Synthèse asymétrique de pipéridines trifluorométhylées

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Par

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Synthèse asymétrique de pipéridines trifluorométhylées

Asymmetric synthesis of trifluoromethylated piperidines

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SUMMARY

INTRODUCTION GENERALE

Si la naissance de la chimie du fluor remonte au 26 juin 1886, jour de l'isolement de cet élément par Henri Moissan[1,2], on peut considérer que la chimie fluoro-organique est encore une discipline « jeune ». Ce n'est en effet qu'au début des années 1950 qu'elle a réellement pris son essor[3,4]. Une constatation permet d'expliquer en partie cette éclosion tardive : si le fluor est le treizième élément en terme d'abondance dans l'écorce terrestre[5] (le premier en ce qui concerne les halogènes), la Nature éprouve de grandes difficultés à l'incorporer au sein de composés organiques et ceci du fait de la trop grande énergie de solvatation de l'ion fluorure dans l'eau[3,6]. En conséquence, elle se montre extrêmement avare en structures organo-fluorées, tellement qu'à ce jour, et à notre connaissance, seuls 13 produits naturels contenant du fluor ont été caractérisés[7,8]. Ces produits, rassemblés en figure 1, sont issus de bactéries (**1**, **2** et **3**), mais surtout de plantes tropicales ou subtropicales (**3** à **13**).

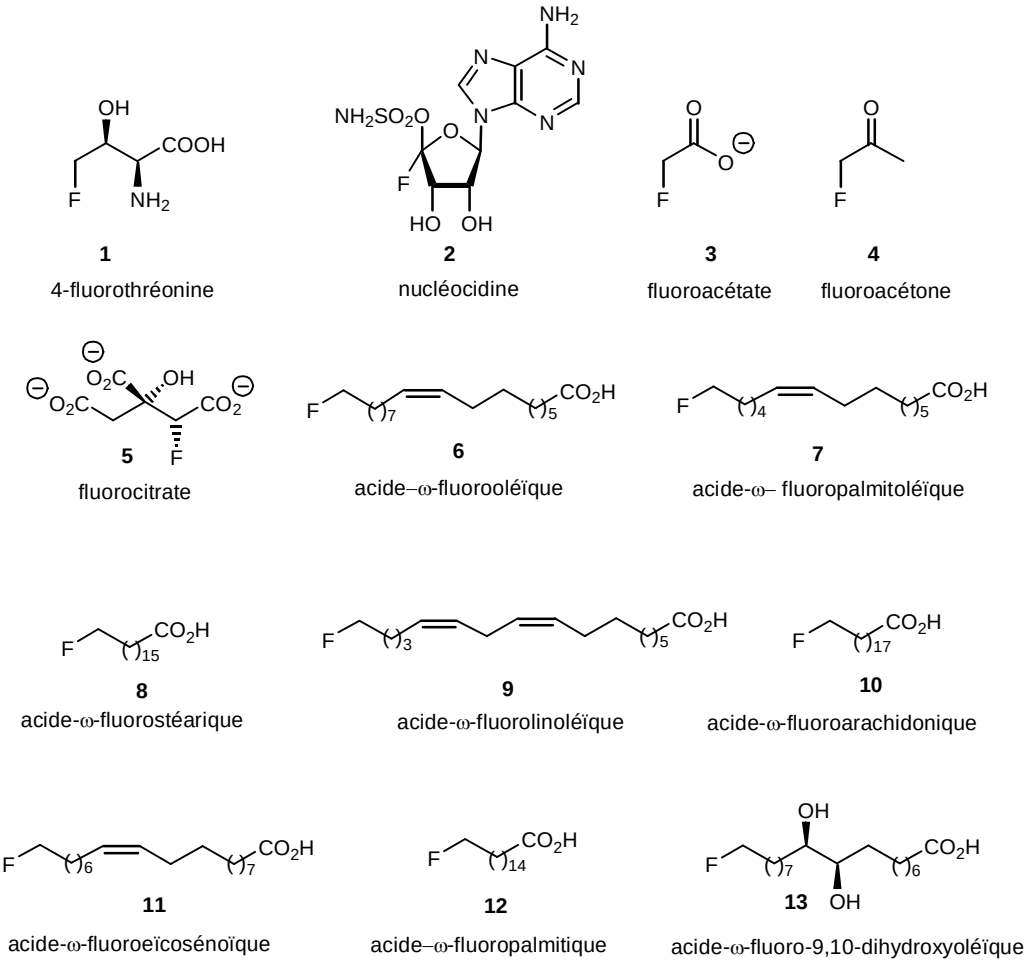
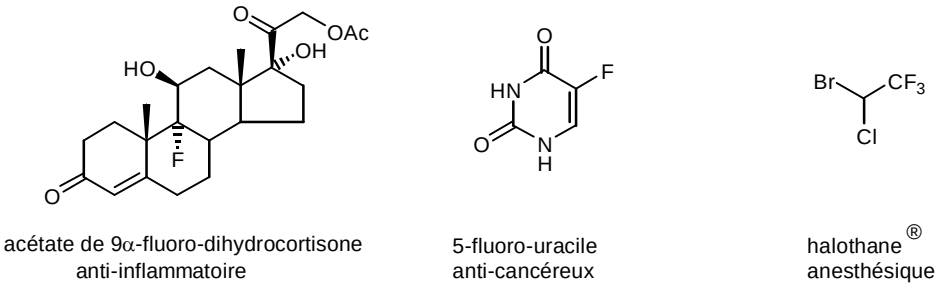


Figure 1. Inventaire exhaustif des composés naturels fluorés connus.

Parce que la Nature a toujours constitué une source majeure d'inspiration pour les chimistes organiciens de synthèse, parce qu'Elle n'avait pas (peu) de modèle(s) fluoré(s) à soumettre à l'inventivité des chercheurs, la chimie fluoro-organique demeurait, relativement, en sommeil.

C'est certainement une découverte décisive de Josef Fried[9] qui allait impulser les développements considérables qu'a connu et que connaît toujours cette discipline[10]. Chercheur de l'industrie pharmaceutique, il a synthétisé en 1954 l'acétate de 9a-fluoro-dihydrocortisone (figure 2), et des études ont montré que ce glucocorticoïde présentait une activité anti-inflammatoire 11 fois supérieure à celle de son analogue non fluoré tout en réduisant ses effets secondaires (rétention de sodium)[4]. L'influence bénéfique de l'introduction d'un atome de fluor sur l'activité biologique d'une substance était mise en évidence. Elle sera confirmée concomitamment par la découverte de l'activité anti-cancéreuse puissante du 5-fluorouracile et de celle des anesthétiques chirurgicaux volatils tel l'halothane® (figure 2)[4, 11].



acétate de 9α-fluoro-dihydrocortisone
anti-inflammatoire

5-fluoro-uracile
anti-cancéreux

halothane®
anesthésique

Figure 2.

Ces événements modifièrent sensiblement le « périmètre moléculaire » de la chimie médicinale. Les composés organo-fluorés devenaient peu à peu des cibles incontournables, à tel point qu'ils représentent désormais[4] près de 25% des parts de marché de l'industrie pharmaceutique (2% en 1970), avec 6 principes actifs dans le « top 12 » des meilleures ventes de médicaments. En 2002, parmi les 31 nouveaux médicaments approuvés aux Etats-Unis, 9 étaient des molécules organofluorées.[12] Pour illustrer ce propos, et le fait que de nombreux domaines de la pharmacopée sont concernés, sont présentés en figure 3 quelques-uns des « F-blockbusters » actuellement commercialisés (sont donnés entre parenthèses les chiffres[13] des ventes 2005 de ces médicaments, en millions de dollars américains).

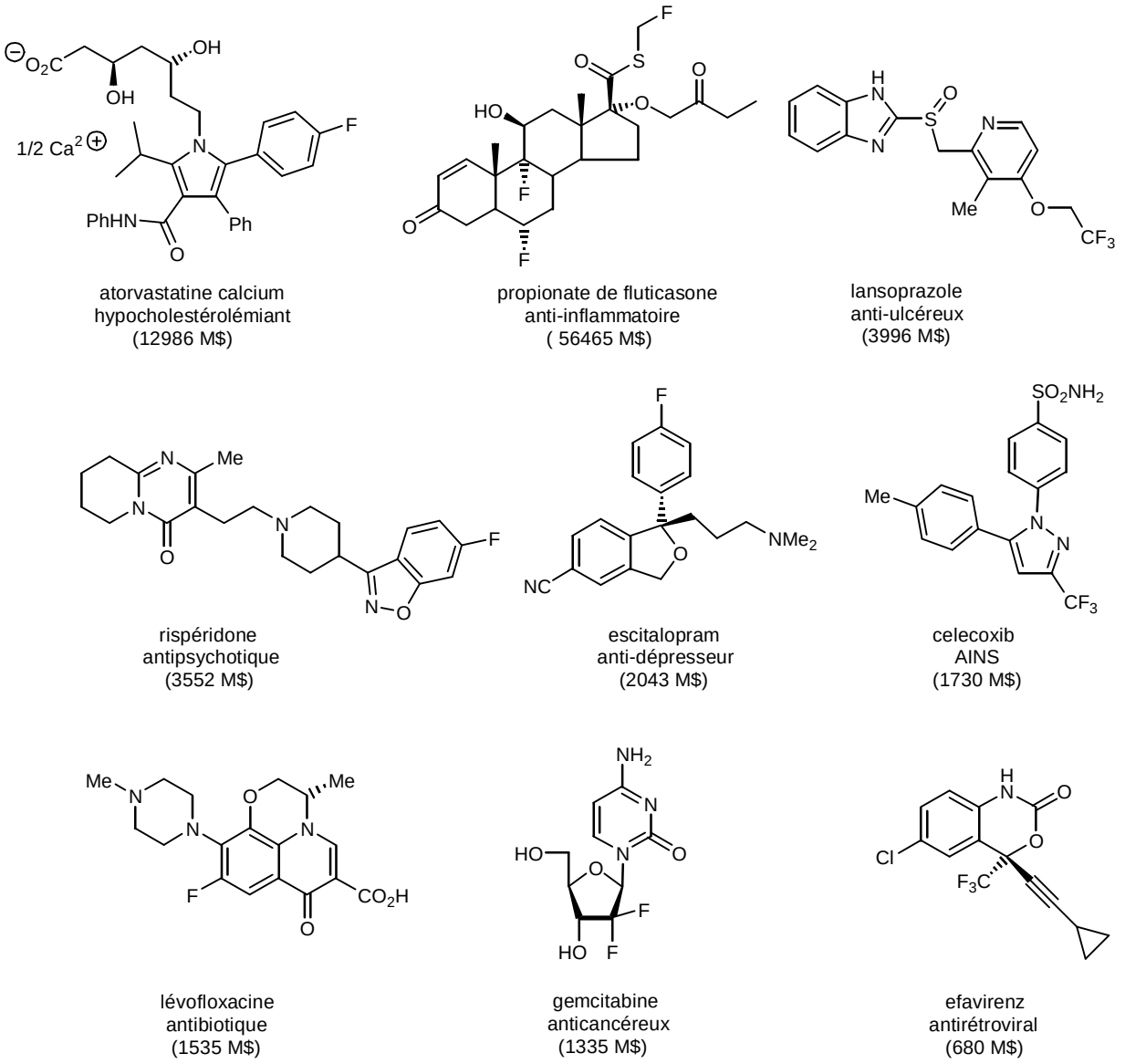


Figure 3. Sélection de principes actifs organofluorés (ventes 2005 en millions de dollars américains).

Les composés fluoro-organiques occupent également une place de choix dans l'industrie agrochimique[3,4], puisque de l'ordre de 50% des parts de marché leur sont aujourd'hui attribuables (3% en 1970) pour des utilisations phytosanitaires variées (fongicide, insecticide, herbicide …, figure 4).

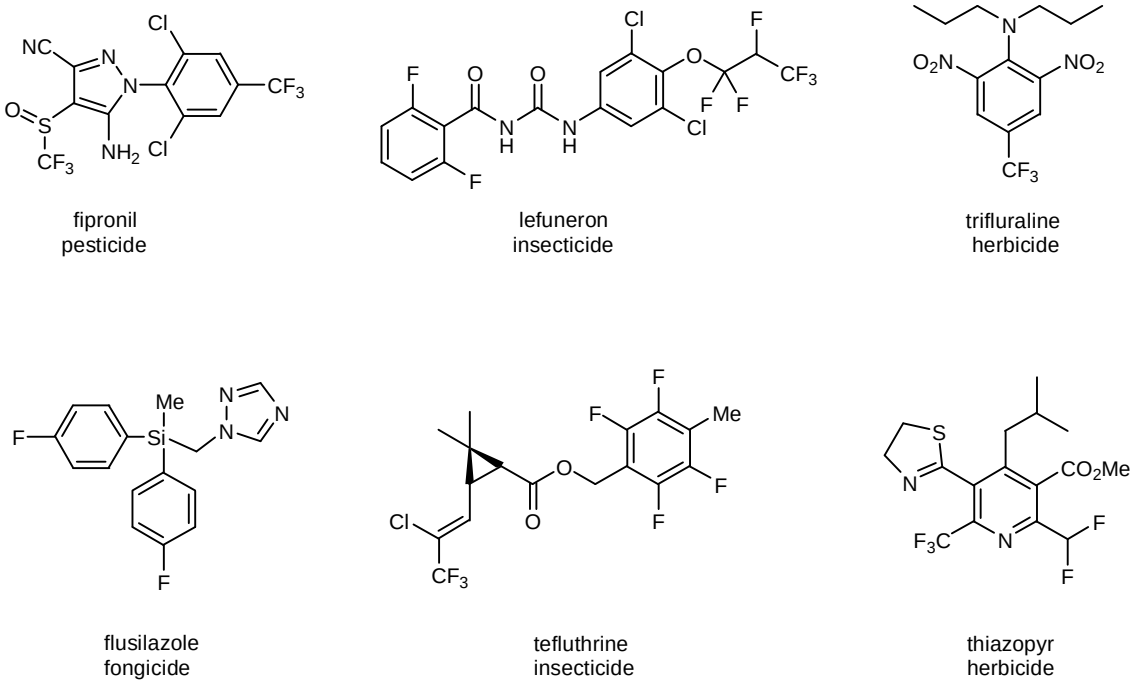


Figure 4. Sélection de produits phytosanitaires organofluorés.

Il est désormais généralement reconnu que l'incorporation d'un ou de plusieurs atome(s) de fluor au sein d'une molécule bio-active peut entraîner des modifications profondes et opportunes de ses propriétés physico-chimiques et biologiques[14], du fait des spécificités physiques uniques de cet élément, le plus petit (excepté l'hydrogène) et le plus électronégatif de la Classification. De la substitution d'un hydrogène par un fluor, ou de celle d'un méthyle par un trifluorométhyle, peut en effet résulter une amélioration significative des profils pharmacocinétique et pharmacodynamique d'un principe actif, ceci bien souvent par augmentation de sa stabilité métabolique mais également par modification simultanée de ses propriétés acido-basiques, électroniques, stériques et d'hydrophobicité[4, 14, 15].

Conséquence directe de l'intérêt biologique indéniable des molécules organo-fluorées, la chimie organique du fluor connaît comme nous le disions, et surtout depuis les années 1970, une expansion tout a fait remarquable et continue. Aujourd'hui de nombreux aspects de cette discipline ont été largement examinés et les avancées méthodologiques qui ont découlé de ces études permettent maintenant d'accéder à une grande variété de structures organiques (poly) fluorées.

Cependant, il demeure certains domaines très peu développés et pour lesquels d'importants progrès restent à accomplir.

C’est particulièrement le cas pour ce qui concerne l’élaboration d’hétérocycles azotés saturés porteurs d’un groupement trifluorométhyle (Tfm), composés pour lesquels peu de méthodes de synthèse ont été décrites. Une remarque de J. Jiang[16], assez récente puisque datant de 1999, fournit une explication à cette lacune : *« si les N-hétérocycles aromatiques trifluorométhylés sont bien documentés, leurs analogues saturés sont beaucoup moins connus. La synthèse d’hétérocycles saturés trifluorométhylés, sous forme de racémique ou énantiomériquement purs, constitue un défi significatif pour le chimiste de synthèse* ». Cette remarque a été relevée par les chercheurs du Laboratoire de Chimie des Hétérocycles et des Glucides, et elle marque le point de départ de la présente Thèse de Doctorat.

Effectivement, l’un des axes de recherche majeurs du Laboratoire est la mise au point de nouvelles méthodes de synthèse stéréosélective d’hétérocycles azotés saturés, notamment de pipéridines, composés intrinsèquement d’intérêt biologique[17]. L’un des résultats marquants obtenu dans ce cadre a été la démonstration qu’une réaction de type Mannich intramoléculaire constituait un outil pertinent pour accéder à une large gamme de pipéridines *cis*-2,6-disubstituées, et ce de manière quasi stéréospécifique[18]. Cette stratégie est décrite dans le schéma 1.

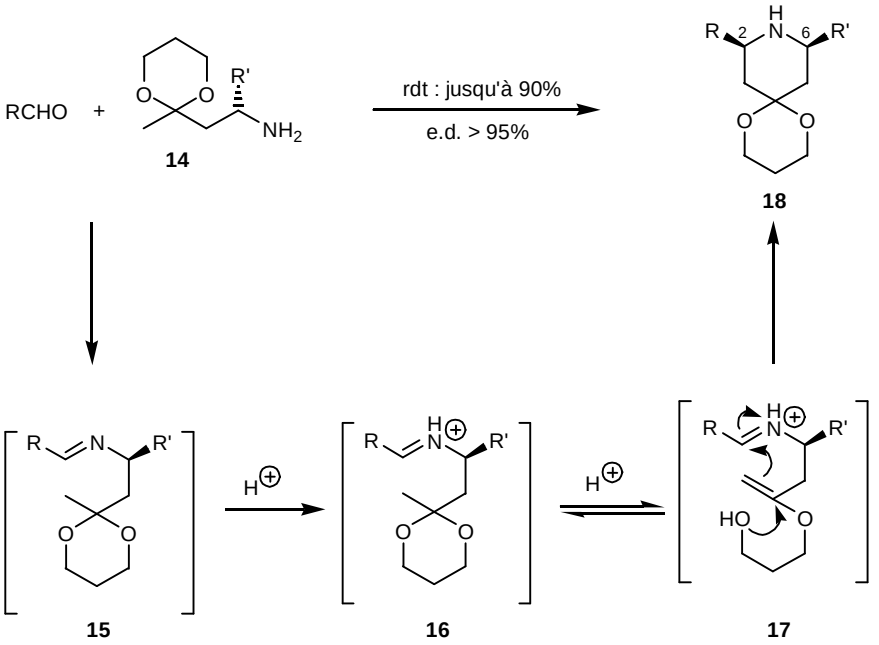


Schéma 1. Synthèse stéréosélective de pipéridines *cis*-2,6-disubstituées par réaction de Mannich intramoléculaire.

La réaction d’un β-aminocétal **14** avec un aldéhyde conduit à l’imine intermédiaire correspondante **15**. Cette dernière, traitée par un acide en milieu anhydre mène à un ion

iminium qui co-existe sous deux formes, l'une cyclique **16** et l'autre dite « ouverte » **17**. Dès que la forme éther d'énol **17** apparaît, toutes les conditions sont réunies pour que, selon un processus de type Mannich intramoléculaire, une double cyclisation se produise, libérant la pipéridine **18.**

Pour rendre compte du haut degré de stéréosélectivité observé lors de cette séquence réactionnelle, les états de transition **A** et **B** ont été considérés[18]. Et comme le montre le schéma 2, il semble qu'une contrainte stérique moindre favorise l'état de transition **A**, précurseur de l'isomère 2,6-*cis*, aux dépens de l'état de transition **B** conduisant à l'isomère 2,6-*trans*.

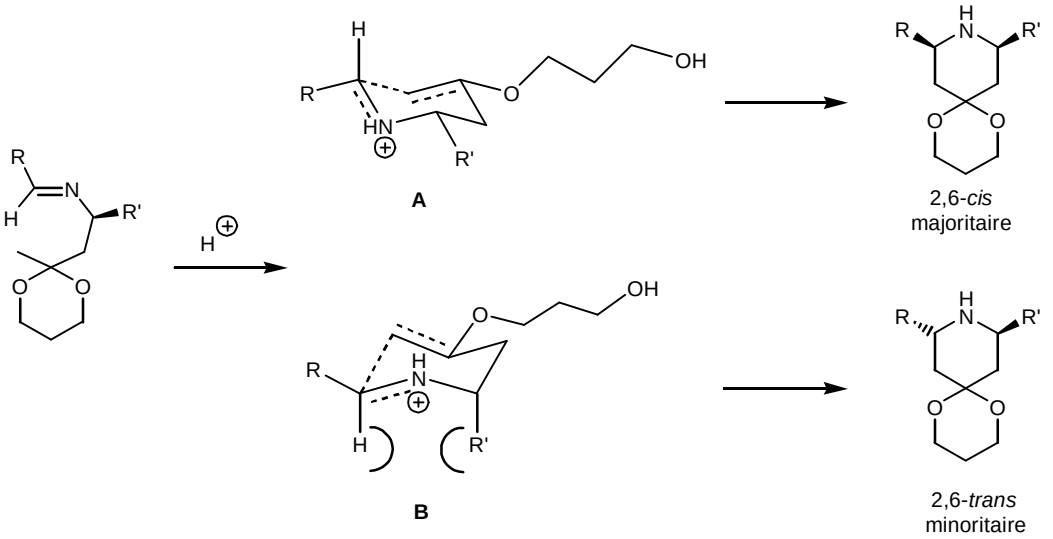


Schéma 2.

