.

Key words: fluorine, piperidines, cyclic amino acids, stereoselectivity, intramolecular Mannich reaction

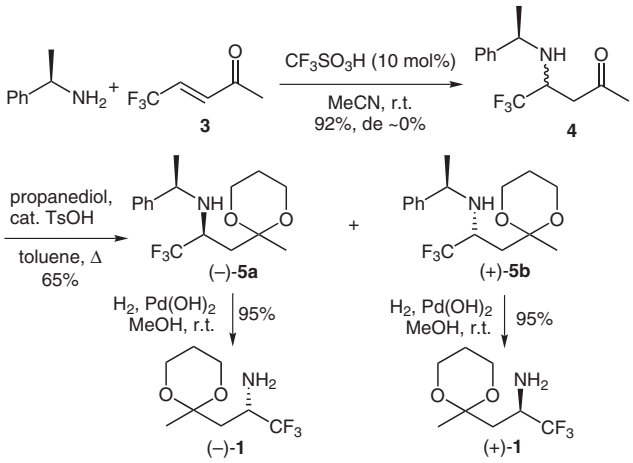
Owing primarily to the benefits on the bioactivity resulting from the incorporation of fluorine atom(s) into organic molecules,[1] fluoroorganic chemistry knows considerable and continuous progress.[2] Nevertheless, some domains need still to be developed as, for instance, the synthesis of selectively trifluoromethylated saturated N-heterocycles. In this area, we recently demonstrated[3] that intramolecular Mannich reaction of β-amino ketal (±)-**1**, constituted a valuable tool for the diastereoselective preparation of piperidines (±)-**2**, bearing a trifluoromethyl (Tfm) group in the α position[4] (Scheme 1).



Scheme 1

This method was successfully employed for the elaboration of new series of (±)-Tfm-piperidines, including trifluoro analogues of alkaloids.[3b] Meanwhile, in our minds, its complete validation passed inevitably through its extension to the field of enantioselective synthesis, and that point constitutes one of the objects of the present letter. As solving this challenging problem[4a,g] required us to possess amine **1** in an enantiomerically pure form, its asymmetric preparation was engaged.

For this purpose, an aza-Michael pathway was considered at first, and the best results are collected in Scheme 2. Thus, treatment of readily available[5] trifluoropentenone **3** with (*R*)-(+)-α-methylbenzylamine in the presence of 10 mol% trifluoromethanesulfonic acid[6] gave, in 92% yield, the expected amino ketone **4**, which was isolated as an inseparable and almost equimolar mixture of diastereomers. Subsequent keto protection with 1,3-propanediol under classical acidic conditions, afforded the corresponding ketals **5a**,**b**. These compounds, of low polarity, could be quite easily separated by silica gel column chromatography. Individual hydrogenolysis of **5a** and **5b** then furnished almost quantitatively antipodes of amine **1**, both showing an excellent optical purity (ee >95%, from ^{1}H NMR in the presence of mandelic acid as chiral solvating agent,[7] in comparison with the racemic material).



Scheme 2

Although allowing a rapid preparation of amines (+)- and (–)-**1** on a multigram scale, the absence of stereoselectivity for the conjugate addition step lowered significantly the interest of this approach, prompting us to investigate an alternative strategy.

We then focused our attention on the asymmetric access to fluorinated β-amino ketones recently proposed by Brigaud.[8] His methodology involved the diastereoselective addition of silyl enol ethers onto the stable oxazolidine **6**, very conveniently obtained from a fluoral hemiacetal and (*R*)-(–)-phenylglycinol. Accordingly, and as depicted in Scheme 3, a 1:2 diastereomeric mixture of oxazolidines **6a**,**b**[9] was treated with enoxysilane **7** in the presence of boron trifluoride etherate, at –15 °C in dichloromethane. Under these conditions, the targeted β-amino ketone (–)-**8** was efficiently obtained (89%), within a few