Cette méthode simple et efficace développée au Laboratoire a permis d'accéder à un grand nombre de nouvelles pipéridines fonctionnalisées[18-20], énantiomériquement pures, et a été entièrement validée par la synthèse totale asymétrique de différents alcaloïdes[20-23].

C'est dans le but d'étendre son champ d'application à des problèmes de synthèse plus délicats, qu'il a été décidé d'évaluer son potentiel dans le domaine de la chimie fluoro-organique, en l'occurrence pour la préparation d'a-Tfm-pipéridines, composés réputés d'accès difficile comme le soulignait Jiang[16, 24], et comme le rappelait encore très récemment Samir Zard[25].

La réaction de Mannich intramoléculaire est apparue tout à fait appropriée pour résoudre ce type de problème puisque offrant une double opportunité pour l'introduction sélective d'un groupement trifluorométhyle en position C-2 d'une pipéridine (schéma 3).

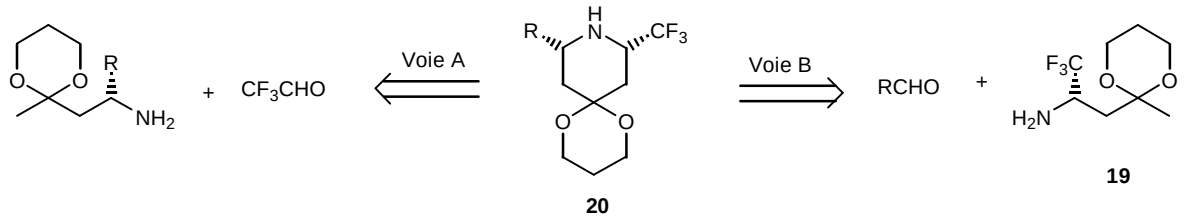


Schéma 3.

En effet, l'incorporation sélective du CF_3 pouvait être raisonnablement envisagée *via* l'implication du trifluoroacétaldéhyde (fluoral) en tant que partenaire carbonylé de la cyclisation de Mannich (Voie A), mais également *via* l'utilisation de la trifluorométhylamine chirale **19** (voie B).

L'accès aux Tfm-Pipéridines cibles **20** apparaissait donc tout à fait réalisable selon l'une et/ou l'autre de ces deux voies.

C'est dans ce contexte qu'en septembre 2005, il m'a été proposé de confronter la réaction de Mannich intramoléculaire développée au Laboratoire en série « conventionnelle », à la synthèse asymétrique de pipéridines a-trifluorométhylées. Les résultats obtenus depuis lors font l'objet du présent mémoire de thèse de doctorat.

Celui-ci se divise en plusieurs parties :

Un premier chapitre sera consacré au recensement et à la description des différentes méthodes de synthèse de pipéridines trifluorométhylées décrites dans la littérature.

Dans un second chapitre, méthodologique, seront détaillés les résultats des études des deux voies, A et B, ayant permis d'accéder diastéréosélectivement à de nouvelles Tfm-pipéridines. Y seront également rapportées les premières applications, concernant notamment la synthèse d'analogues trifluorés de pipéridines alcaloïdes.

Enfin, un dernier chapitre traitera de l'adaptation de la stratégie mise au point à la Synthèse Enantiosélective. Le propos sera illustré par la description de la première synthèse asymétrique d'acides Tfm-pipécoliques, mais également par celle de structures polycycliques trifluorométhylées originales, énantiomériquement pures.

GENERAL INTRODUCTION

If the chemistry of fluorine was born on 26 June, 1886, the day of the isolation of this element by Henri Moissan[1, 2], one can consider that fluoro-organic chemistry is still a "young" discipline. It is indeed only in the early 1950s that it really started to develop[3,4]. A possible explanation to this late rising of fluoro-organic chemistry, inspite the fact that fluorine is the thirteenth element in term of abundance in the Earth's crust[5] (the first with regard to the halogens), Nature experiences great difficulties of incorporating it within organic compounds and this because of the high energy of solvation of the fluoride ion in water[3,6]. Consequently, it shows extremely miserly of fluoro-organic structures, so much that to date, and to our knowledge, only 13 natural organic compounds containing fluorine have been characterized. These compounds[7,8] depicted in figure 1, are issued from bacteria (**1**, **2** and **3**), but mainly from seeds and tropical or subtropical plants (**3** to **13**).

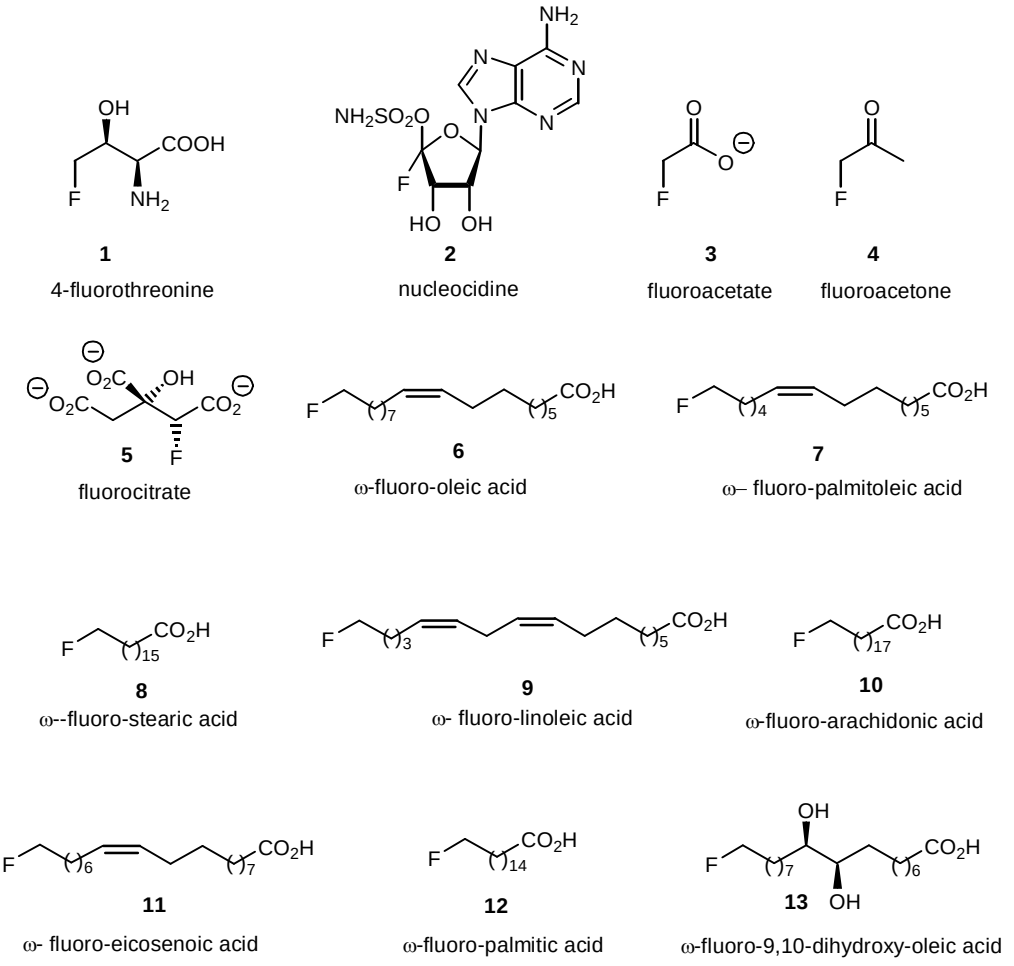
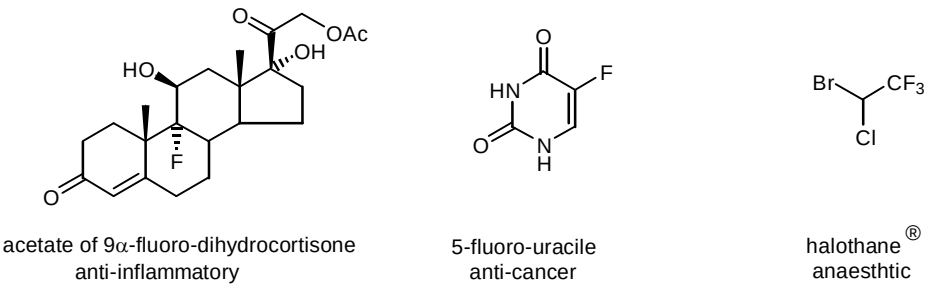


Figure 1. Exhaustive inventory of the known fluorinated natural compounds.

As Nature always constituted a major source of inspiration for the synthetic organic chemists, and as It did not have (very few) of fluorinated model(s) to submit to inventiveness of researchers, fluoro-organic chemistry remained, relatively, in sleep.

It was certainly a decisive discovery of Josef Fried[9] which provided basis for the considerable developments yet known and that this discipline knows always[10]. Researcher of pharmaceutical industry, he synthesized in 1954 the acetate of 9α-fluoro-dihydrocortisone (figure 2), and the studies showed that this glucocorticoide presented an anti-inflammatory activity 11 times higher than that of its non-fluorinated analogue while reducing its side effects (retention of sodium)[4]. The beneficial influence of the introduction of a fluorine atom on the biological activity of a substance was recognized. It was confirmed unambigiously by the discovery of the potential anti-cancer activity of the 5-fluorouracile and that of volatile surgical anesthetic such as halothane® (figure 2)[4, 11].



acetate of 9α-fluoro-dihydrocortisone
anti-inflammatory

5-fluoro-uracile
anti-cancer

halothane®
anaesthtic

Figure 2.

These events appreciably modified the "molecular parameters" of medicinal chemistry. The organo-fluorinated compounds became little by little inevitable targets, at such point that they represent today[4] nearly 25% of the shares of market of pharmaceutical industry (2% in 1970), with 6 medicines in the "top 12" of the best saled drugs. In 2002, among the 31 new drugs approved in the United States, 9 were fluoro-organic molecules[12]. To illustrate this matter, and the fact that they are concerned to many fields of the pharmacopeia, in figure 3 are presented some of the "F-blockbusters" currently marketed (in between brackets are given the figures[13]of sales 2005 of these drugs, in million US dollars).

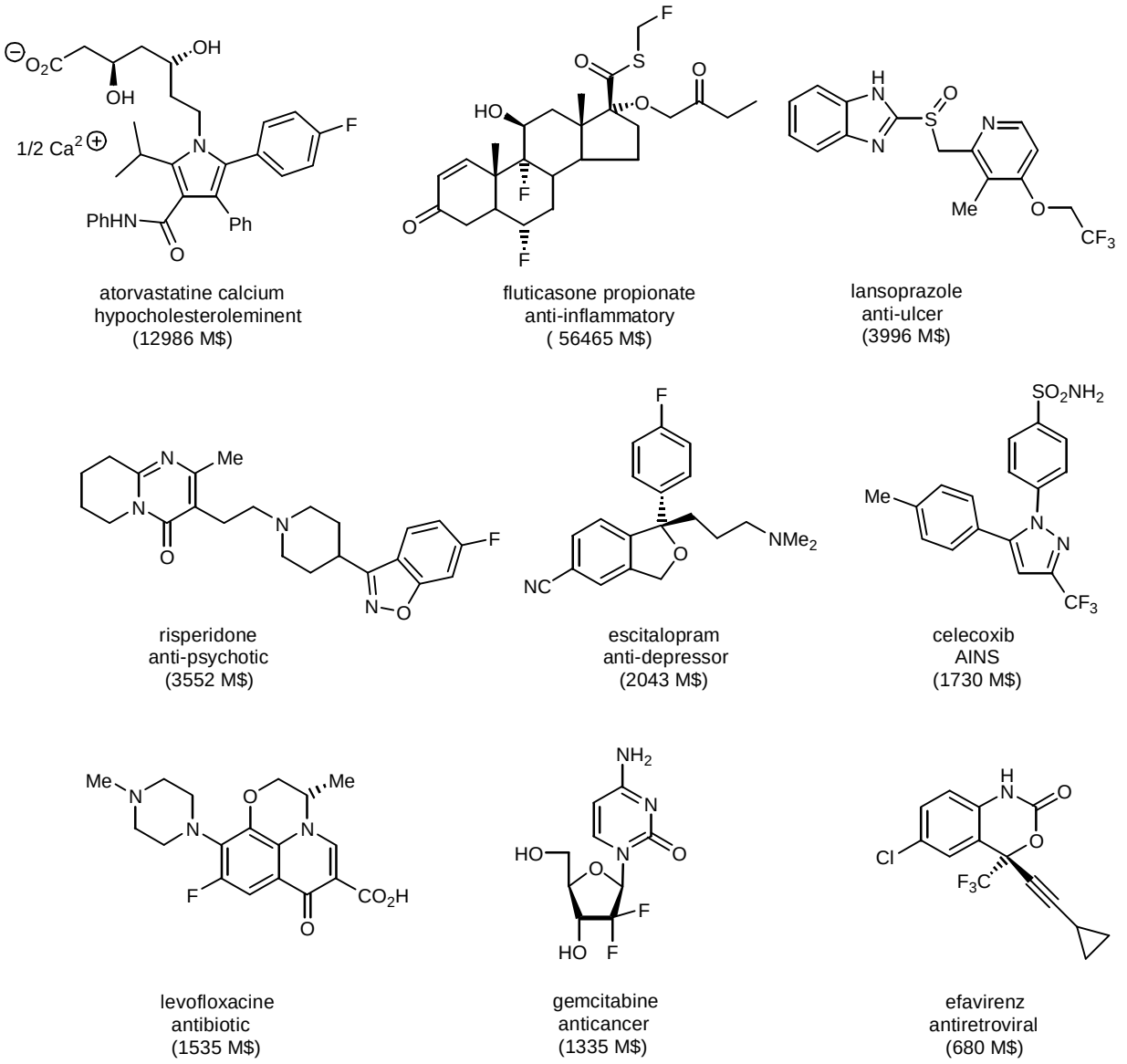


Figure 3. Selection of organofluorinated drugs (sales 2005 in millions of US dollars).

The fluoro-organic compounds also occupy an important place in agrochemical industry[3,4], since about 50% of the shares of market are today ascribable for them (3% in 1970) for vorious plant diseases (fungicidal, insecticidal, herbicidal..., figure 4).

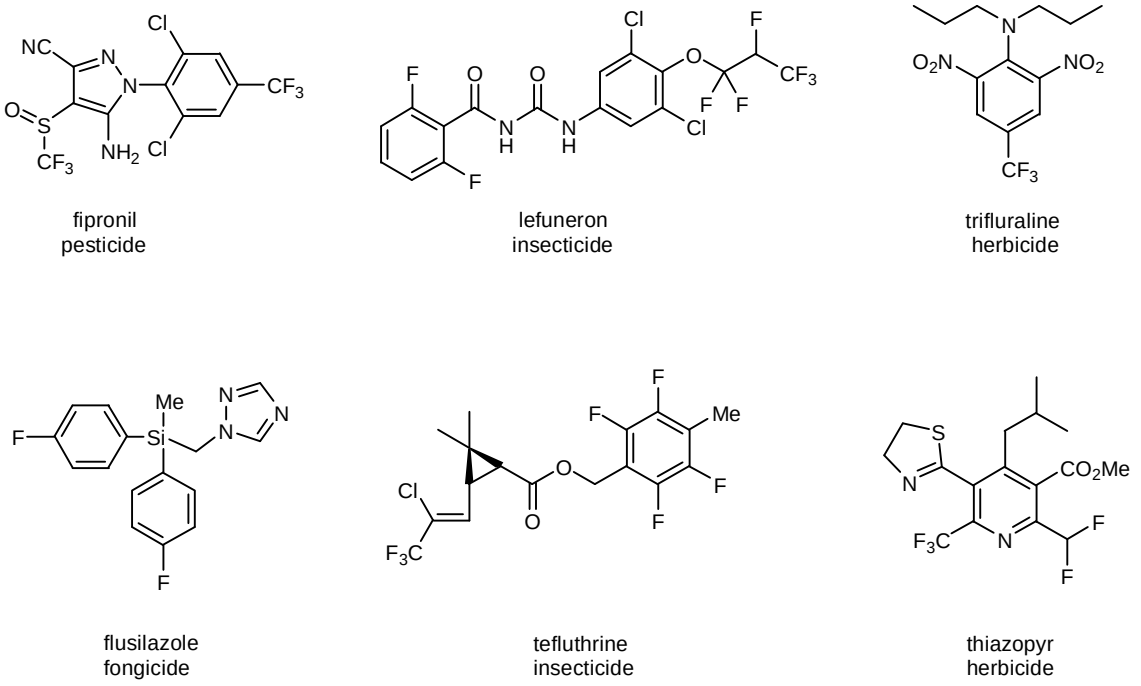


Figure 4. Selection of organofluorinated agrochemicals.

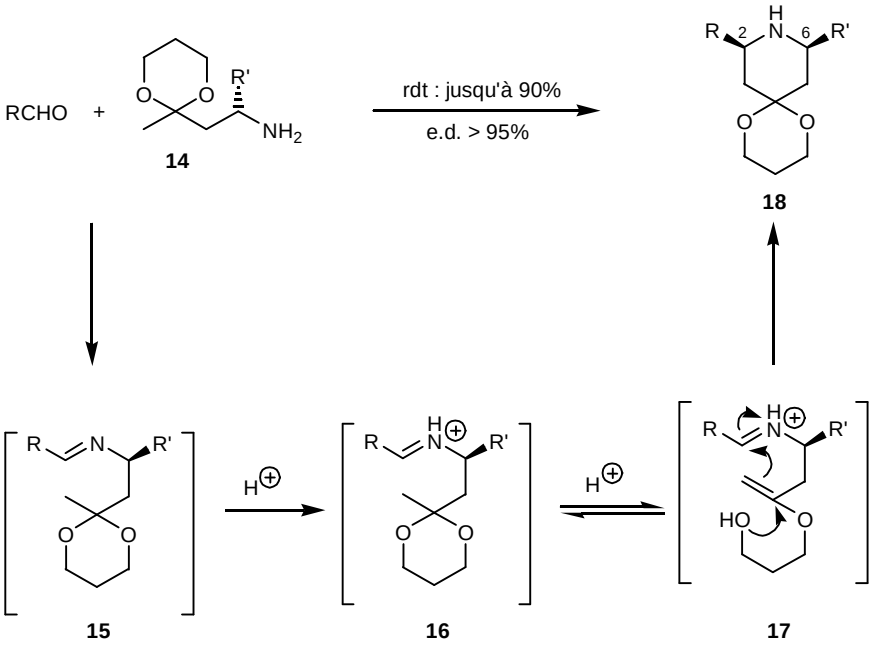
It is henceforth generally acknowledged that the incorporation of one or several atoms of fluorine within a bio-active molecule can involve profound changes by modifying its physico-chemical and biological properties[14], because of the unique physical specificities of this element, smallest (except hydrogen) and most electronegative of periodic classification. Substitution of a hydrogen by a fluorine, or of a methyl by a trifluoromethyl, may indeed result in significant improvement of the pharmacokinetic and pharmacodynamic profiles of a drug, very often by modification of its metabolic stability but also by simultaneous alterations of its acido-basic, electronic, steric and lipophilic properties[4,14,15].

Direct consequences of the undeniable biological interest of the organo-fluorinated molecules, the organic chemistry of fluorine knows as we said it, and especially since the years 1970, completely remarkable and continuous expansion. Today many aspects of this discipline have been largely examined and the methodological projections which rose from these studies now make possible to reach a large variety of (poly)fluorinated organic structures. However, certain fields remained poorly developed and for which important progresses needs to be achieved.

It is particularly the case concerning the development of saturated nitrogen heterocycles carrying a trifluoromethyl (Tfm) group, compounds for which few methods of

synthesis were described. A remark of Jinlong Jiang[16], recently in 1999, provides an explanation to this gap: *"if the trifluoromethylated aromatic N-heterocycles are well documented, their saturated analogues are much less known. The synthesis of saturated trifluoromethylated heterocycles, in the racemic or enantiomerically pure form, constitutes a significant challenge for the synthetic chemist*." This remark was raised by the researchers of the Laboratoire de Chimie des Hétérocycles et des Glucides, and that makes the starting point of this Ph.D thesis.

Indeed, one of the major research orientations of the Laboratory is the development of new methods for stereoselective synthesis of saturated *N*-heterocycles, in particular of piperidines, compounds of intrinsic biological interest[17]. One of the outstanding results obtained within this framework was the demonstration that a Mannich type intramolecular reaction constituted a relevant tool to reach a wide range of *cis*-2,6-disubstituted piperidines, in an almost stereospecific manner[18]. This strategy is described in scheme 1.

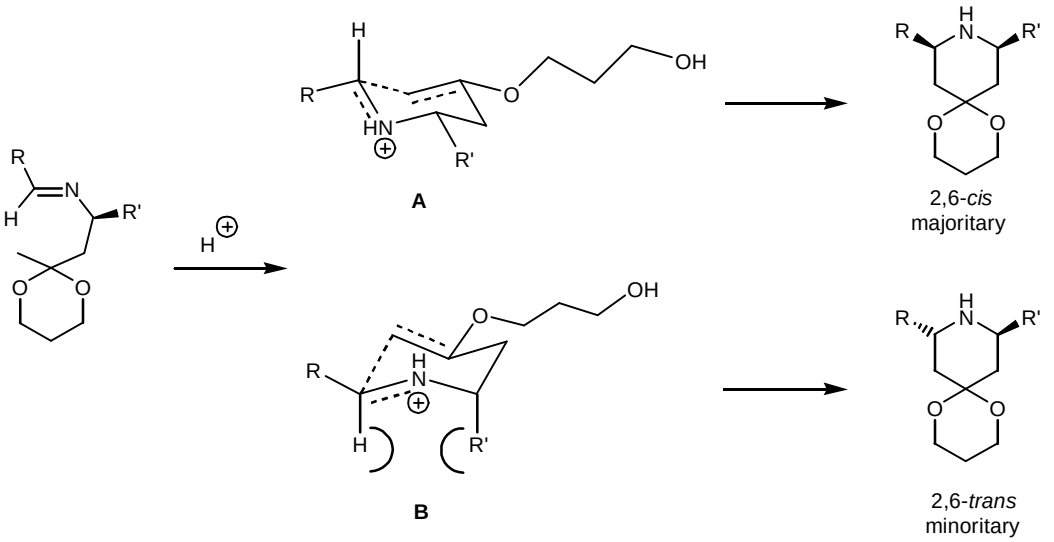


Scheme 1. Stereoselective synthesis of *cis*-2,6-disubstituted piperidine by Mannich intramolecular reaction.

Reactions of a β-aminoketal **14** with an aldehyde lead to the corresponding imine intermediate **15**. The latter, treated by an acid in anhydrous medium gives an iminium ion which coexists in two forms, one cyclic **16** and the other known as "open" **17**. As soon as the

form enol ether **17** appears, all the conditions are met so that, according to intramolecular Mannich type process, a double cyclization occurs, releasing piperidine **18**.

To explain the high degree of stereoselectivity observed at the time of this reactional sequence, the transition states **A** and **B** were considered[18]. And as shown in scheme 2, it seems that a less steric constraint supports the transition state **A**, precursor of the isomer 2,6-*cis*, while transition state **B** leading to 2,6-*trans* isomer is disfavored.

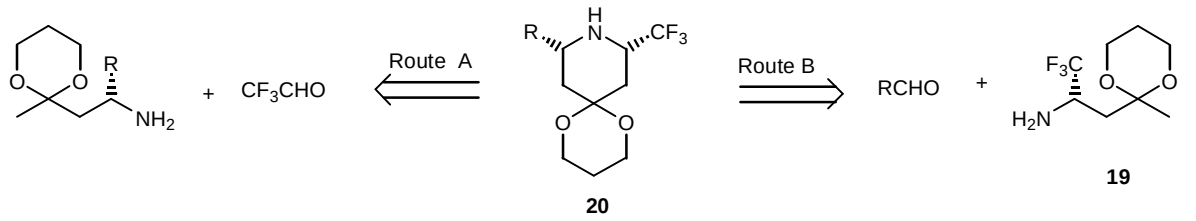


Scheme 2.

This simple and effective method developed at the Laboratory made it possible to reach a great number of new functionalized piperidines[18-20], enantiomerically pure, and was entirely validated through the asymmetric total synthesis of different alkaloids[20-23].

We thought of extending its field of application to more delicate problems of synthesis, and it was decided then to evaluate its potential in the field of fluoro-organic chemistry, especially for the preparation of α-Tfm-piperidines, compounds known for a difficult access, as underlined by Jiang[16, 24], and as still very recently pointed out by Zard[25].

The intramolecular Mannich reaction appeared completely suitable to solve this type of problem since offering a double opportunity for the selective introduction of a trifluoromethyl group at C-2 position of a piperidine ring (scheme 3).



Scheme 3

Indeed, the selective incorporation of the CF_3 could be reasonably envisaged via the implication of the trifluoroacetaldehyde (fluoral) as a carbonyl partner of the cyclization of Mannich (route A), but also via the use of the chiral trifluoromethylamine **19** (route B).

The access to target Tfm-piperidines **20** thus appeared completely attainable according to one and/or the other of these two ways.

It is in this context that in September 2005, it was proposed me to confront the intramolecular Mannich reaction developed at the Laboratory in "conventional" series, to the asymmetric synthesis of α-trifluoromethylated piperidines. The results obtained since then are the subject of the present report of thesis of doctorate.

This one is divided into several parts:

A first chapter will be devoted to the census and the description of the various methods of synthesis of trifluoromethylated piperidines described in the literature.

In a second chapter, the results of the studies of the two ways, A and B will be detailed, having made it possible diastereoselectively to reach new Tfm-piperidines. Will also be described the first applications, in particular relating to the synthesis of trifluormethylated analogues of piperidine alkaloids.

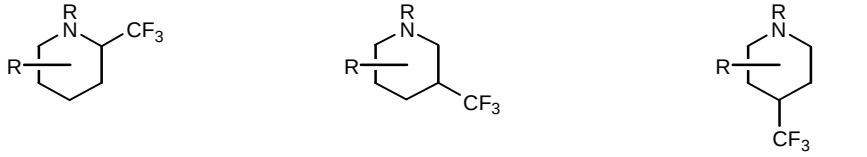
Lastly, a final chapter will treat about adaptation of the developped strategy to the field of enantioselective synthesis. The subject will be illustrated by the description of the first asymmetric synthesis of Tfm-pipecolic acids, but also by that of original enantiomerically pure trifluoromethylated polycyclic structures.

CHAPTER 1

Synthesis of trifluoromethyl-piperidines: A bibliographical survey

I. Introduction

In this chapter are collected the synthetic methods giving an access to trifluoromethylated piperidines we could find in the chemical literature. It mainly concerns the synthesis of 2-trifluoromethyl piperidines **21**, since a very few examples of pathways to 3- and 4-Tfm piperidines **22** and **23** (figure 5) have been reported.



21
2-Tfm-piperidine

22
3-Tfm-piperidine

23
4-Tfm-piperidine

Figure 5.

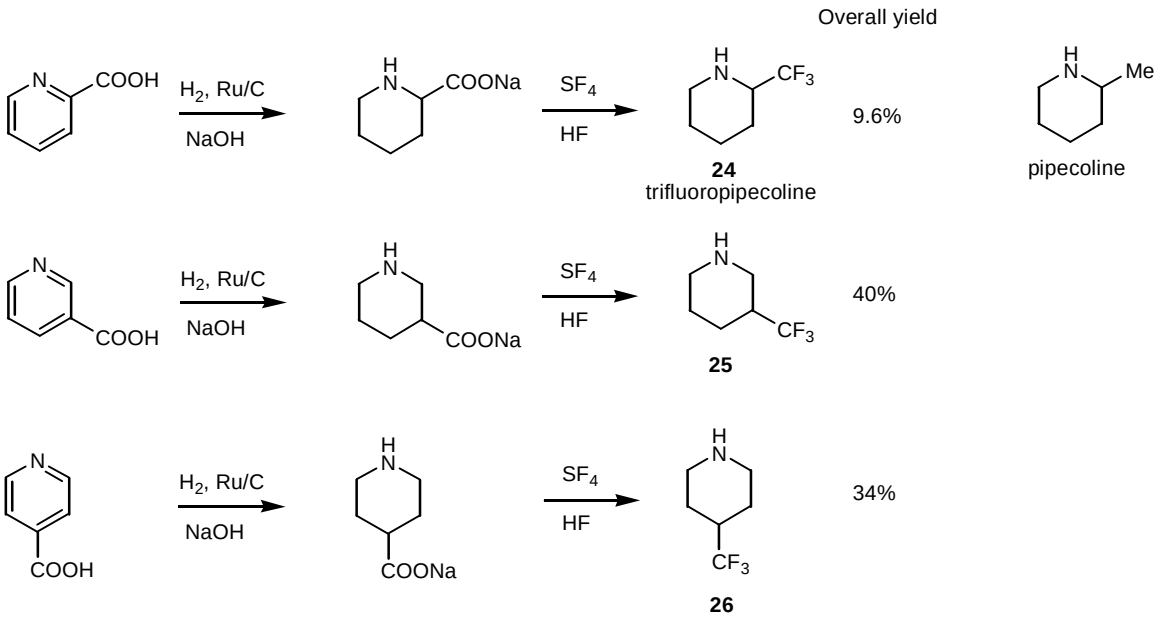
The accesses to Tfm-piperidines are classed here in a chronological order, but similar approaches are grouped together.

Some strategies leading to analogues possessing one intracyclic double bond are also described herein, as these compounds seem obviously easily transformable into the parent saturated heterocycles.

I.1. Conversion of piperidine carboxylates to Tfm-piperidines using sulfur tetrafluoride

To our knowledge, the first synthesis of mono-Tfm-piperidines was pioneered in 1962 by Maynard Raasch[26] in the *Du Pont de Nemours Company* laboratories. His method (scheme 4) lies on the conversion of a carboxyl group into a trifluoromethyl group using sulfur tetrafluoride in hydrogen fluoride. Accordingly, he could prepare the three simplests Tfm-piperidines **24-26**, in two steps from the corresponding pyridine carboxylic acids.

It has to be noted here that Raasch realized the first synthesis of a trifluoro-analogue of a naturally occuring piperidine, compound **24** being a fluorinated analogue of the alkaloid pipecoline.

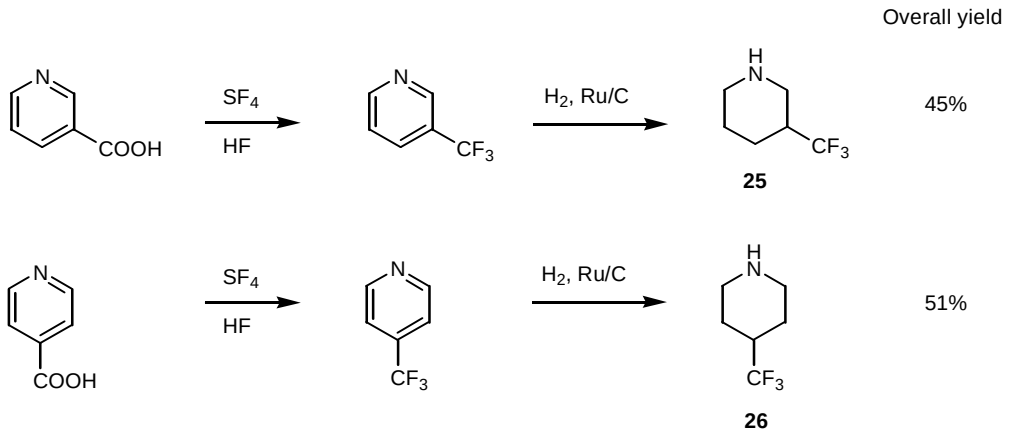


Scheme 4.

Although of quite low efficiency (10-40% yield), this method permitted the formation of Tfm-piperidines on a large scale. Its main inconvenience resulted from the use of toxic reagents in a very corrosive medium, requiring a high resistance stainless steel reaction vessel.

I.2. Catalytic hydrogenation of trifluoromethyl pyridines

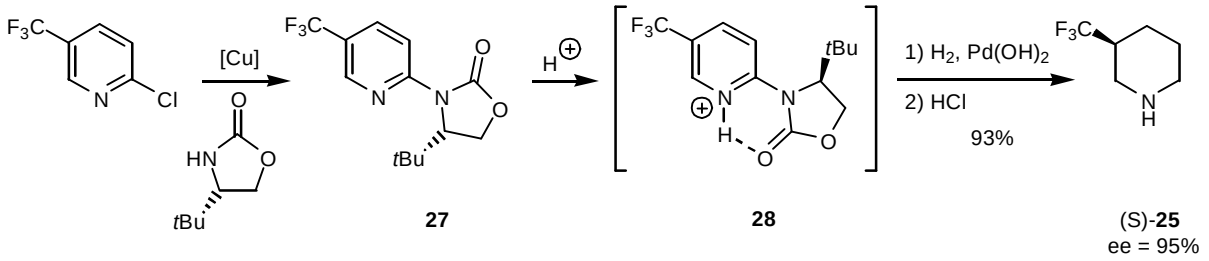
Two years later, from the same laboratories, H. K. Hall Jr.[27] encountered some difficulties to reproduce Raasch's experiments. To overcome these problems he proposed an alternative route, consisting in the inversion of the original reaction sequence (scheme 5).



Scheme 5.

By the way, he could improve the overall yields for compounds **25** and **26** but also facilitated their experimental isolation.

A diastereoselective version of this approach to Tfm-piperidines was proposed after fourty years by Franck Glorius *et al*[28]. They used as key synthon the substrate **27**, prepared by a copper catalyzed coupling of 2-chloro-3-Tfm-pyridine with an Evans' chiral oxazolidinone. Submitted to protic conditions, intermediate **27** was supposed to lead to the corresponding pyridinium salt in the favoured conformation **28** (scheme 6).

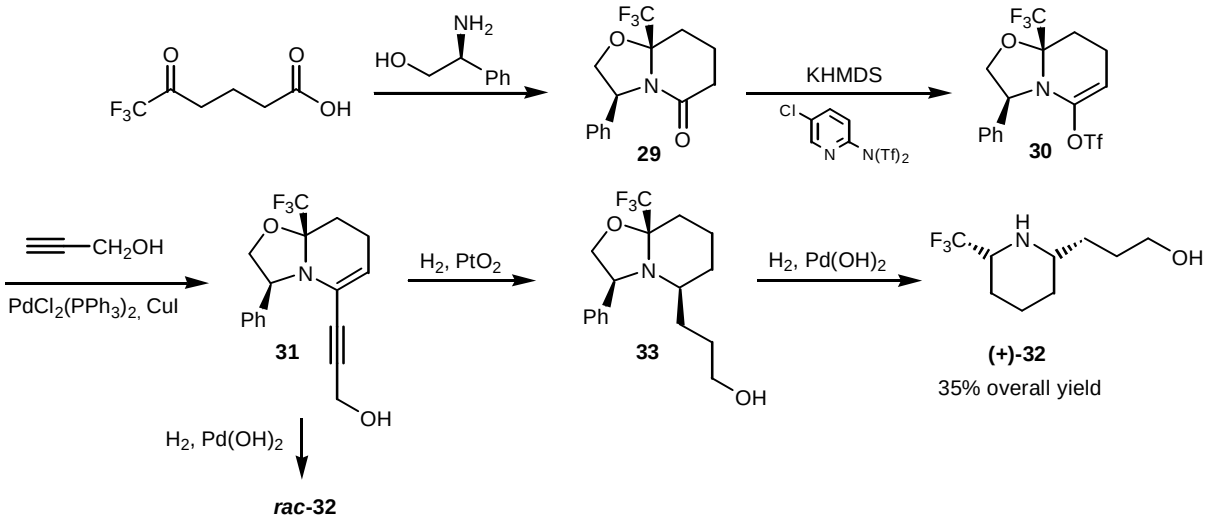


Scheme 6.

In such a conformation, attack of the pyridine moiety was expected to occur *anti* from the bulky *tert*-butyl group. Indeed, palladium-catalyzed hydrogenation of **27** in an acidic medium, followed by cleavage of the chiral auxiliary, gave the Tfm-piperidine (*S*)-**25** as an almost single enantiomer (95% ee).

I.3. Synthesis of Tfm-piperidines using the "chiral lactam" route

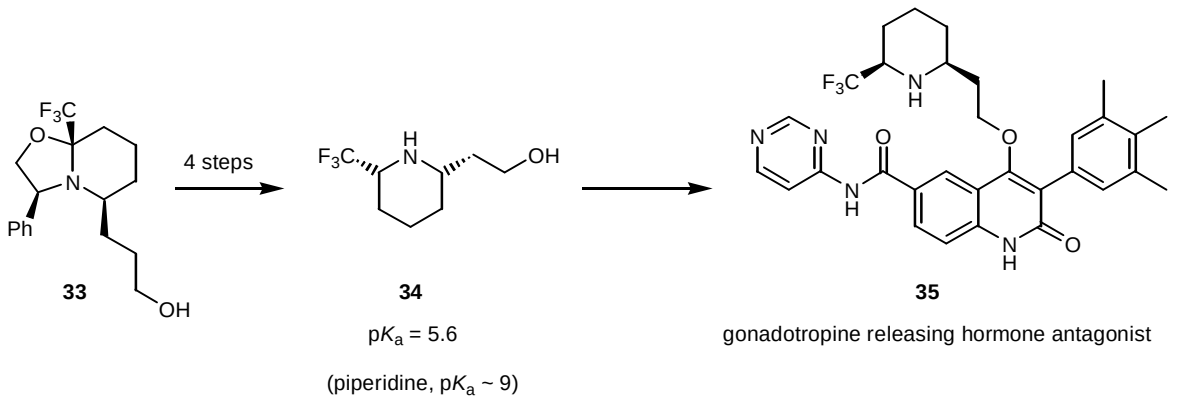
In 1999, Jinlong Jiang and co-workers, from the *Merck Research Laboratories*, described[16] a "chiral lactam" strategy for the asymmetric synthesis of α-trifluoromethyl piperidines (scheme 7), inspired from A.I. Meyers' work[29]. Thus, trifluoromethyl bicyclic chiral lactam **29** was obtained from condensation of phenylglycinol with the appropriate carboxylic acid. Conversion to triflate **30** followed by a Sonogashira coupling reaction afforded the propargyl alcohol **31**. At this stage, and in order to prevent any racemization, **31** was twice hydrogenated, using as catalysts, at first PtO_2 to selectively reduce the acetylenic and olefinic bonds, then $Pd(OH)_2$ for the cleavage of the oxazoline ring.



Scheme 7.

Accordingly, enantiopure piperidine (+)-**32** was efficiently prepared (35% over 5 steps). The authors could experimentally verify the necessity of the sequential hydrogenation process, as direct employment of Pearlman's catalyst afforded partially racemized **32**.

The same research group converted[30] oxazolidine **33** in Tfm-piperidine **34** using a conventional four steps sequence, and this fluorinated scaffold was coupled with a functionalized quinolone to give the gonadotropine releasing hormone antagonist **35** (scheme 8).

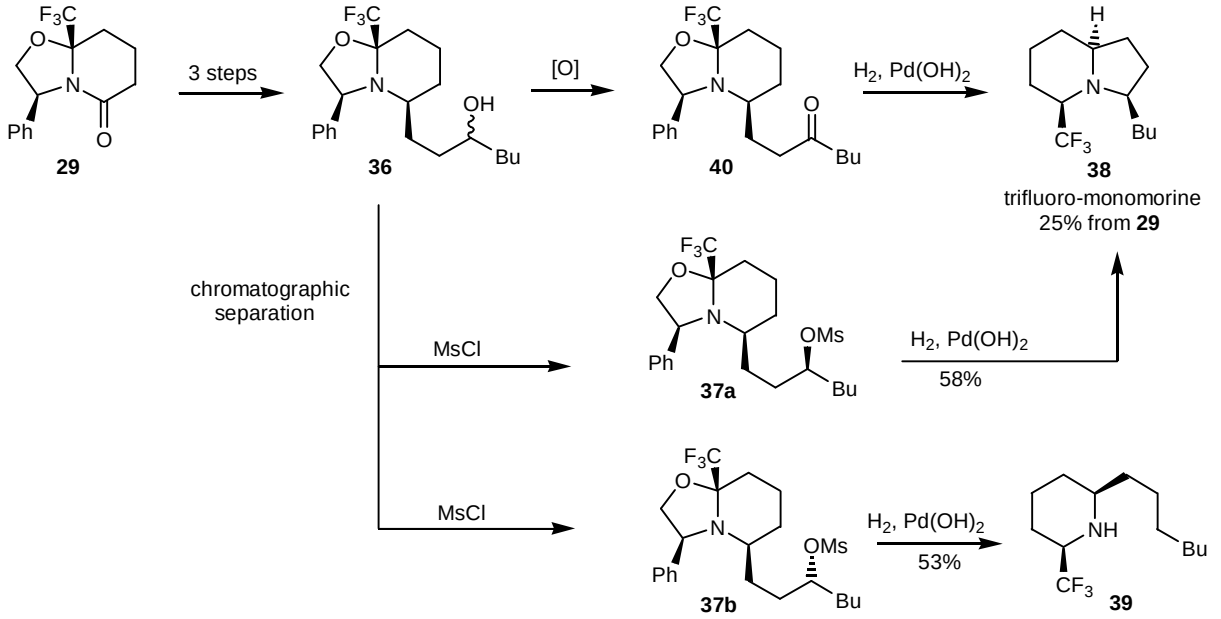


Scheme 8.

During this study, they could determine that piperidine **34** ($pK_a = 5.6$) was about 1000-fold less basic than a non-fluorinated one (piperidine: $pK_a \sim 9$). They also showed, by comparison of the pharmacokinetic parameters of **35** with those of parent fluorine-free

compound, that presence of the trifluoromethyl group could improve by 3-fold the oral bioavailability.

Jiang's methodology was later extended to the asymmetric synthesis of Tfm-indolizidine by G. Kim and N. Kim[31]. Applying the same synthetic scheme, they prepared epimeric alcohol **36** in three steps from Jiang's bicyclic lactam **29** (scheme 9).



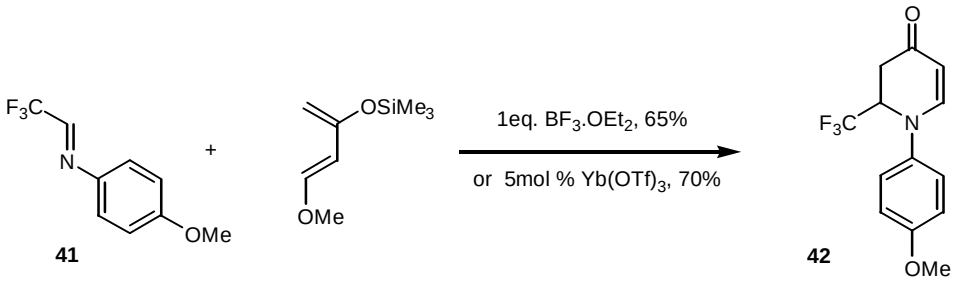
Scheme 9.