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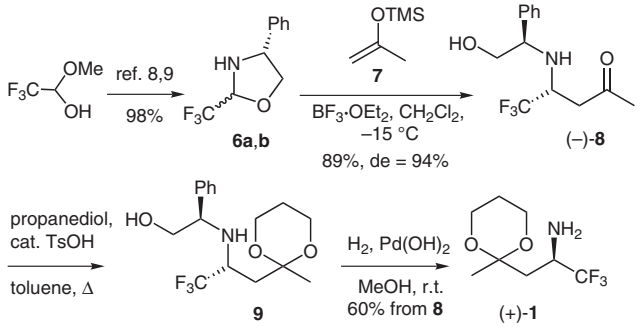
minutes and highly predominantly (de = 94% from GC-MS of the crude, diastereomers separated by column chromatography). Subsequently, a conventional keto protection–hydrogenolysis sequence afforded in 60% yield the desired amine (+)-**1**, whose NMR analysis (vide supra) showed once again a high enantiomeric purity (>95%). At this stage, absolute configuration of compounds (+)-**1**, (–)-**1**[10] and intermediates (represented in Schemes 2 and 3) were assigned, in comparison to Brigaud's observations.[8]



Scheme 3

Our next goal was to evaluate the potential of homochiral amine **1** towards the preparation of enantioenriched Tfm-piperidines, with the aim to select as application examples original structures of synthetic and/or biological interest. In this context, pipecolic acids were considered.[11] Effectively, examination of the literature data revealed that, despite the numerous efforts devoted to fluorinated amino acids,[12] none asymmetric synthesis of Tfm-homoprolines has been reported to date.[13] The elaboration of α′-trifluoromethyl analogue of the simplest pipecolic acid (**10**) was thus targeted, together with those of its 4-oxo and 4-hydroxy congeners **11** and **12**, compounds of undeniable biological interest[14,15] (Figure 1).

Treatment of (*R*)-(+)-**1** with ethyl glyoxylate at room temperature in toluene led to the corresponding imine, which, submitted to our standard acidic cyclization conditions, yielded, in an interesting 85:15 ratio, the 2,6-*cis*- and 2,6-*trans*-ethyl Tfm-pipecolates **13a**,**b** (65%, Scheme 4). These diastereoisomers were easily separated by column chromatography.

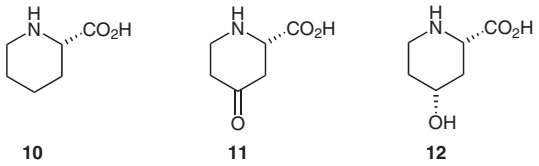
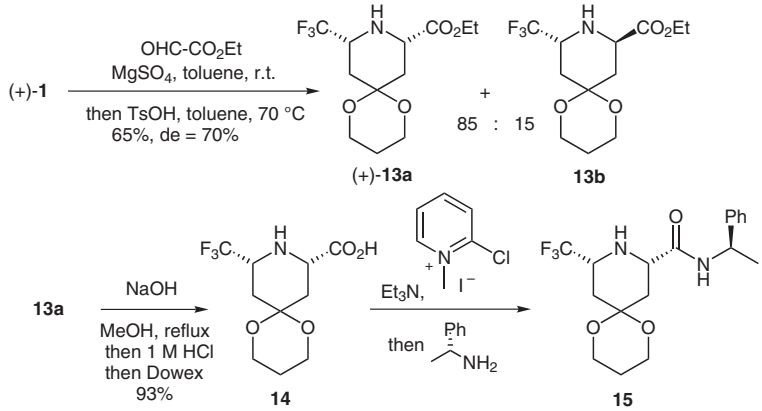