After a chromatographic separation followed by mesylation, substrates **37a,b** were isolated. Catalytic hydrogenation of mesylate **37a** led to trifluoro-monomorine **38**, through cleavage of the oxazolidine appendage then intramolecular nucleophilic substitution. Surprisingly, same conditions applied to **37b** failed to give any bicyclic compound, affording only the unexpected *cis*-2,6-disubstituted Tfm-piperidine **39**. Alternatively, the authors developped a more direct route: mixture **36** was oxidized in **40** under Dess-Martin conditions and subsequent hydrogenation furnished expected homochiral Tfm-monomorine **38**, through elimination of the phenylglycinol moiety and stereospecific reduction of the iminium ion intermediate.

It has to be noted that, as far as we know, this work constituted the first and unique synthesis of a Tfm-analogue of an indolizidine alkaloid.

I.4. Synthesis of Tfm-piperidines using an Aza Diels-Alder methodology

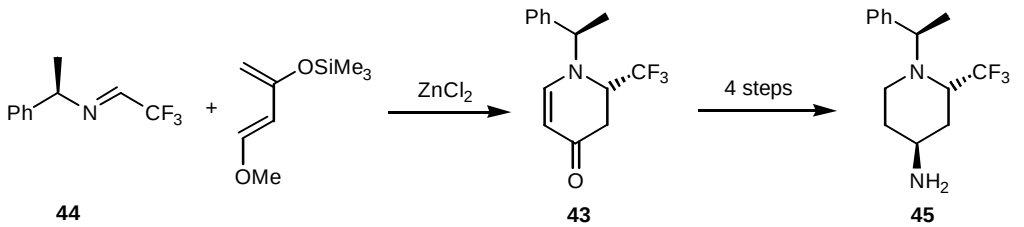
In 2000, Châtenay's group (D. Bonnet-Delpon, J.-P. Bégué, B. Crousse) described an Aza Diels-Alder route to CF_3-containing cyclic enaminones[32] (scheme 10).



Scheme 10.

They reported that *N*-heterocycloaddition between *E*-Tfm-aldimine **41** and Danishesky's diene, under ytterbium triflate catalysis, proceeded smoothly to yield the Tfm cyclic adduct **42**, which was isolated as a sole regioisomer. Meanwhile, this polyfunctionalized product of high synthetic potential has not been subjected to further chemical transformation.

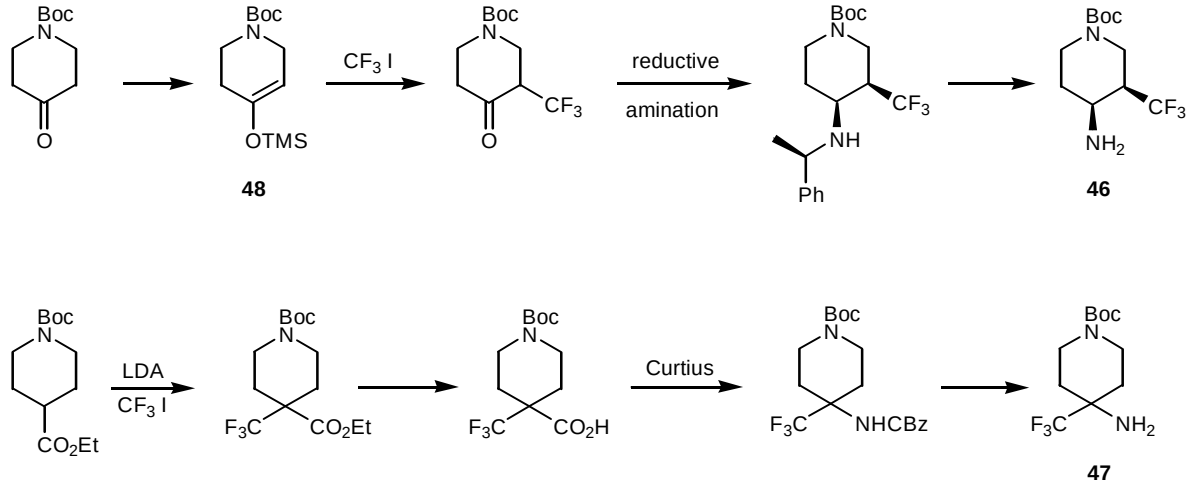
An application of the Aza Diels-Alder strategy for the preparation of enantiomerically pure Tfm-piperidines arose in 2003[33]. In this contribution from the *Glaxo Group* laboratories, concerning the design of new potent antibiotics, isomeric piperideinone **43** was synthetized from chiral phenylethylamine fluoral aldimine **44** as depicted in scheme 11. Following, four standard reduction/oxydation and reductive amination steps, yielded the original *trans*-4-amino-2-Tfm-piperidine **45**. Unfortunately, important details related neither to stereoselection degrees nor to the efficiency (% yield) of this very interesting sequence were not described in the referenced patent.



Scheme 11.

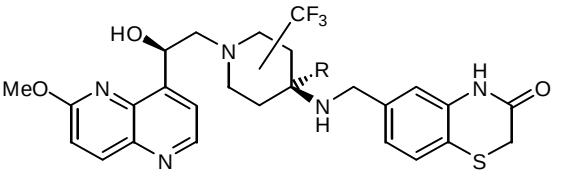
I.5. Synthesis of Tfm-piperidines by electrophilic trifluoromethylation

In the same time and in the same goal, the *Glaxo* team reported[33] pathways to 4-amino-3-Tfm- and 4-amino-4-Tfm-piperidines **46** and **47**, both involving an electrophilic trifluoromethylation as key step (scheme 12). Introduction of the CF_3 group in C-3 position of the heterocycle was achieved by trapping the intracyclic enol ether **48** with trifluoromethyl iodide, the supplementary amino function being placed later by stereoselective reductive amination. For the elaboration of the 4-Tfm-piperidine skeleton, an exocyclic enolate was trapped using the same reagent, before amination by the mean of a Curtius rearrangement.



Scheme 12.

The 4-amino-Tfm-piperidine frameworks **45-47** thus obtained (schemes 11 and 12) in *Glaxo*'s laboratories were further converted into antibiotics **49** (figure 6). Once again, we could not find some crucial information in the patent, concerning either experimental analytical details or biological activities.



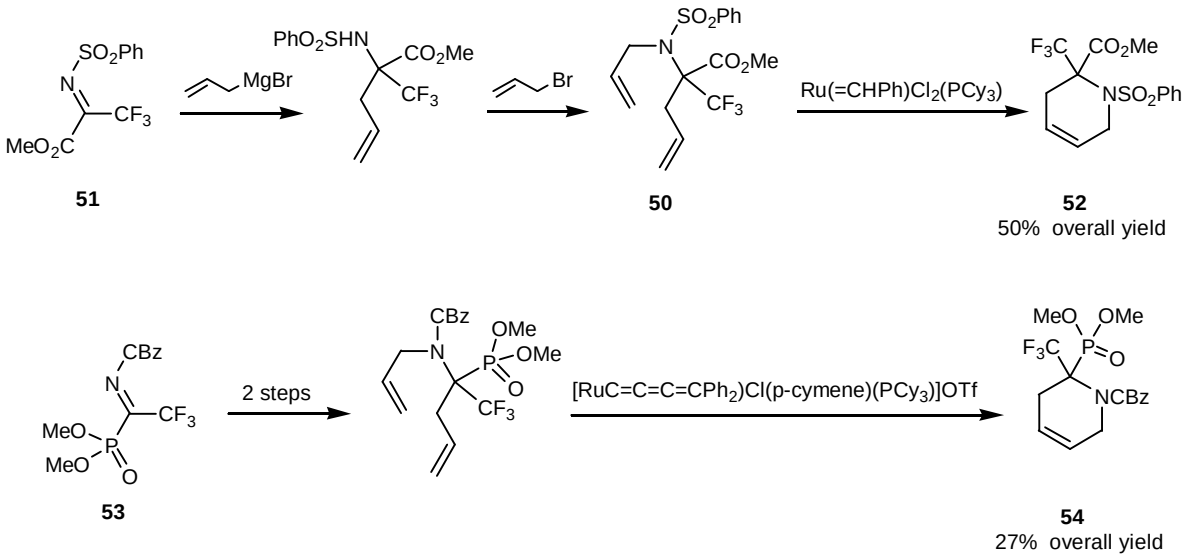
49
antibacterial agents

Figure 6.

It has to be noticed here that we did not find in the literature any example of Tfm-piperidine elaboration using a nucleophilic trifluoromethylation.

I.6. Synthesis of Tfm-piperidines through Ring-Closing Metathesis (RCM).

Ring-closing metathesis became a popular strategy for the construction of heterocyclic patterns[34]. As far as we know, P. Dixneuf, S. Osipov and co-workers were the first who applied a RCM strategy for the synthesis of CF_3-containing N-heterocycles[35]. The key di-olefinic synthon **50** was prepared in two steps from readily available N-protected trifluoropyruvate imine **51**, by addition of allyl magnesium bromide followed by N-alkylation of the resulting sulfonamide (scheme 13).

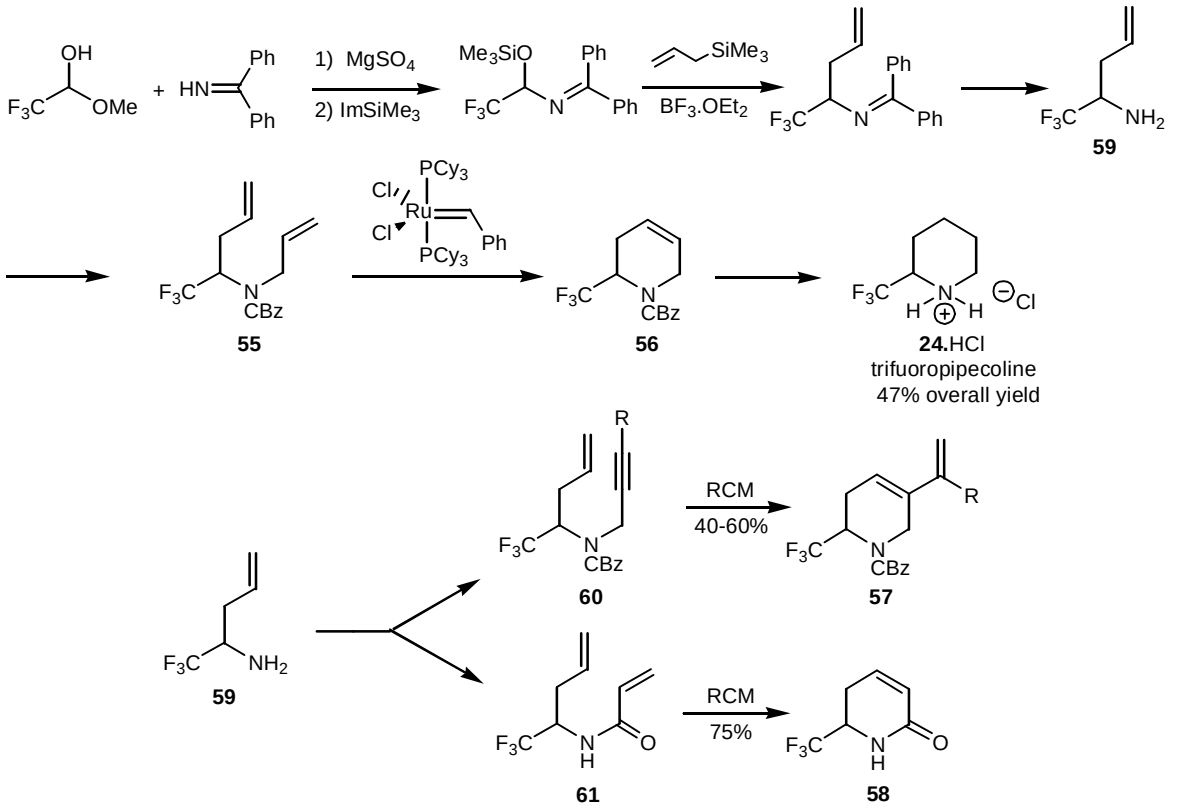


Scheme 13.

Ring-closing metathesis of **50** using a Grubbs' catalyst then proceeded almost quantitatively to afford the expected homoprolinate **52**. A similar synthetic three steps sequence from ketimine **53** furnished the methyl phosphonate analogue **54**, albeit less efficiently. By the way, they contributed to the first approach to α-Tfm-piperidine-based α-amino phosphonic acids.

In 2003, Billard's group from Lyon adopted also a RCM route to α-Tfm-piperidines[36]. For this purpose, they perfected a synthesis of allyl homoallyl benzyl carbamate **55,** in five

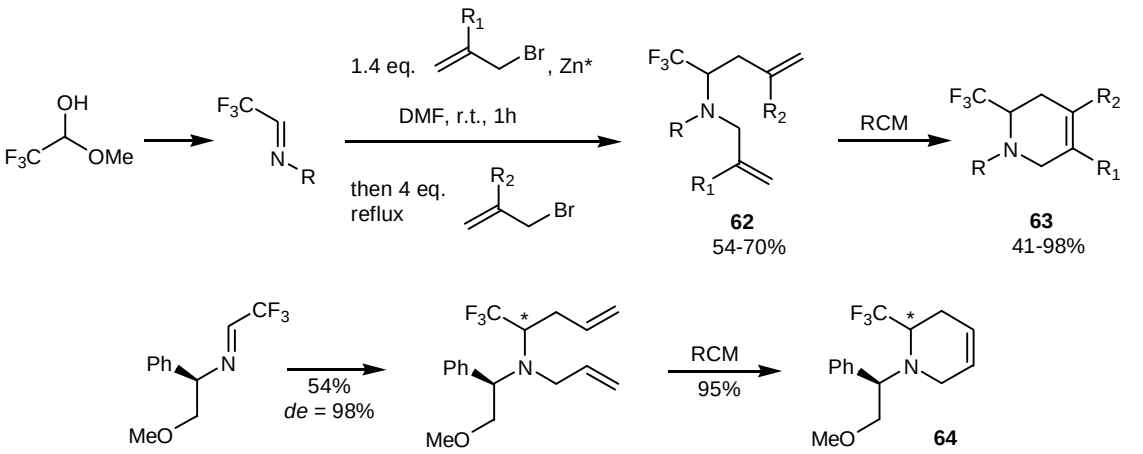
steps from a commercial fluoral hemiacetal (scheme 14). Grubbs' catalyst mediated RCM of **55** yielded the corresponding unsaturated six-membered ring heterocycle **56** which, under simple hydrogenation conditions, was converted into trifluoro analogue **24** of naturally occuring pipecoline.



Scheme 14.

As depicted in scheme 14, substituted Tfm-piperidines **57** and Tfm-δ-lactam **58** could be similarly prepared from the common precursor **59**, through respective enyne **60** and acrylamide **61**.

Two years later, a closely related version of this RCM strategy was reported[37]. The main progress concerned the access to the doubly unsaturated key intermediate **62,** for which a significantly shorter (2 steps vs 5 steps) pathway was proposed (scheme 15). Effectively, they showed that a 1h treatment of a fluoral aldimine with 1.4 equivalents of an allyl bromide at room temperature in DMF, in the presence of activated zinc, before addition of an excess of another allyl bromide then heating at reflux, directly gave an entry to the desired diethylenic compounds **62**.

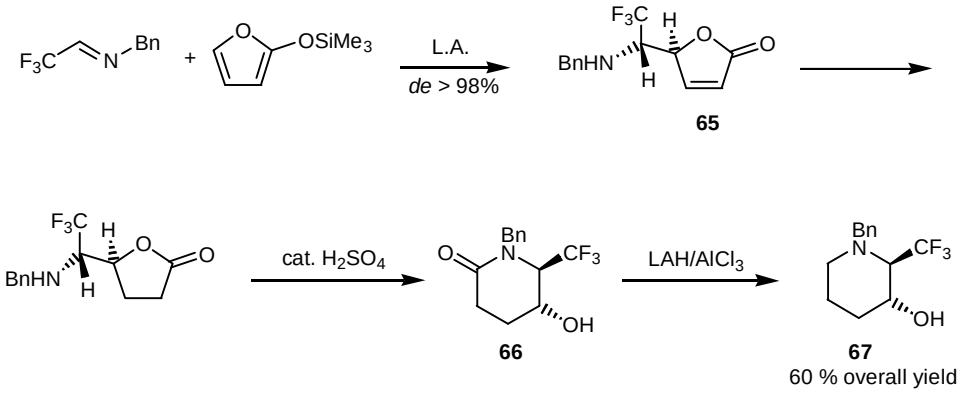


Scheme 15.

This one-pot procedure permitted the formation of various amines **62** which, upon ring-closure metathesis (Grubbs' catalyst), generated the expected substituted α-Tfm-4-piperideines **63**. An interesting transposition of this method to the field of asymmetric synthesis was achieved by the rapid and diastereospecific construction of product **64**, starting from a phenylglycinol-derived trifluoromethyl imine. However, the absolute configuration of the created stereogenic carbon was not assigned.

I.7. A vinylogous Mannich reaction way to α-Tfm-piperidines

Before focusing on RCM, the same research team published[38] a short route to a 2-Tfm-3-piperidinol involving as key step a Lewis acid-assisted vinylogous Mannich reaction, between a fluorinated N-benzyl imine and a trialkylsilyloxyfuran (scheme 16).

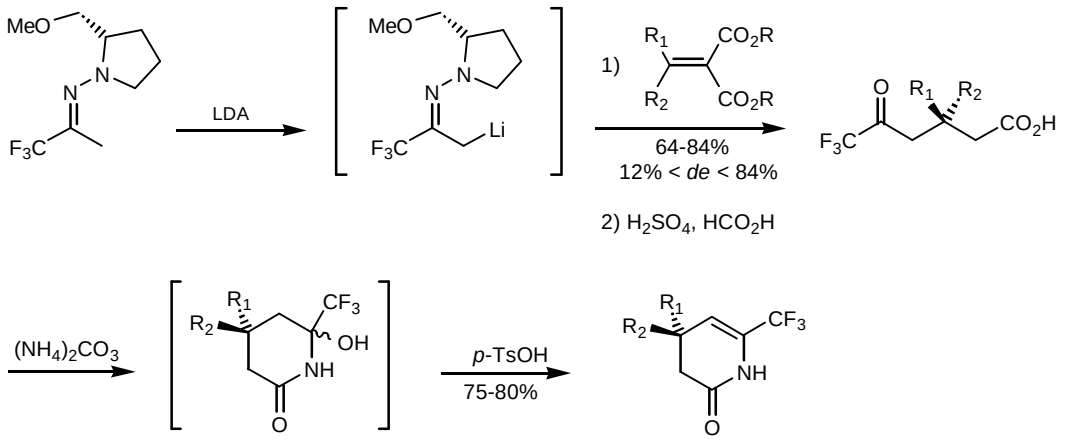


Scheme 16.

This first application of the vinylogous Mannich process with trifluoromethyl aldimines led to butenolide **65** in a highly diastereoselective manner. Saturation of **65** and subsequent acid-catalyzed *trans* lactamization produced the aza-heterocycle **66**. Deoxygenation of the latter with $LiAlH_4/AlCl_3$ then allowed the isolation of a unique diastereomer of the original piperidinol **67**.

I.8. Synthesis of Tfm-dihydropyridinones by intramolecular enamide formation.

In 2002, T. Okano's group reported[39] the synthesis of optically active cyclic Tfm-enamides using as building blocks chiral ω-trifluoroacetyl carboxylic acids, obtained by stereoselective conjugated addition of a lithiated SAMP-hydrazone onto unsaturated diesters, followed by chromatographic separation of the diastereomers, then by a one-pot hydrolysis/decarboxylation sequence (scheme 17).

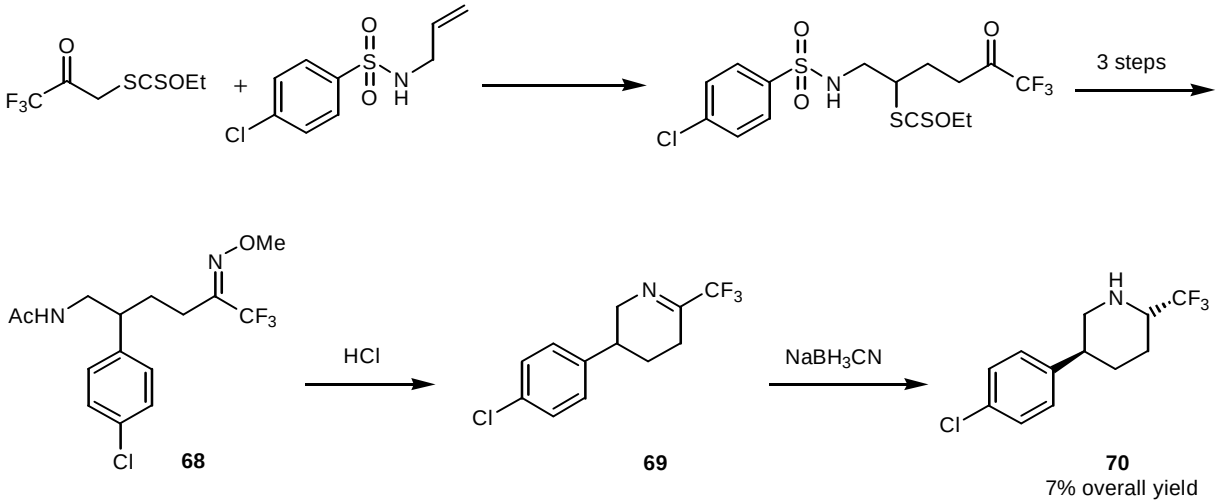


Scheme 17.

Treatment of the oxo-acids such prepared by ammonium carbonate led efficiently to the corresponding 6 membered ring cyclic enamides, bearing at C-4 an enantiopure stereogenic center, *via* presumably an O-exocyclic *N,O*-hemiaminal intermediate.

I.9. Synthesis of α-Tfm-piperidines by reductive amination

In their recent contribution, S. Z. Zard and co-workers[25] have developed a sequential reductive amination to elaborate the α-Tfm-piperidine framework (scheme 18). Profiting from the rich radical chemistry of xanthates, they synthetized in four steps substrate **68**. Hydrolysis of the oxime ether and acetamide functions of **68**, under strong acidic conditions, promoted the formation of piperideine **69** through intramolecular reaction of the amino-aldehyde intermediate. Standard cyanoborohydride reduction of this cyclic imine then gave the parent saturated Tfm-heterocycle **70**, *stereospecifically*.

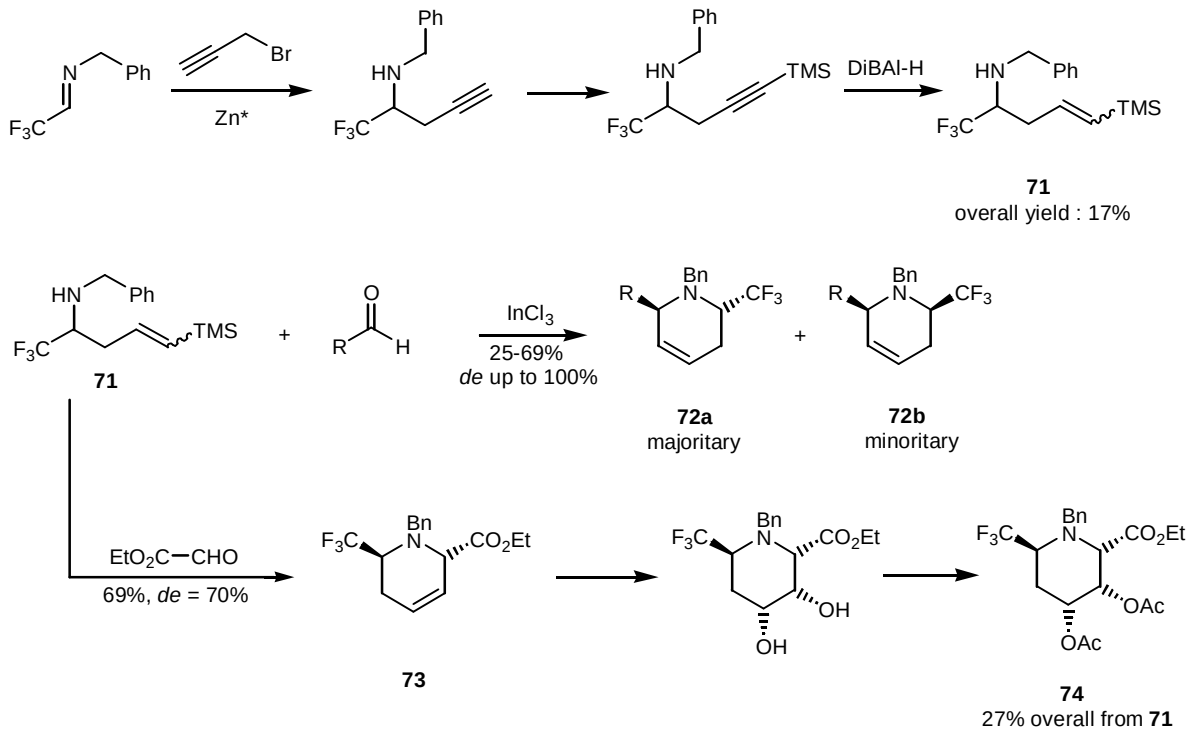


Scheme 18.

Although of moderate global efficiency (7% overall yield), this strategy provided one of the rare sources of aryl substituted Tfm-piperidines.

I.10. Synthesis of α-Tfm-piperidines using an aza-silyl-Prins methodology

In the very recent past, A. P. Dobbs *et al.*[40] described a diastereoselective access to *trans*-2,6-disubstituted-2-Tfm piperidines lying on an aza-silyl-Prins process (scheme 19). The synthesis of the required trifluoromethyl homoallyl secondary amine **71** was achieved in four steps from a fluoral imine. This amine **71** treated with various aldehydes in the presence of indium chloride, underwent the formation of the targeted 2,6-disubstituted heterocycles **72.**



Scheme 19.

This aza-silyl-Prins reaction proceeded generally with nice stereoselectivity (*de* up to 100%) and always in favor of the *trans* diastereomer. First application of this methodology resulted in the efficient elaboration of Tfm-pipecolic acid derivative **73**, from **71** and ethyl glyoxylate. The authors then caught the opportune presence of the olefinic bond to introduce two supplementary asymmetric centers. This was achieved by the mean of a *cis*-dihydroxylation. Highly functionalized Tfm-piperidine thus obtained revealed readily degradable but could be stabilized under its triester form **74**. This last compound (racemic) is the only example of a Tfm piperidine bearing four stereogenic carbons.

Conclusion

If the first-ever efforts dedicated to the synthesis of trifluoromethyl substituted piperidines were carried out fourty six years ago, we can consider that this research area remains an emerging one since the *quasi* entirety of the developments was accomplished during the last decade.

Even if not numerous, the progresses already achieved (among which an important part is issued from the French academical research) now permit to envisage an access to a relatively wide structural diversity.

Nevertheless, many aspects of the chemistry of these attractive targets need still to be explored. This applies noteworthy for their enantioselective preparation, since a very few examples of enantiopure ones are known.

The present Ph.D Thesis was built in regard to these observations. First of all, we wished to perfect a valuable and general tool allowing the synthesis of a wide range of Tfm-piperidines. Our ultimate objective was to manage this tool, in order to open a new route to such but *enantiopure* compounds.

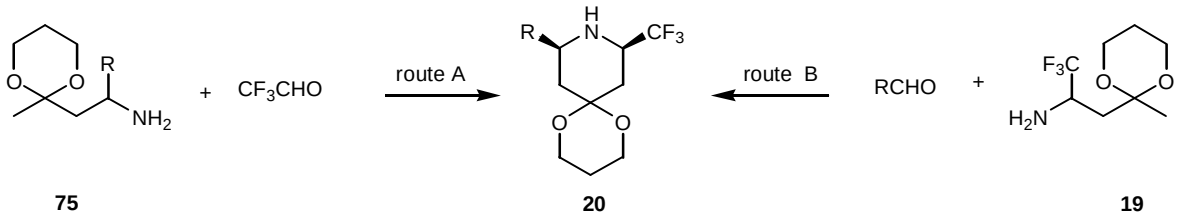
CHAPTER 2

Diastereoselective synthesis of a-trifluoromethyl piperidines

II. Introduction

As it has been presented before (see page 8), we planned to synthetize 2-trifluoromethylpiperidines **20** using for the cycle formation an intramolecular Mannich reaction.

We reasoned that this strategy seemed particularly suitable for the elaboration of such a framework, offering a double opportunity for the selective incorporation of the trifluoromethyl group (scheme 20).



75 **20** **19**

Scheme 20.

Accordingly, piperidines **20** should be obtained from fluoral or from a synthetic equivalent as the aldehydic Mannich partner. This constitutes the route A. This approach may appear quite restricted since it implies the systematic preparation of amines **75**, which, depending on the nature of the R substituent, may be not so trivial.

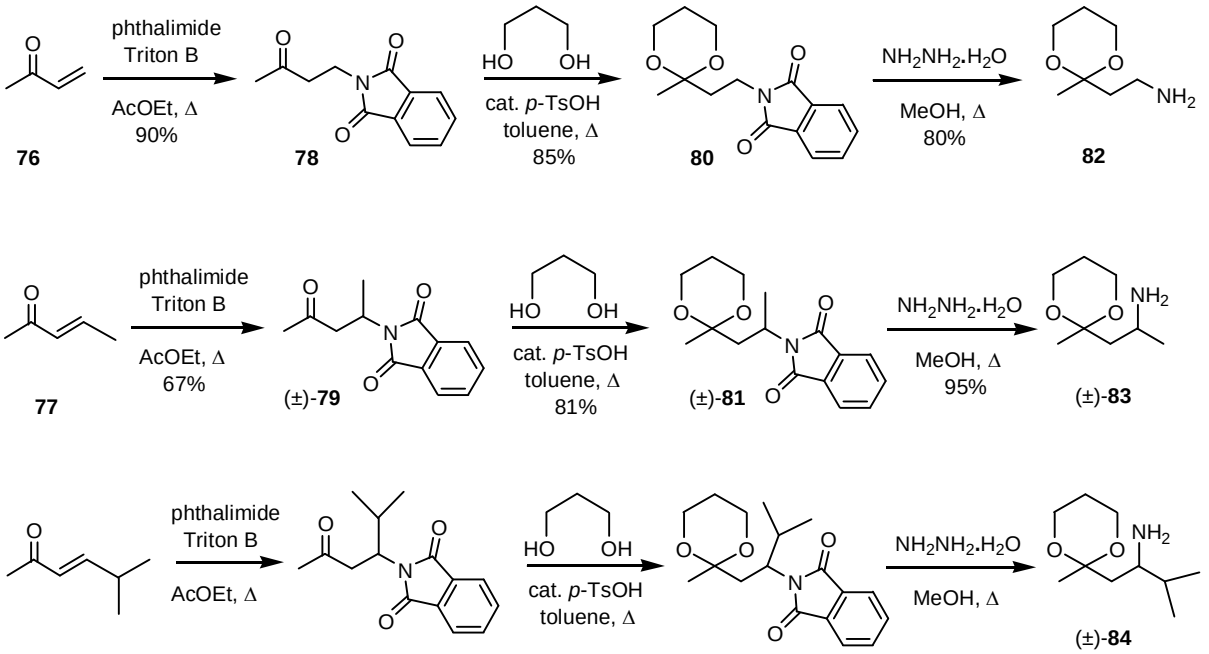
More generally, and this is the route B, the employment of a pre-formed α-trifluoromethylamine **19**, if tolerating a wide range of aldehydes, should give a direct and broader access to a new family of α-trifluoromethylpiperidines. Both of these routes were examined. Results and applications are reported in the present chapter.

II.1. Synthesis of α Tfm-piperidines using a fluoral synthetic equivalent: route A

As some of amines **75** were well known in our laboratory and readily available, route A was studied at first.

II.1.1. Synthesis of required amines for route A

These products were prepared following a conventional three steps Gabriel-type sequence (scheme 21). Treatment of commercial α,β-unsaturated methyl ketones **76** and **77** with phthalimide in refluxing ethyl acetate and in presence of benzyltrimethylammonium hydroxide (Triton B®) led to the corresponding phthalimido-compounds **78** and **(±)-79**.



Scheme 21.

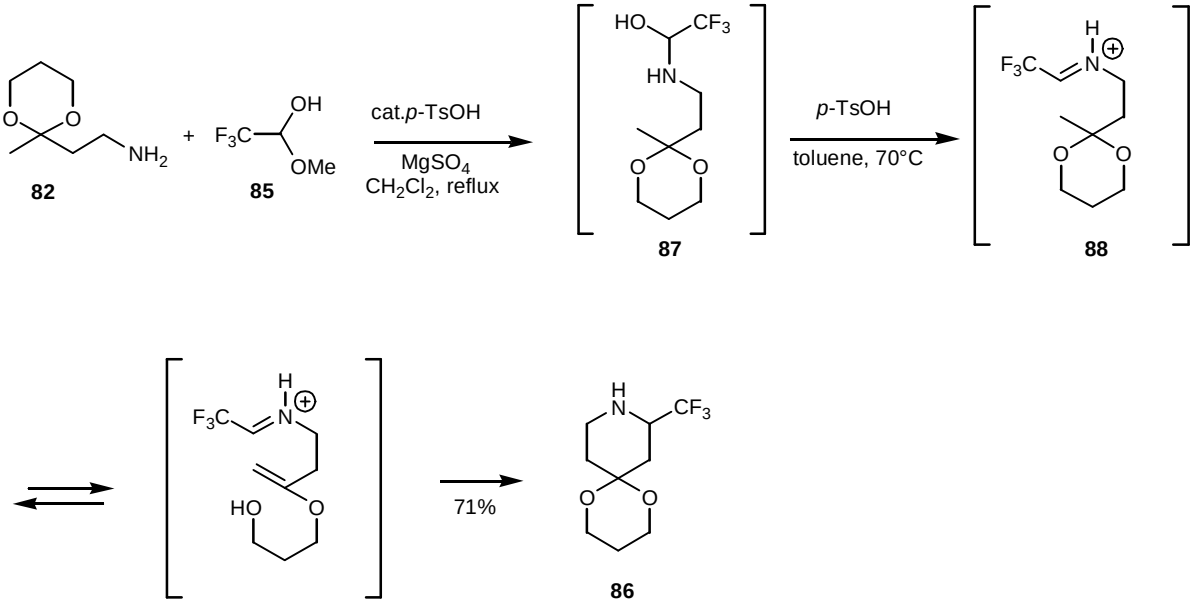
The keto function of these aza-Michael adducts was then converted into a ketal one, by reaction with 1,3-propanediol under Dean-Stark conditions. Hydrazinolysis of ketals **80** and **(±)-81** thus obtained, finally afforded the expected primary amines **82** and **(±)-83**. By this standard pathway, these synthons could be prepared efficiently (52-61% overall yield) and on a large scale. For amine **(±)-84**, we could benefit from a generous gift from our colleague Jean-Philippe Roblin, *Maître de Conférences*, who realized its synthesis for other applications but using an identical synthetic scheme.

II.1.2. Route A: Mannich cyclization using a fluoral hemiacetal

Synthesis of α-trifluoromethyl piperidines by Mannich cyclization starting from β-aminoketals **82**-**84** implied the use of trifluoroacetaldehyde. Instead of this gazeous and highly reactive substrate, its commercial methyl hemiacetal **85**, a stable liquid synthetic equivalent, was prefered.

First attempts of heterocycle formation were carried out with the structurally simplest amine **82**. Thus reaction of **82** with fluoral methyl hemiacetal **85** in refluxing dichloromethane, in the presence of a catalytic amount of *para*-toluenesulphonic acid (*p*-TsOH), directly followed by acidic treatment with 1.4 equivalents of anhydrous *p*-TsOH in toluene for one hour, gave very cleanly the expected piperidine **(±)-86** in 71% yield after simple work-up (scheme 22).

The mechanism of the process was presumably initiated by the formation of the *N*,*O*-hemiacetal[41] **87**, which upon degradation in the strong acidic medium furnished the iminium ion **88**, indispensable intermediate of the Mannich cyclization.

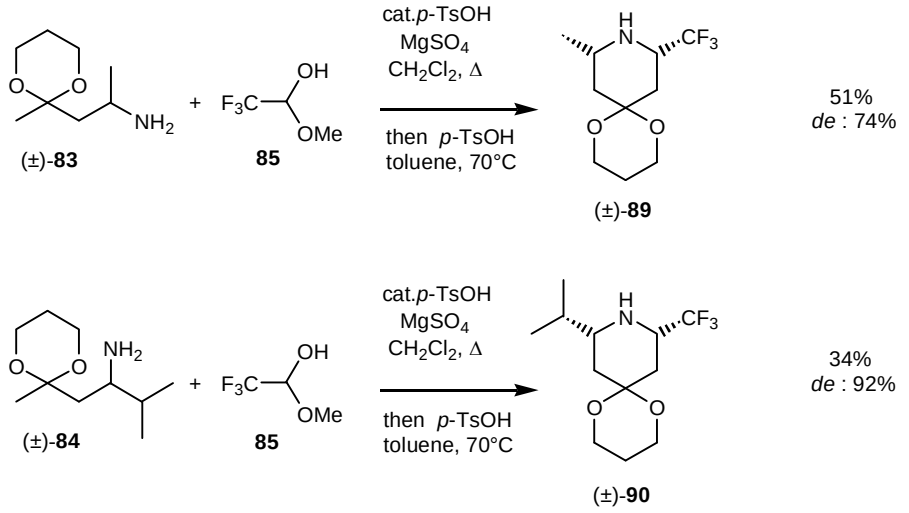


Scheme 22.

Crude piperidine **(±)-86** so obtained, which solidified upon standing in a freezer, revealed quite pure as evidenced by chromatographic (TLC, GC/MS) and NMR analysis.

Presenting a low polarity (R_f ~ 0.8 in ethyl acetate vs R_f < 0.2 for parent non fluorinated piperidines), this compound was very easily purified by column chromatography, but it has to be noted that this purification step entailed surprisingly a loss of material (isolated yield 49%). Anyway, the crude product was enough pure to be submitted to further chemical transformations.

Fluoral methylhemiacetal **85** was then treated under similar conditions with α-substituted amines **(±)-83** and **(±)-84** to give 2,6-disubstituted piperidines **(±)-89** and **(±)-90** in respectively 51% and 34% isolated yields (scheme 23).



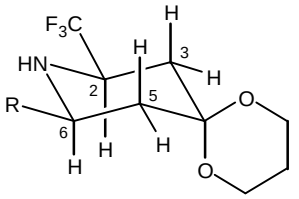
Scheme 23

(*de* determined from GC/MS analysis of the crude reaction mixtures, yields refer to the pure isolated diastereomers).

In order to avoid any over-evaluation, the diastereoselection degrees (*de*) were determined on the crude reaction mixtures, by gas chromatography coupled with a mass detector. In the case of **(±)-89**, and even if lower than results previously observed in a *conventional* series[18], an interesting 74% *de* was reached. We could not find a rational explanation for the discrepancy observed between the two series (non fluorinated: *de* > 95%). Bearing a more bulky alkyl group in the C-6 position, piperidine **(±)-90** was formed with an excellent diastereoselectivity (92% *de*), albeit less efficiently (34% yield).

Next was the essential verification of the relative stereochemistry of products **(±)-89** and **(±)-90**. It has to be remembered here that a *cis*-2,6-disubstitution of the aza ring was

expected (see pages 7 and 8). This *cis*-relative configuration was unambiguously confirmed from the ^{1}H-NMR spectroscopic data, notably from the signals corresponding to axial H-3 and axial H-5 (figure 7).



axial H-3 : t, J = 12 Hz
axial H-5 : t, J = 12 Hz

Figure 7.

Effectively, for such a disubstitution, a doublet of doublets (eventually a triplet) of large coupling constants was expected for each of these protons, both being in interaction with its equatorial congener (J~12Hz) and presenting a *trans*-diaxial (J~12Hz) relationship with its neighbour, H-2 and H-6 respectively. The fact that two triplets were clearly detected on the ^{1}H-NMR spectra (1H and J = 12Hz for each), indicated an inevitable axial position for H-2 and H-6. In consequence (figure 7), the *only* structural possibility is that in which the CF_3 and the R groups occupy the same semi-space compared to the medium plane of the aza-heterocycle.

With these results, we could demonstrate that Mannich cyclization of β-aminoketals constituted a new diastereoselective entry to α-Tfm-piperidines.

II.1.3. Applications of route A

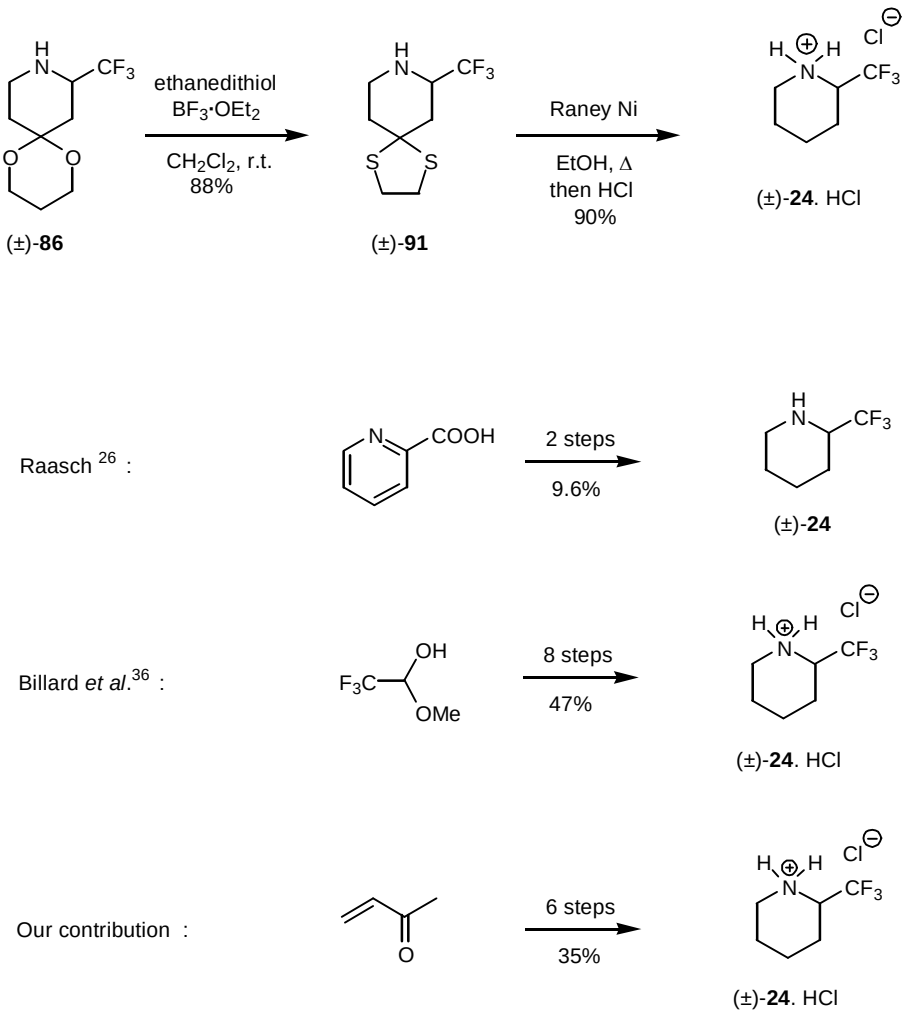
These promising preliminary results prompted us to consider direct applications of this methodology and we naturally focused our attention on piperidine-based natural products, but also on original 4-hydroxy and 4-amino derivatives.