Figure 1

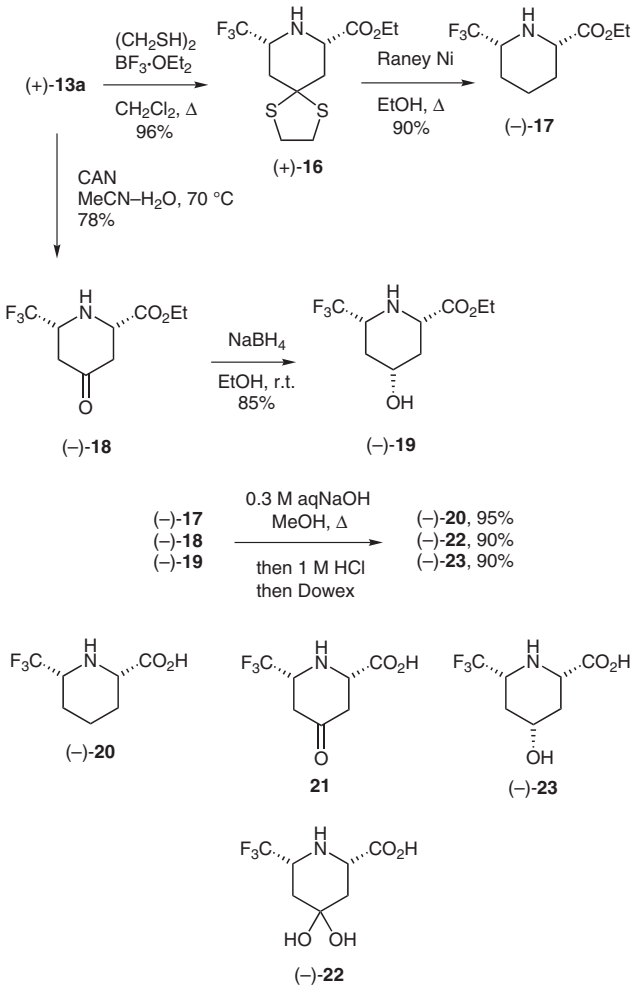
A crucial point to be checked here was the enantiomeric composition of the predominant compound (+)-**13a**. Unfortunately this couldn't be achieved directly by usual NMR or chromatographic techniques, imposing therefore its derivation. Ester **13a** was so transformed into free amino acid **14** whose reaction with (*R*)-(+)-α-methylbenzylamine in the presence of Mukaiyama's coupling reagent[16] gave the parent amide **15** (Scheme 4). Comparison of GC-MS traces of crude **15**, prepared from racemic **13a** and from its (+)-isomer, then demonstrated an excellent stereoisomeric ratio (>95%), proving that no racemization occurred under the acidic and alkaline conditions used for the cyclization and the saponification steps.

Asymmetric synthesis of α′-Tfm analogues of **10**–**12** could then be undertaken. As mentioned in Scheme 5, *trans*-dithioketalation of piperidine (+)-**13a** led to dithiolane (+)-**16**, which, after treatment with excess Raney nickel in refluxing ethanol, furnished very cleanly the pipecolate (–)-**17** in 86% overall yield.

In contrast to previous observations on the parent free Tfm-piperidines,[3b] direct keto-function regeneration of (+)-**13a** was here realized by means of treatment with ceric ammonium nitrate[17] at 70 °C in acetonitrile–water for eight hours (78%, other acidic conditions being ineffective). The 4-piperidone (–)-**18** thus rapidly obtained was then reduced with sodium borohydride at room temperature in ethanol, to afford in 85% yield the desired[3b] *all-cis*-piperidinol (–)-**19**, as sole detectable isomer. Finally, saponification of amino esters **17**–**19**, using 0.3 M aqueous sodium hydroxide in refluxing methanol, followed by HCl acidification and migration through an ion-exchange resin gave efficiently (90–95%) the trifluoromethylated analogues of free amino acids **10**, **11**, and **12**, respectively, (–)-**20**, **21** [which exists as its hydrate[14b] (–)-**22**], and (–)-**23**.[18]