II.1.3.1. Synthesis of trifluoropipecoline

As far as we know, the simplest monosubstituted piperidine alkaloid, pipecoline (figure 8), is also the unique for which the preparation of a trifluoro analogue has been reported (see chapter 1, pages 11 and 18).

Figure 8.

In our case, we thought that trifluoropipecoline **(±)-24** should be easily accessible from **(±)-86**, prepared by route A, and we therefore decided to embark upon its synthesis (scheme 24).



Scheme 24.

Piperidine **(±)-86** was treated with an excess of ethanedithiol in the presence of excess boron trifluoride etherate, in dichloromethane at room temperature, to give the trans

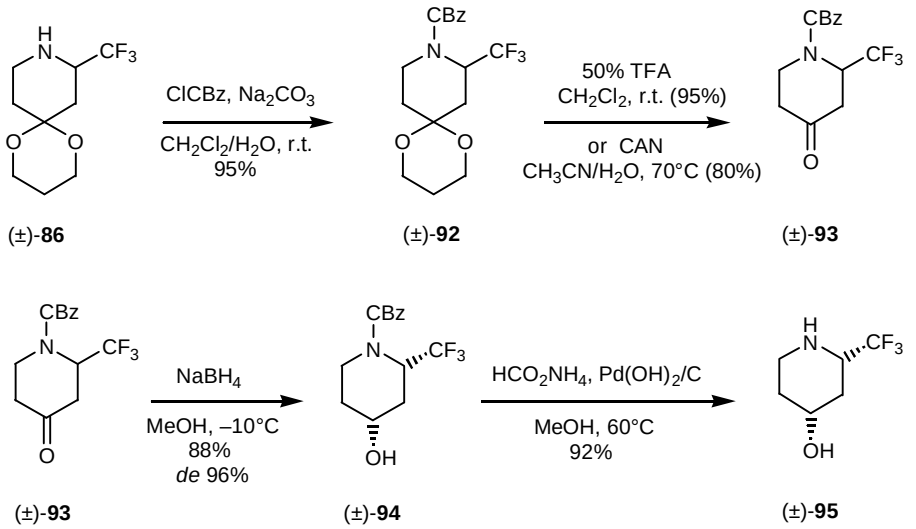
dithioketalization product **(±)-91** in 88% yield. Hydrogenolysis of the latter, conducted in refluxing ethanol using an excess of W2 Raney nickel[42] as catalyst, furnished the volatile trifluoropipecoline **(±)-24** which was isolated (90% yield) as its hydrochloride salt. Our synthetic sample exhibited physical and spectroscopic characteristics consistent with those already reported by Billard *et al.*[36]

By the way, synthesis of racemic trifluoropipecoline was achieved in six steps starting from methyl vinyl ketone, in a 35% overall yield. This first application validated our strategy.

II.1.3.2. Diastereoselective synthesis of *cis*-2-Tfm-4-piperidinol

As the intramolecular Mannich-type process affords heterocycles possessing masked keto function, it provides the opportunity to apply further selective transformations of these compounds. We then decided to regenerate the carbonyl group in order to examine its "stereoreactivity" under some reductive conditions.

Many attempts for direct keto-deprotection of free amine **(±)-86**, under standard acidic conditions, failed to give satisfactory results (no reaction was usually observed). For this reason, this compound was at first transformed into the parent benzyl carbamate **(±)-92** (scheme 25). Regeneration of the carbonyl group of **(±)-92** were then quantitatively achieved after a three days exposure period to 50% aqueous trifluoroacetic acid in dichloromethane at room temperature. We also noticed that the same transformation could be accomplished within a few minutes (80% yield) with ceric ammonium nitrate[43] at 70°C in water/acetonitrile.

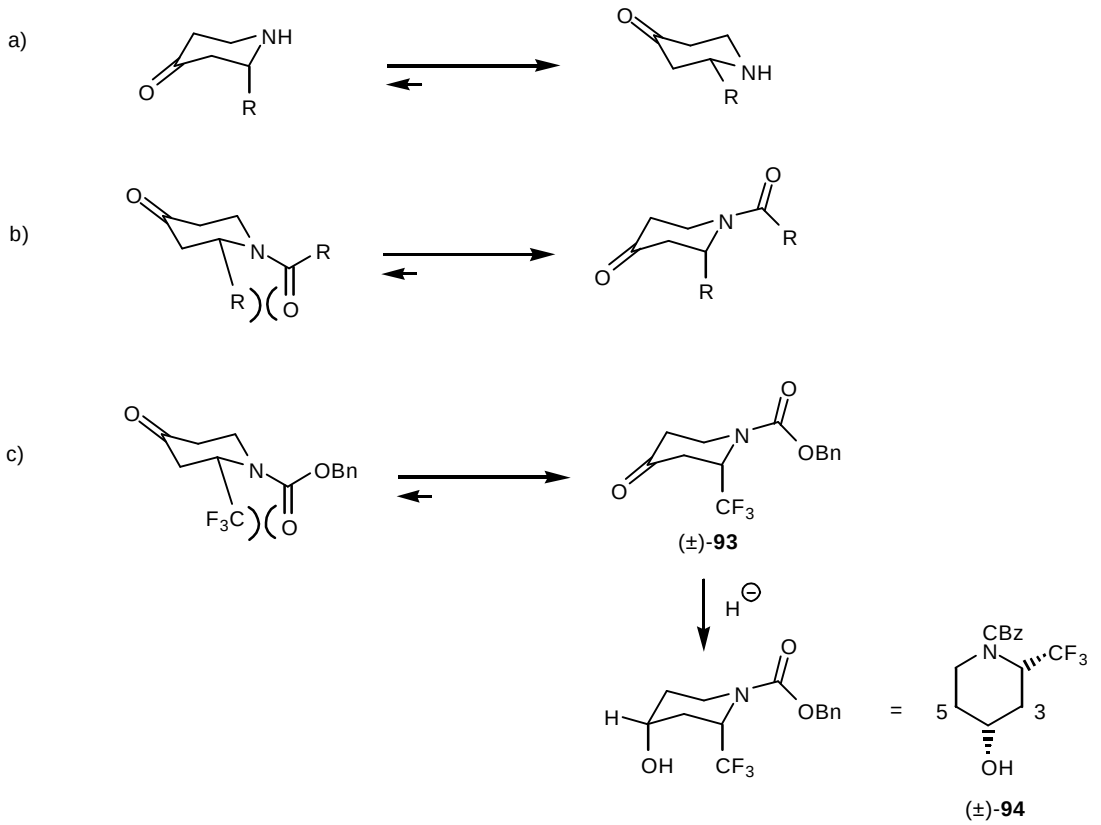


(±)-**86** (±)-**92** (±)-**93**

(±)-**93** (±)-**94** (±)-**95**

Scheme 25.

To anticipate the stereochemical behavior of the *N*-protected-4-piperidone **(±)-93** under reductive conditions, it has to be considered that its conformational equilibrium, unlike that of a free cyclic amine, should be displaced in favor of a pseudo-axial position of the trifluoromethyl group in order to minimize pseudo A (1,3) strain[17,44-46](scheme 26).

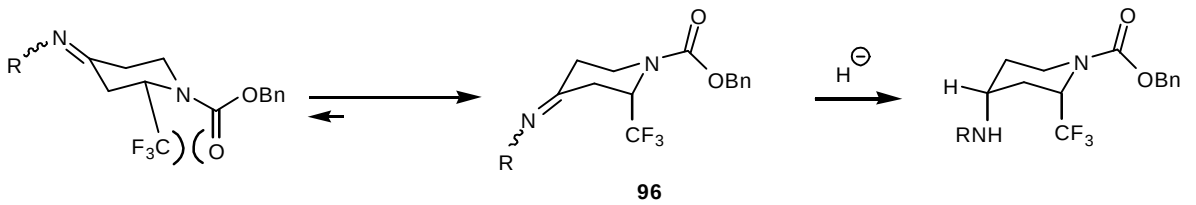


Scheme 26. Expected conformational equilibrium for: a) 2-substituted-4-piperidone free amines ; b) *N*-protected 2-substituted-4-piperidones ; c) carbamate **(±)-93.**

Accordingly, and due to a more important steric hindrance of the drawn "south face" (scheme 26), a predominantly equatorial hydride attack on piperidone **(±)-93** was foreseen. This could be verified by treatment of **(±)-93** with sodium borohydride in methanol at -10°C (scheme 25), which furnished the axial 4-piperidinol **(±)-94** almost exclusively (88% yield, *de* = 96% from GC/MS of the crude). The relative *cis* configuration of **(±)-94** was confirmed undoubtedly after catalytic hydrogenolysis into **(±)-95** (92% yield) : ^{1}H-NMR spectroscopic data clearly indicated a 2,4-diequatorial disubstitution pattern in a chair conformation. (H-5 axial: qd, J = 12 and 3 Hz, H-3 axial: q, J = 12 Hz).

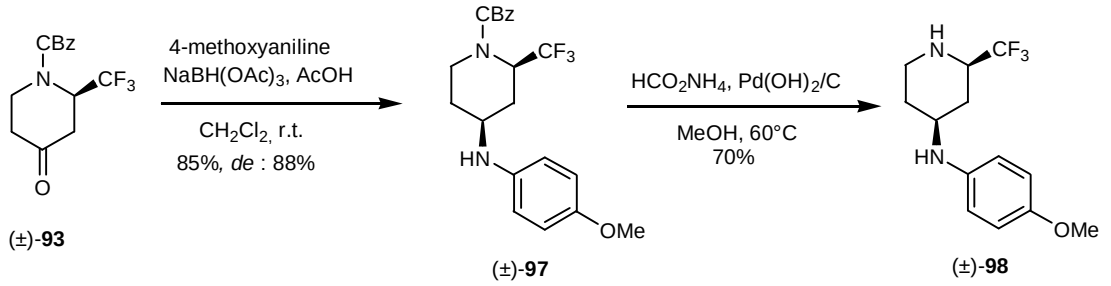
II.1.3.3. Diastereoselective synthesis of *cis*-2-Tfm-4-aminopiperidines

Next was the examination of the diastereoselective amino-reduction of *N*-protected piperidone **(±)-93**. For identical reasons with those evoked above, we reasonned that reaction of keto-function of **(±)-93** with a primary amine should lead to an imine, the conformational equilibrium of which should be displaced towards conformer **96** (scheme 27).



Scheme 27.

Thus, treatment of piperidone **(±)-93** with *p*-methoxyaniline at room temperature in dichloromethane, in the presence of sodium acetoxyborohydride and acetic acid[47] gave the desired *cis*-4-aza-2-trifluoromethyl piperidine **(±)-97** in 85% yield and with an interesting 94:6 diastereomeric ratio (scheme 28).

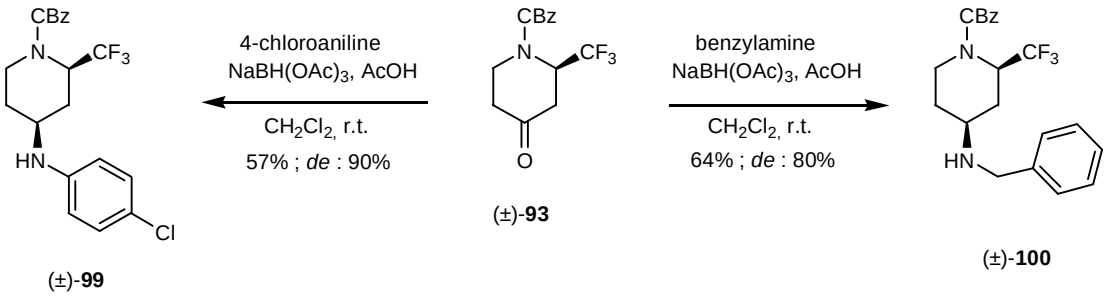


Scheme 28.

Such discrimination pleaded in favor to the anticipated imine conformer **(±)-96** as the probable intermediate.

The *cis* relationship of the heterocycle substituents in **(±)-97** was clearly established through ^{1}H-NMR analysis of diamine **(±)-98**, conveniently obtained by the selective removal of the piperidine *N*-protective group (catalytic hydrogenolysis, 70% yield).

Employment of other primary amines (i.e. 4-chloroaniline, benzylamine) for the reductive amination of piperidone (±)-**93** permitted the formation of 4-aminopiperidines (±)-**99** and (±)-**100** which were isolated with comparable stereoselectivities (scheme 29).



Scheme 29.

II.1.3.4. Synthesis of α-Tfm-piperidines by route A: conclusion

From the results described above, we assume that the intramolecular Mannich-type strategy involving a fluoral hemiacetal as fluorine source, constitutes a pertinent approach to α-trifluoromethylpiperidines. Indeed, this method allowed a rapid and diastereoselective access (de up to 92%) to such heterocycles, substituted by an alkyl group in the α'-position, and its validation was achieved through the efficient synthesis of a known trifluorinated analogue of the alkaloid pipecoline.

In the process, we were able to demonstrate that readily available piperidone (±)-**93** represented a valuable entry to new functionalized α'-trifluoromethylated piperidine scaffolds, compounds of undeniable interest for pharmaceutical research[17]. It is noteworthy that the generalisable stereoselective reductive amination of (±)-**93** should open a way to a broad library of original 2-trifluoromethyl-4-aza-piperidines.

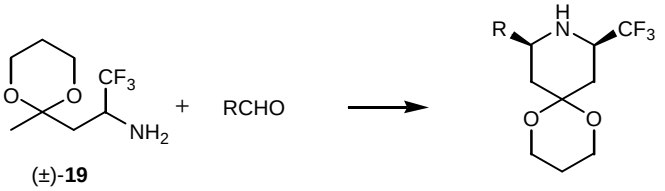
However, some limitations of route A must be pointed out here. It effectively does not permit the facile introduction of a wide diversity of substituents at C-6 position, since this objective requires the systematic synthesis of β-aminoketal key synthons. Its direct extension to the field of enantioselective synthesis seems also quite restricted. Although the basically needed enantio-enriched β-aminoketals are accessible, **48** their actual multi-step preparation will inevitably affect the attractivity of the global synthetic scheme.

Because route B implies, "on the paper", a sole fluorinated synthon for a general access to cis-2,6-disubstituted Tfm-piperidines, this alternative strategy may give a much more convenient answer to these challenging questions.

At this stage of the work, all our attention was thus converged on this promising pathway.

II.2. Synthesis of α-Tfm-piperidines using a pre-formed α-trifluoromethylated amine: route B.

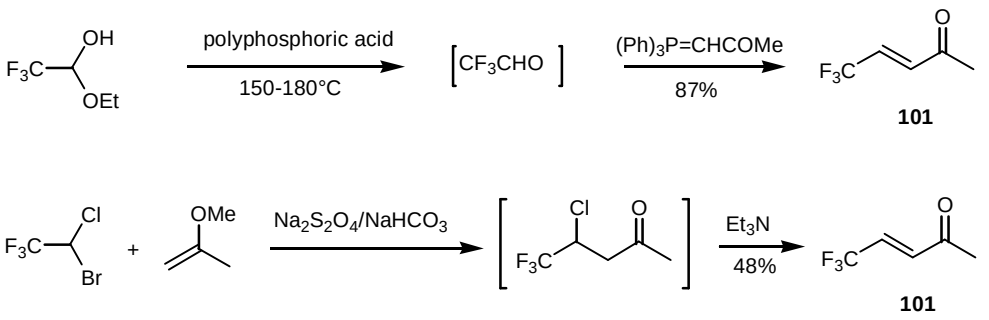
According to our synthetic analysis, reminded in scheme 30, perfection of route B demanded first of all the synthesis of the designed α-trifluoromethylamine (±)-**19**, if possible on a large scale.



Scheme 30.

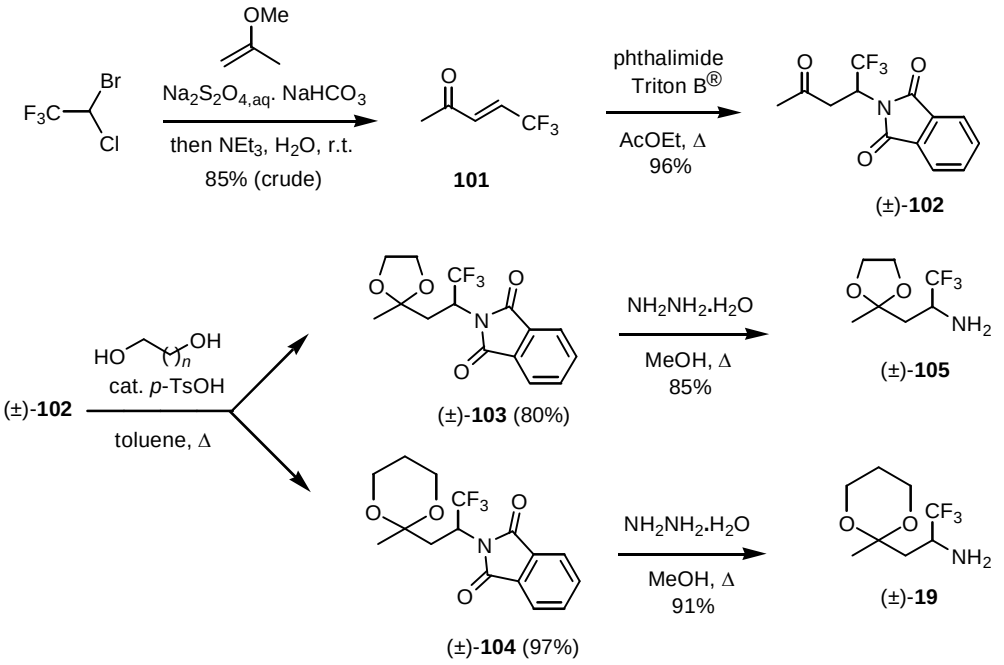
II.2.1. Synthesis of the α-Tfm-amine building block

Following our synthetic protocol for the preparation of suitable β-aminoketal, we focused on the preparation of trifluoropentenone **101** which was described as an N-hetero-Michael acceptor[49], and was considered as an intermediate for the preparation of amine (±)-**19**. Two synthesis of enone **101** have been described (scheme 31). The first one, reported by Wakselmann and Molines[50] and modified by Ogoshi et al.[49], lied on a Wittig olefination between (acetylmethylene)triphenyl phosphorane and gaseous trifluoroacetaldehyde, generated by decomposition of fluoral ethyl hemiacetal in hot (150-180°C) polyphosphoric acid



Scheme 31.

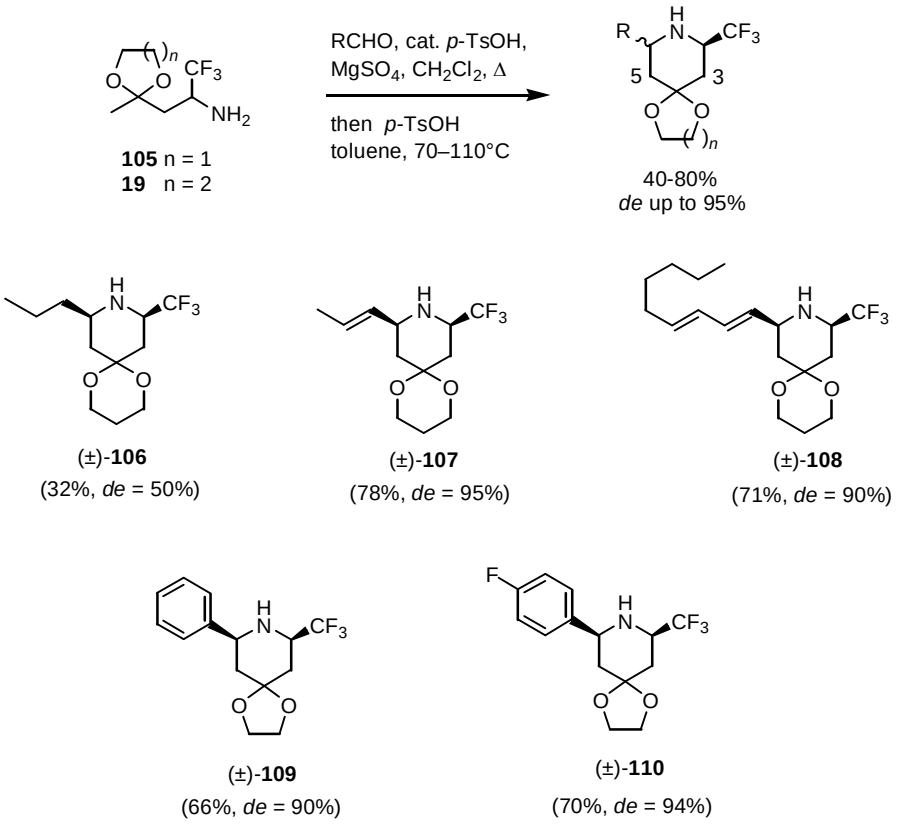
Later, Dmowski and co-workers[51] prepared the same enone in two steps: a sodium dithionite initiated reaction of halothane® with 2-methoxypropene followed by a dehydrochlorination. Although Dmowski's procedure proved to be less efficient (48% yield vs 87%) it was prefered for practical and safety reasons. Accordingly, volatile compound **101** was very conveniently obtained in large quantities from halothane® and we found that the crude (>85% yield, 51% after distillation) was pure enough to be used without purification. Conjugated addition of phthalimide on **101** in refluxing ethyl acetate in the presence of Triton B® afforded phthalimido derivative (±)-**102** (96% yield, scheme 32). This product was converted into the corresponding ketals (±)-**103** and (±)-**104** by treatment with ethylene glycol or propane-1,3-diol in toluene at reflux, in the presence of p-toluenesulphonic acid under Dean-Stark conditions. Protection of the keto function of (±)-**102** as 1,3-dioxane (±)-**103**, as well as the 1,3-dioxolane (±)-**104**, is justified by the fact that both kind of ketals (5 and 6 membered rings) are suitable for the intra-molecular Mannich process. Furthermore, dioxanes are much more easily cleaved than the parent dioxolanes[52], and this difference of stability may constitute a non negligible advantage for the further transformations. Finally, hydrazinolysis of the phthalimide moiety furnished the wished trifluoro-substituted 1,3-aminoketals (±)-**105** and (±)-**19** in respectively 65% and 85% overall yield from enone **101** (scheme 32).



Scheme 32.

II.2.2. Route B: Intramolecular Mannich reaction

Racemic fluorinated β-aminoketals thus prepared were next engaged in the crucial Mannich cyclization step. Fist attempt involved amine (±)-**19** and *n*-butanal (scheme 33). While the expected piperidine (±)-**106** could be isolated from a complex reaction mixture, it has to be noted that disappointing results in terms of efficiency (32% isolated yield) and selectivity (*de* = 50%) were obtained, due to partial butanal aldol condensation prior to the ring formation.



Scheme 33. (*de* determined from GC/MS analysis of the crude reaction mixture, yields refer to the pure isolated diastereomer).

Consequently, from that moment, only non enolizable aldehydes were considered. Results are summarized in scheme 33.

Reaction of crotonaldehyde with amine (±)-**19** in refluxing dichloromethane in the presence of magnesium sulphate led quantitatively (facile TLC monitoring) to the corresponding imine. This intermediate was treated directly, for 1 hour, with two equivalents of para-toluenesulphonic acid (previously dried under Dean-Stark conditions) at 80°C in toluene. Under these standard conditions, the desired cis-2,6-disubstituted-Tfm-piperidine (±)-**107** was obtained, this time efficiently (78% yield) and highly stereoselectively (*de* = 95%). Amines (±)-**19** or (±)-**105** submitted to the same treatment with *trans, trans*-deca-2,4-dienal, benzaldehyde or 4-fluorobenzaldehyde yielded (~70%) the desired heterocycles, respectively (±)-**108** to (±)-**110**. Consistently with results previously observed for a closely related series[18] the targeted cis 2,6-diastereomer was in each case formed with a high stereoselection degree (de ranging from 90% to 94%, GC/MS analysis of the crude products).

The relative configuration of **107-110** were unambiguously deduced from their ^{1}H NMR spectroscopic data and particularily from the signals corresponding to axial H-3 and axial H-5, which exhibited typical J values for a 2,6-diequatorial disubstitution arrangement in a chair conformation.

At this stage of the work the relevance of route B was demonstrated, direct applications could be envisaged.

Because naturally occurring products are commonly regarded as models for testing new methodologies and because, despite their biological potential[39] the chemistry of Tfm analogues of natural aliphatic nitrogen heterocycles remained a quasi unexplored research area, we decided to confront our strategy to the stereoselective elaboration of trifluorinated derivatives of polysubstituted piperidine alkaloids.

II.2.3. Applications: synthesis of trifluoro analogues of polysubstutued piperidine alkaloids

Compounds **111-113**, trifluoro analogues of the representative di- and trisubstituted piperidine alkaloids dihydropinidine[53], isosolenopsin[54] and alkaloid 241D[55], were selected as targets, as was **114**, an analogue of the less well known[56] natural *cis,cis*-2-methyl-6-propylpiperidin-4-ol (figure 9).

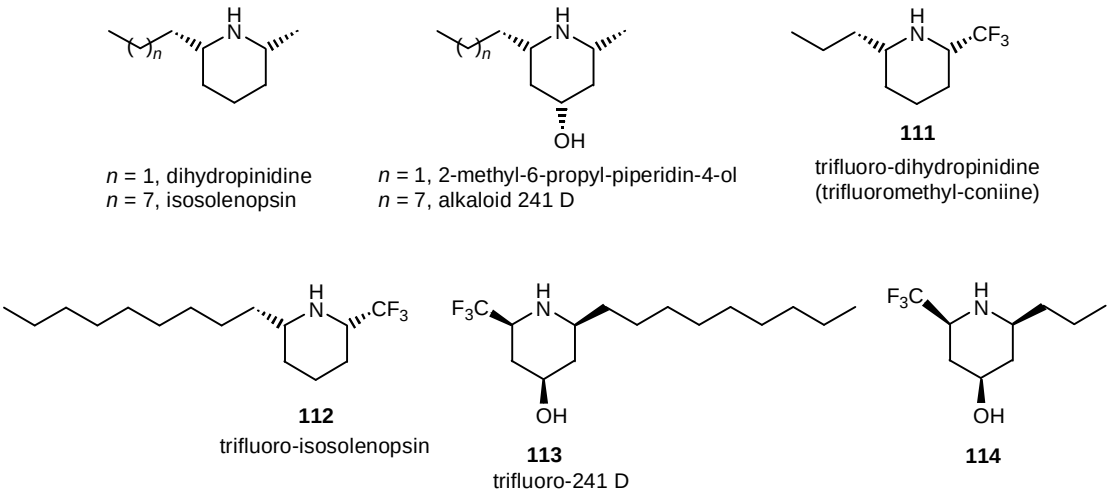
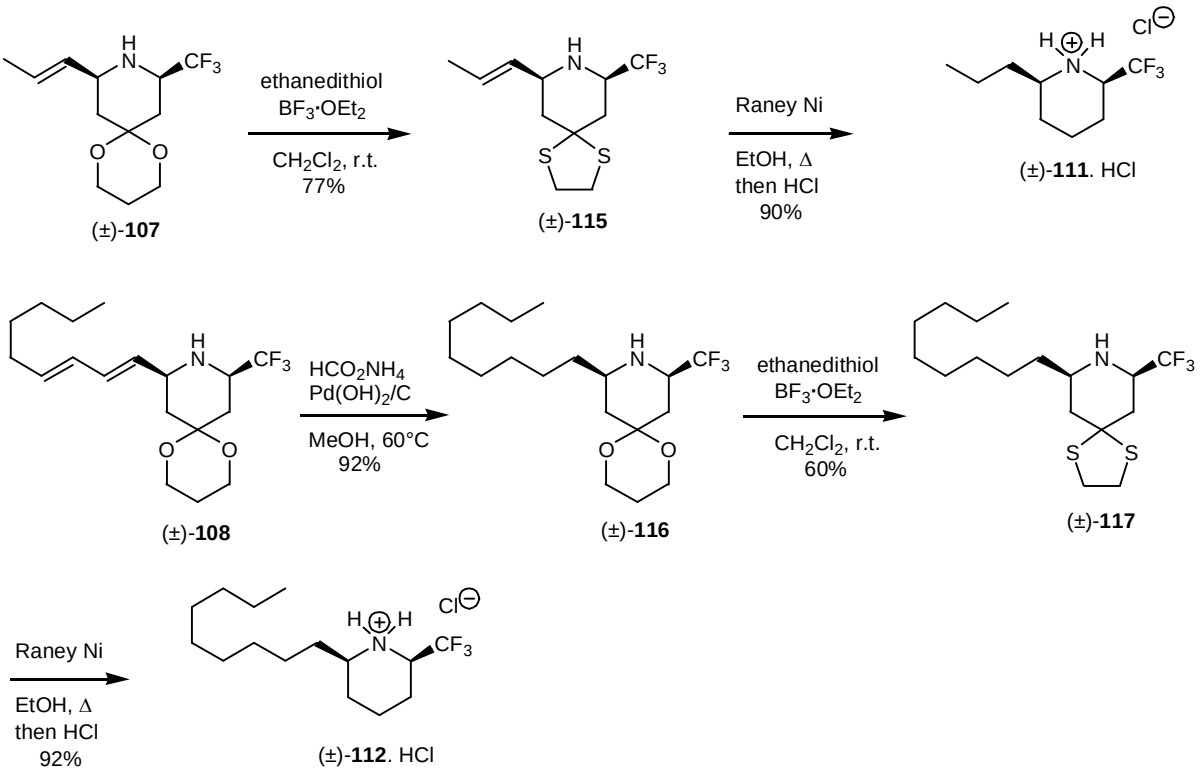


Figure 9.

The synthesis of trifluorodihydropinidine (±)-**111** (which may also be regarded as the α'-trifluoromethylated analogue of well known poisonous alkaloid coniine) was examined in priority. It was easily achieved in two steps from Tfm-piperidine (±)-**107**, by trans-dithioketalization into unsaturated dithiolane (±)-**115**, followed by a Raney nickel mediated hydrogenation/hydrogenolysis process (70% overall yield, scheme 34).



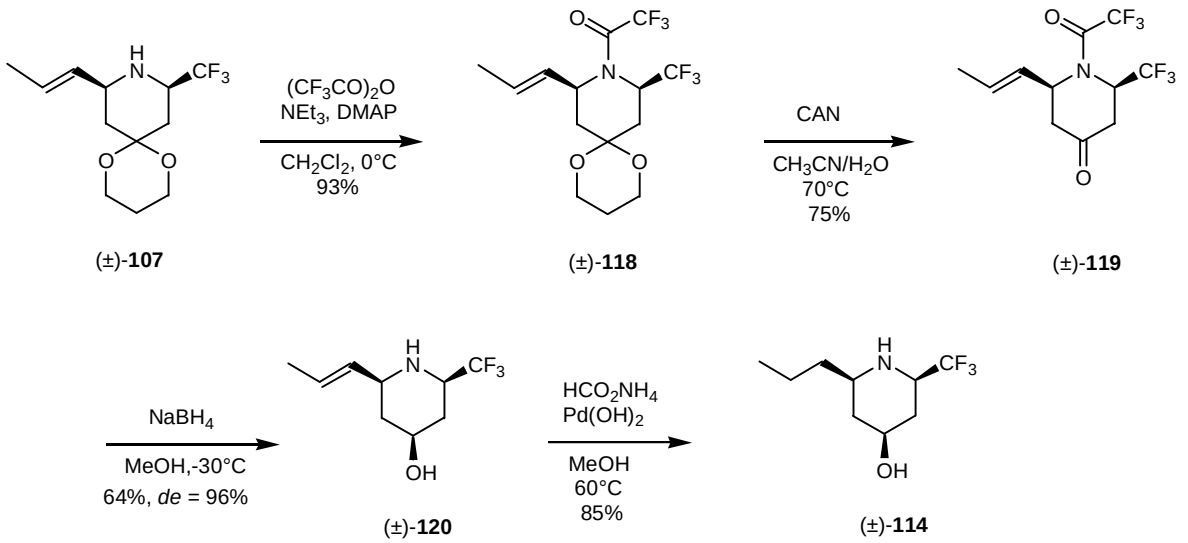
Scheme 34.

Volatile synthetic trifluorodihydropinidine (±)-**111** accordingly prepared was characterized and stored as its stable hydrochloride salt.

If an identical pathway could be a priori reasonably envisaged for the preparation of trifluoroisosolenopsin (±)-**112** from (±)-**108**, its synthesis started meanwhile by the saturation of the dienic side chain. Although not necessary, this reduction of crude (±)-**108** was performed here, if only in order to confirm the degree of diastereoselection (90% de) of its formation. Effectively, the commercial *trans,trans*-2,4-decadienal employed for the elaboration of (±)-**108** revealed (GC/MS) contamination with a few percent of geometrical isomers, perturbing therefore any accurate valuation of its diastereomeric excess. This problem could be simply solved after the facile hydrogenation of the nonadienyl moiety (confirmation of the 90% de). Then deoxygenation of piperidone (±)-**116** through W2 Raney nickel hydrogenolysis of the parent dithiolane (±)-**117** liberated the wished trifluoroisosolenopsin (±)-**112** hydrochloride salt (51% overall yield from piperidine (±)-**108**).

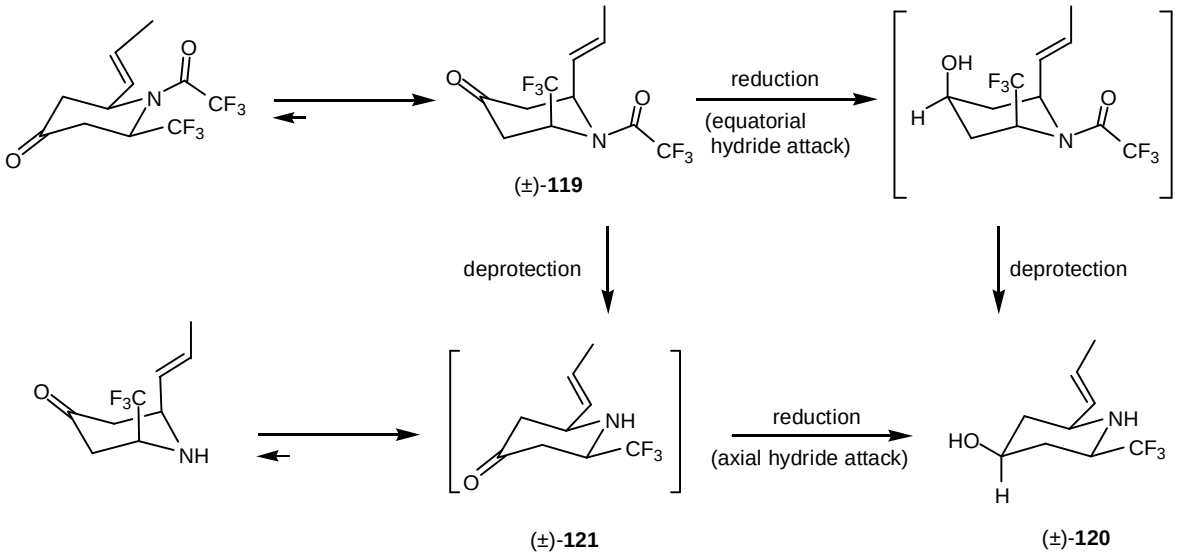
We next turned our attention to the preparation of the trifluoro-analogues of *cis,cis*-2,4,6-piperidine alkaloids : trifluoro-241D (±)-**113** and 4-piperidinol (±)-**114**. Once again (*vide supra*), direct attempts to regenerate the keto function of the free piperidine (±)-**107** under acidic conditions (HCl, p-TsOH, trifluoroacetic acid ; CAN) failed to give the corresponding piperidone in a reasonable time, necessiting the protection of the amino function. Surprisingly, it remained impossible to protect it either as a benzyl or as a tert-butyl carbamate by classical procedures. We thus decided to protect piperidine (±)-**107** as an amide, even though those functional groups are reputed resistant to hydrolysis. For this reason the trifluoroacetamide group[57], one of the more easily cleaved amides, was selected.

Treatment of compound (±)-**107** with trifluoroacetic anhydride at 0°C, in dichloromethane, in the presence of triethylamine and N,N-dimethylaminopyridine, afforded trifluoroacetamide (±)-**118** in 93% yield (scheme 35). Keto-deprotection of the latter was then cleanly and rapidly achieved by the mean of reaction with ceric ammonium nitrate[43] at 70°C in acetonitrile/water to give the 4-piperidone (±)-**119** in 75% yield. To reach the targeted fluorinated piperidinol (±)-**114**, the last synthetic problems to solve were here the stereoselective reduction of the keto function of (±)-**119** together with its *N*-deprotection.



Scheme 35. (de determined from GC/MS analysis of the crude reaction product, yields refer to the pure isolated epimers).

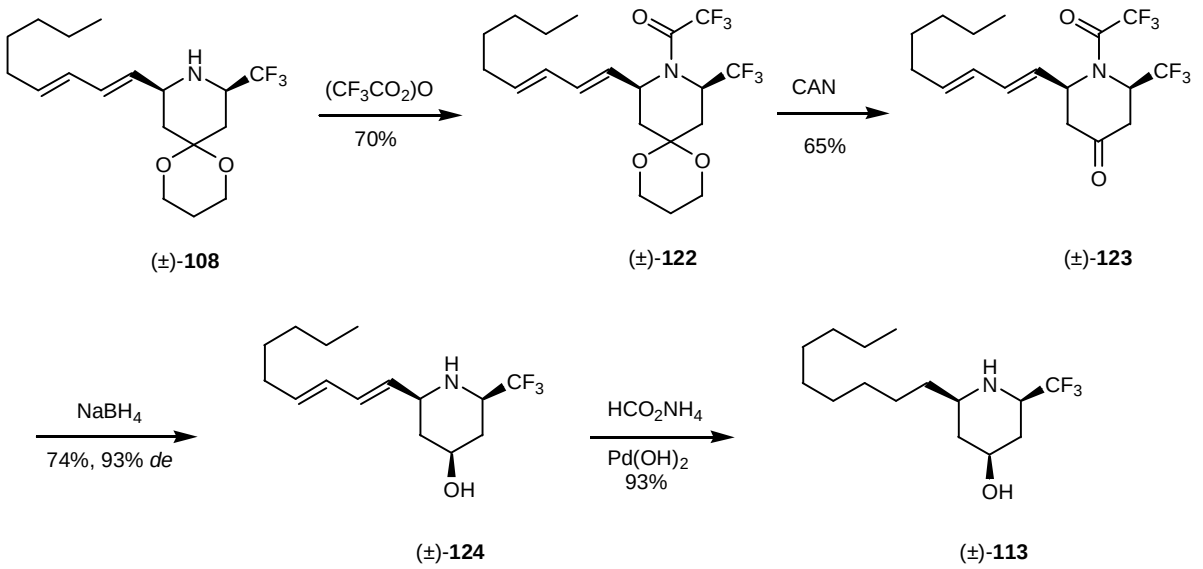
Interestingly, whilst sodium borohydride may be used for the ketone reduction, this reagent is also prone to degrade some trifluoroacetamides into amines[57], making these transformations simultaneously possible. However, as an all-cis relative stereochemistry was required for the target, arose inevitably the question of the influence of the scheduling of the reaction sequence (reduction/deprotection versus deprotection/reduction) on the reduction stereoselectivity. As depicted in scheme 36, and with arguments identical to those evoked above in this chapter, we thought that the conformational equilibrium of (±)-**119** should be strongly displaced in favor of a 2,6-diaxial disubstitution (scheme 36).



Scheme 36.

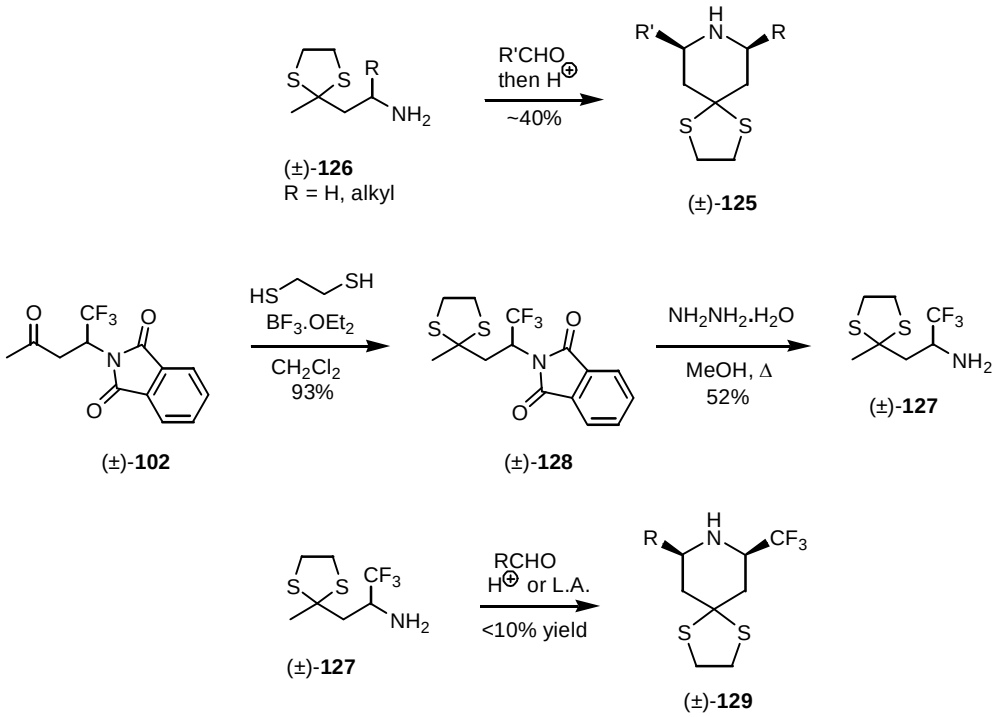
If deprotection was to occur at first, the diequatorial conformer (±)-**121**, liberated from pseudo A (1,3) strain, would be expected as the more stable intermediate. In this case, and as already observed with similar but non fluorinated systems[22], an axial hydride attack from sodium borohydride should predominate[58] mostly giving the *cis,cis*-piperidinol (±)-**120**. The inversion of the reactional sequence should entail an equatorial hydride attack on ketone (±)-**119**, due to significant steric hindrance of the presented north face (scheme 36), but still conducting after deprotection to the same all-cis reaction product (±)-**120**.