Scheme 4



Scheme 5

In conclusion, with the results disclosed here we have demonstrated that the intramolecular Mannich reaction of α-trifluoromethyl-β-amino ketals constitutes a pertinent tool for the synthesis of highly enantioenriched Tfm-piperidines. Validity of this method was illustrated by, at our knowledge, the first asymmetric synthesis of Tfm-pipecolic acids. These original conformationally constrained amino acids, compounds of synthetic and biological interest, were simply and efficiently prepared in a maximum of eight steps starting from commercial fluoral hemiacetal. Furthermore, applicable to a wide range of aldehydes,[3] this strategy opens a new way to series of homochiral α-Tfm-piperidines. Complete experimental details, together with extensions to enantioselective synthesis of Tfm-piperidine based α-, β-, and γ-amino acids but also of saturated Tfm-N-heterobicyclic systems, will be proposed in due course.

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(10) *R*-(+)-**1**, $[\alpha]_D^{25}$ 16.0 (*c* 1.30, $CHCl_3$); *S*-(–)-**1**, $[\alpha]_D^{25}$ –16.5 (*c* 1.15, $CHCl_3$).

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(18) **Selected Data for Compounds 20, 22, and 23**

(–)-(2*S*,6*R*)-6-Trifluoromethyl-pipecolic Acid (20)

White solid; mp 118 °C; $[\alpha]_D^{25}$ –11.2 (*c* 1.00, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 3.61 (m, 1 H), 3.37 (dd, *J* = 12, 3 Hz, 1 H), 2.11 (m, 1 H), 2.06–1.95 (m, 2 H), 1.65–1.37 (m, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 177.2, 124.6 (q, J_{CF} = 277 Hz), 60.3, 56.7 (q, J_{CF} = 30 Hz), 27.4, 22.5, 22.0. ^{19}F NMR (376 MHz, CD_3OD): δ = –78.0. HRMS: *m/z* calcd for $C_7H_{11}F_3NO_2$ [M + H$^+$]: 198.0742; found: 198.0724.

(–)-(2*S*,6*R*)-4,4-Dihydroxy-6-trifluoromethyl-pipecolic Acid (22)

White solid; mp 95 °C; $[\alpha]_D^{25}$ –2.1 (*c* 1.00, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 4.34 (m, 1 H), 4.23 (dd, *J* = 13.0, 3.5 Hz, 1 H), 2.53 (dt, *J* = 14.0, 3.5 Hz, 1 H), 2.37 (dt, *J* = 14.0, 3.0 Hz, 1 H), 2.08 (t, *J* = 13.5 Hz, 2 H). ^{13}C NMR (100 MHz, D_2O): δ = 169.5, 122.6 (q, J_{CF} = 279 Hz), 90.4, 56.1, 54.6 (q, J_{CF} = 33 Hz), 36.8, 33.2. ^{19}F NMR (376 MHz, CD_3OD): δ = –75.1. HRMS: *m/z* calcd for $C_7H_9NO_3F_3$ [(M – H_2O) + H$^+$]: 212.0535; found: 212.0545.

(–)-(2*S*,4*S*,6*R*)-4-Hydroxy-6-trifluoromethyl-pipecolic Acid (23)

White solid; mp 145 °C; $[\alpha]_D^{25}$ –9.3 (*c* 0.95, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 3.92 (tt, *J* = 11.5, 4.5 Hz, 1 H), 3.62 (m, 2 H), 3.40 (dd, *J* = 12.5, 3.0 Hz, 1 H), 2.37 (m, 1 H), 2.26 (m, 1 H), 1.44 (q, *J* = 12.0 Hz, 1 H), 1.38 (td, *J* = 12.5, 11.0 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O): δ = 176.6, 124.4 (q, J_{CF} = 277 Hz), 66.3, 58.3, 54.9 (q, J_{CF} = 30 Hz), 36.2, 31.3. ^{19}F NMR (376 MHz, CD_3OD): δ = –77.8. HRMS: *m/z* calcd for $C_7H_{11}F_3NO_3$ [M + H$^+$]: 214.0691; found: 214.0700.