We thus reasoned that, whatever the pathway involved, there was no concern since they were stereoconvergent and should both selectively give the desired epimer. This reflection proved to be justified (scheme 35), since treatment of piperidone (±)-**119** with an excess of sodium borohydride at -30°C in methanol furnished the predicted *cis,cis*-2,4,6-trisubstituted piperidine (±)-**120** as an almost unique epimer (64% yield, de = 96%, GC/MS analysis of the crude product). Subsequent hydrogenation using ammonium formate at 60°C in methanol in the presence of Pearlman catalyst then gave efficiently (85%) piperidinol (±)-**114**. This first trifluoro analogue of a trisubstituted piperidine alkaloid was synthetized in a 38% overall yield, in four steps from intramolecular-Mannich adduct (±)-**107**. Exactly the same synthetic scheme, applied from piperidine **108**, then led in four steps (31% global yield) and in a highly stereoselective manner ($NaBH_4$ reduction step: *de* = 93%) to the 4-piperidinol (±)-**113**, a trifluorinated analogue of alkaloid **241 D** (scheme 37).



Sheme 37. (*de* determined from GC/MS analysis of the crude reaction product, yields refer to the pure isolated epimers).

Finally, in order to shorten the accessibility to deoxygenated Tfm-heterocycles, a “thio version” of the intramolecular Mannich process was imagined. Indeed, it has been discovered in the laboratory that dithiolanes (±)-**125** could be reached in one step from sulfur containing amines (±)-**126** (scheme 38, unpublished results).



Scheme 38.

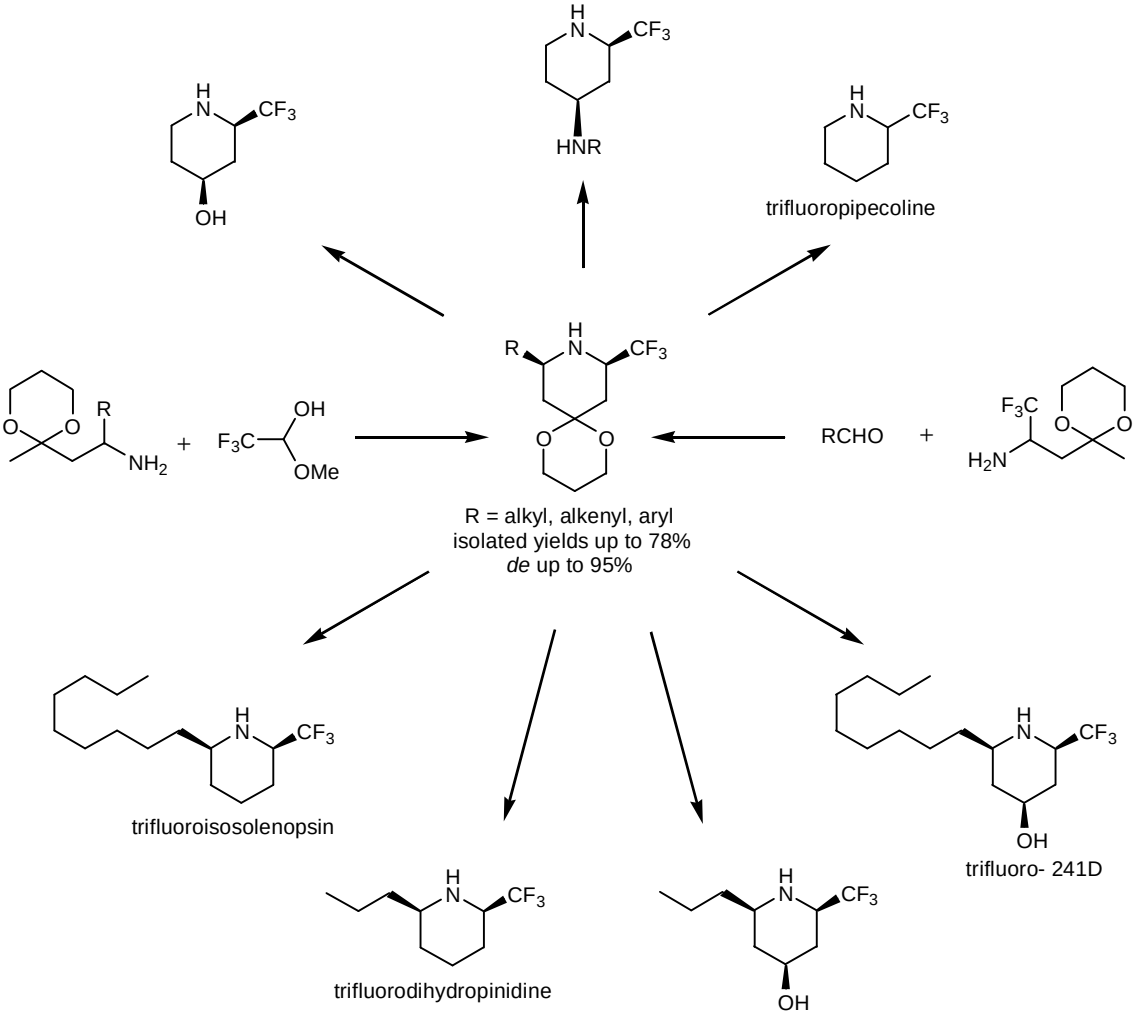
The feasability of such transformation was studied and for this purpose sulfurated α-Tfm amine (±)-**127** was prepared in two steps from phthalimido compound (±)-**102** via the dithiolane (±)-**128**. Unfortunately, all attempts of cyclization of (±)-**127**, with various aldehydes and using either a Brönsted or a Lewis acid, failed to give the expected bicyclic dithioketals (±)-**129** with acceptable yields.

II.2.4. Synthesis of α-Tfm-piperidines by route B: Conclusion

As it permitted to synthetize diastereoselectively numerous new α-Tfm piperidines from a unique building block, we think that route B represents a significant progress compared to route A. Validated by the total synthesis of four fluorinated di- or trisubstituted piperidine alkaloids, we hope that route B will be considered as an interesting approach to such molecular skeletons.

II.3 Conclusion

From all the results detailed in this chapter, summarized in scheme 39, we assume that we have demonstrated that intramolecular Mannich-type reactions of 1,3-aminoketals, and notably those involving α-(trifluoromethyl)amines, constitute a valuable tool for the stereoselective elaboration of α-Tfm piperidines, compounds of relevant biological interest.



Scheme 39. An intramolecular Mannich-type approach towards α-Tfm-piperidines.

Giving a rapid access to heterocycles possessing a protected keto function, prone to undergo multiple selective transformations, this method may be now regarded as an important potential source of a broad range of new functionalized trifluoromethyl-piperidine scaffolds.

Meanwhile, in our minds, its complete validation passed inevitably through its extension to the field of enantioselective synthesis.

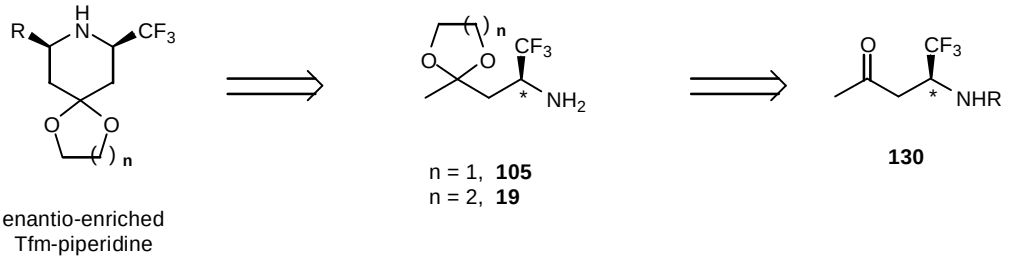
The solution of this crucial and challenging problem makes the object of the next chapter.

CHAPTER 3

Asymmetric synthesis of α-trifluoromethyl piperidines

III. Introduction

We have shown in the preceding chapter that intramolecular Mannich reaction of β-aminoketals could be successfully employed for the highly diastereoselective synthesis of new series of **(±)-**Tfm-piperidines, including trifluoro-analogues of alkaloids. However, in our minds, the complete validation of this strategy passed inevitably through its extension to the field of enantioselective synthesis. To be solved, this synthetic problem imposed us, in priority, to possess quantities of amine(s) **19** and/or **105** in an homochiral form, and which seemed easily accessible from the chiral parent aminoketone **130** (scheme 40).



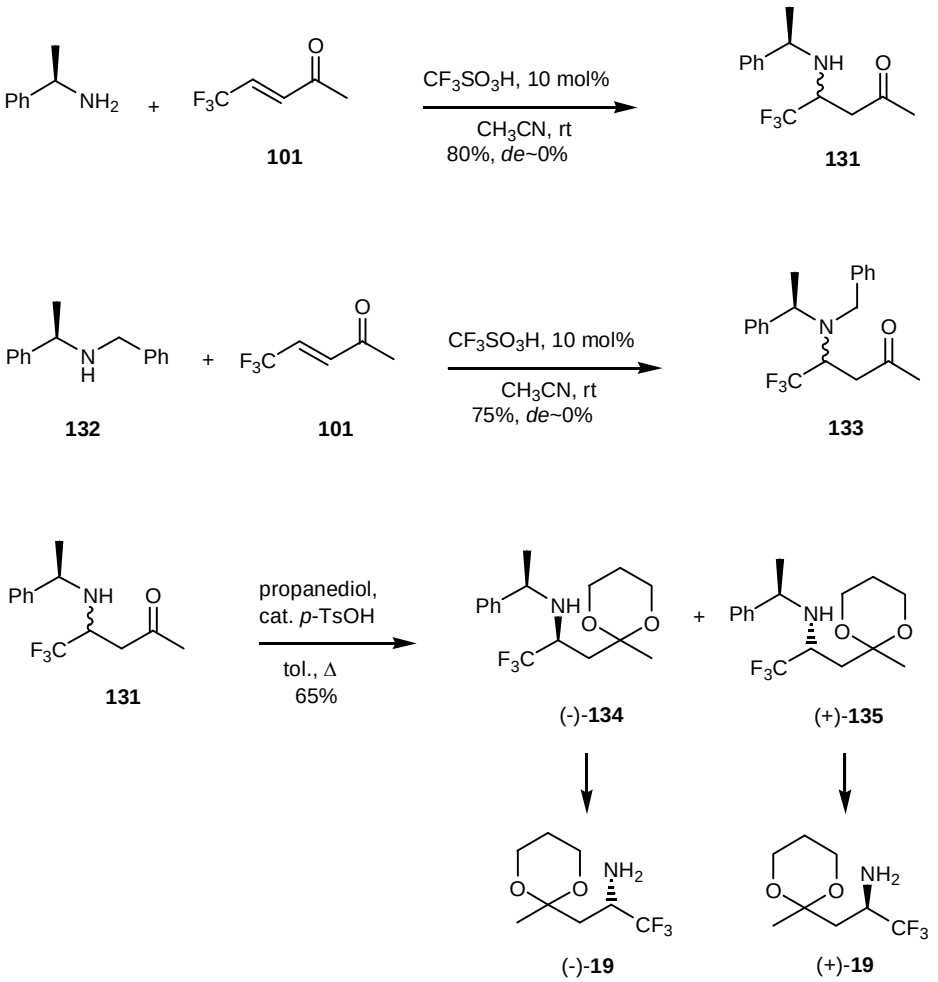
Scheme 40.

III. 1. Asymmetric synthesis of the Tfm-amine chiron

The asymmetric synthesis of amines **19** and **105** was at the beginning studied in regard to the fluorochemicals immediately available in the laboratory. For this reason, and having at our disposal trifluoropentenone **101**, a diastereoselective aza-Michael pathway involving a chiral amine was considered at first (scheme 41).

Thus, treatment of trifluoropentenone **101** with (*R*)-(+)-α-methylbenzylamine at room temperature in acetonitrile in the presence of 10 mol% trifluoromethane sulfonic acid[59], gave within a few minutes the expected aminoketone **131**, which was isolated (92%) as an inseparable mixture of diastereomers. The absence of stereoselectivity prompted us to examine the use of another nucleophile. Unfortunately the stereoselection degree could not be improved with Davies' amine **132** (**133** obtained in 75%, *de* ~ 0%) nor with its lithium amide,

whose employment at -78°C in tetrahydrofuran entailed the complete degradation of the Michael acceptor.



Scheme 41.

Diastereomeric mixture **131** was then treated by 1,3-propanediol in toluene, in the presence of toluene sulfonic acid under Dean-Stark conditions, to furnish the corresponding dioxanes (-)-**134** and (+)-**135**. We found here that 0.4-0.5 equivalent of *p*-TsOH was needed to reach an acceptable efficiency for this simple transformation (65% optimized isolated yield). Compounds of low polarity, aminoketals (-)-**134** and (+)-**135** could be quite easily separated by silica gel column chromatography (respectively 34% and 31% isolated yields) and proved to be diasteromerically pure after GC/MS analysis.

Individual hydrogenolysis of (-)-**134** and (+)-**135**, carried out in a Parr apparatus under hydrogen pressure (*ca*. 50 psi) using palladium hydroxyde as catalyst, then afforded very cleanly and almost quantitatively antipodes of amine **19**. Separated enantiomers such

prepared exhibited matching optical rotations: (+)-**19** $[\alpha]_D^{25}$ = 16.0 (*c* 1.30, $CHCl_3$) ; (-)-**19** $[\alpha]_D^{25}$ = -16.5 (*c* 1.15, $CHCl_3$). The important point of the enantiomeric excess determination was realized here with compound (+)-**19**, by ^{1}H-NMR in the presence of mandelic acid as chiral solvating agent,[60] in comparison with the racemic material.

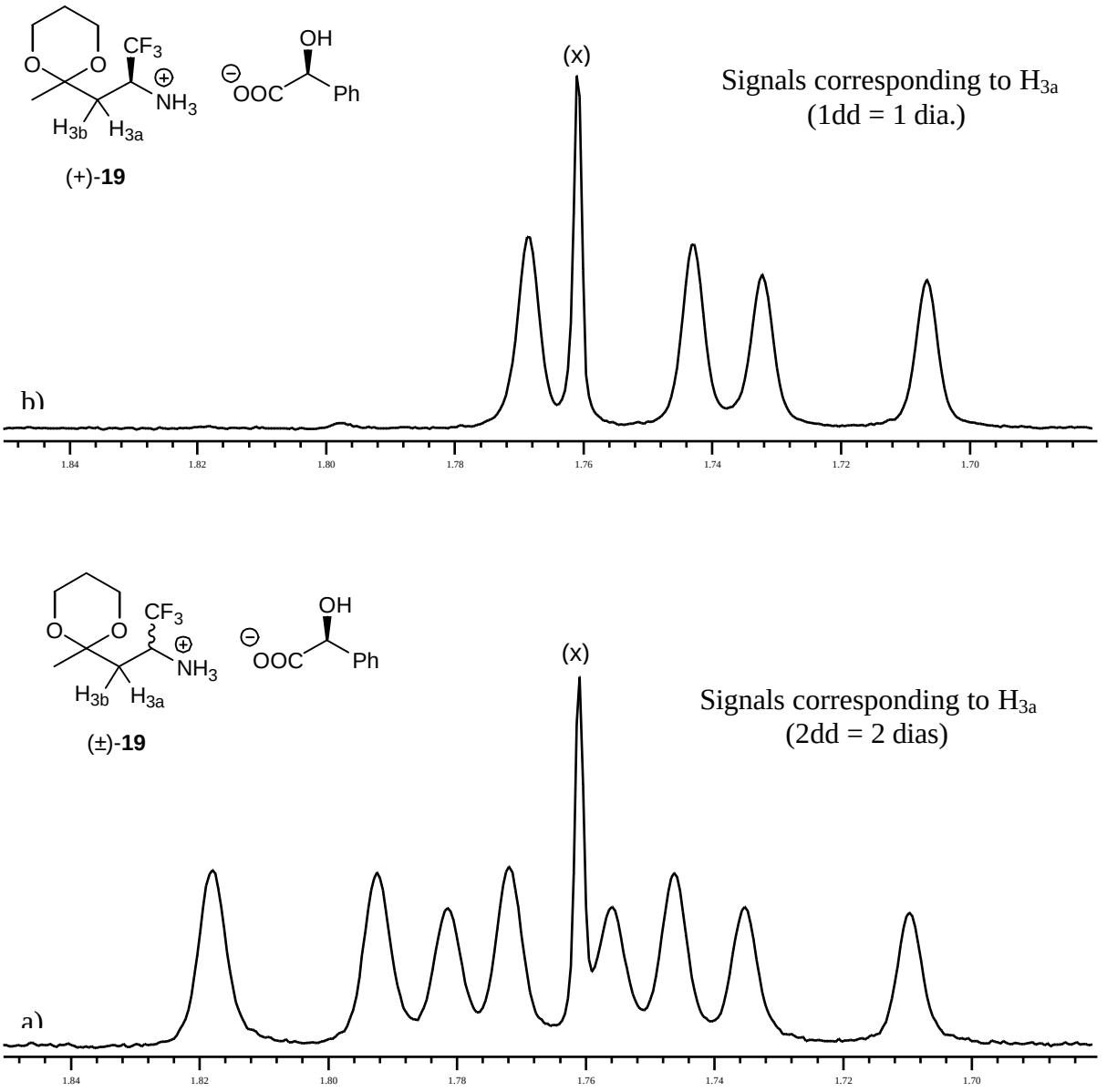
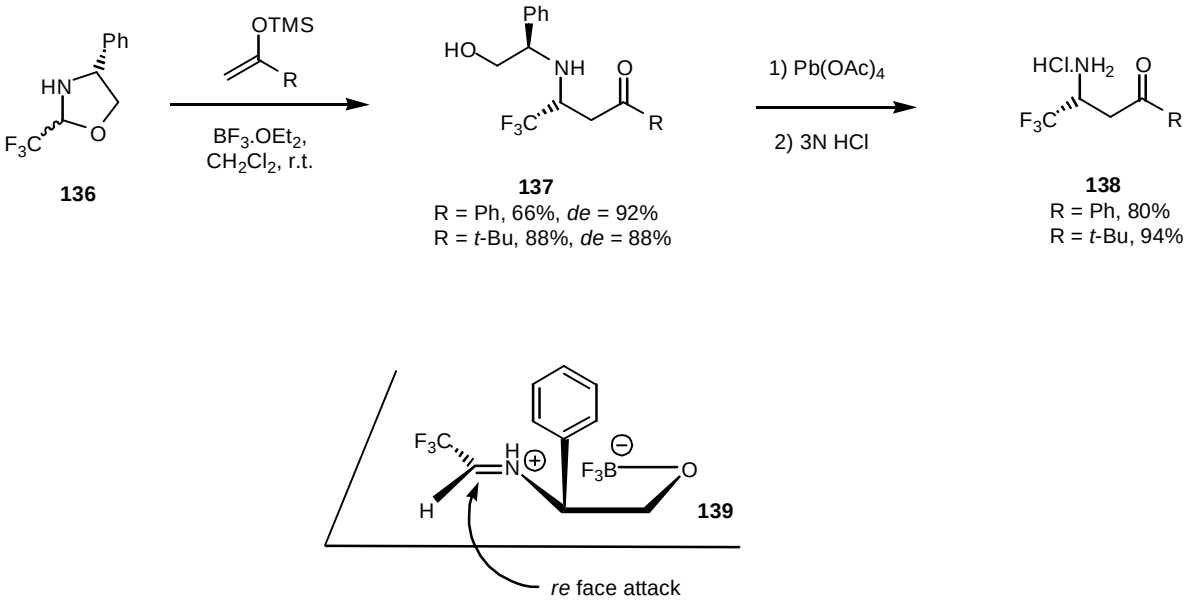


Figure 10. ^{1}H-NMR spectra (400 MHz, C_6D_6) of : a) racemic **19** + mandelic acid; b) (+)-**19** + mandelic acid; (x): mandelic acid impurity.

As illustrated in figure 10, two doublets of doublets (dd) were observed on the spectrum of the mandelate salt prepared from racemic **19**, each dd corresponding to H-3a of each *pseudo* diastereomer. The disappearance of one of the dd on the spectrum obtained in the same conditions from (+)-**19** signed clearly the absence of one of the *pseudo* diastereomers and, in consequence, an excellent enantiomerical purity for this amine (ee > 95%). At this stage it remained not possible to assign an absolute configuration to amine (+)- and (-)-**19**. Those drawn in scheme 41 and figure 10 may be considered as arbitrary.

Although allowing a rapid elaboration of amines (+)-**19** and (-)-**19** on a multigram scale, the lack of stereoselectivity for the conjugate addition step decreased significantly the interest of this first 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 *et al*.[61] (scheme 42).

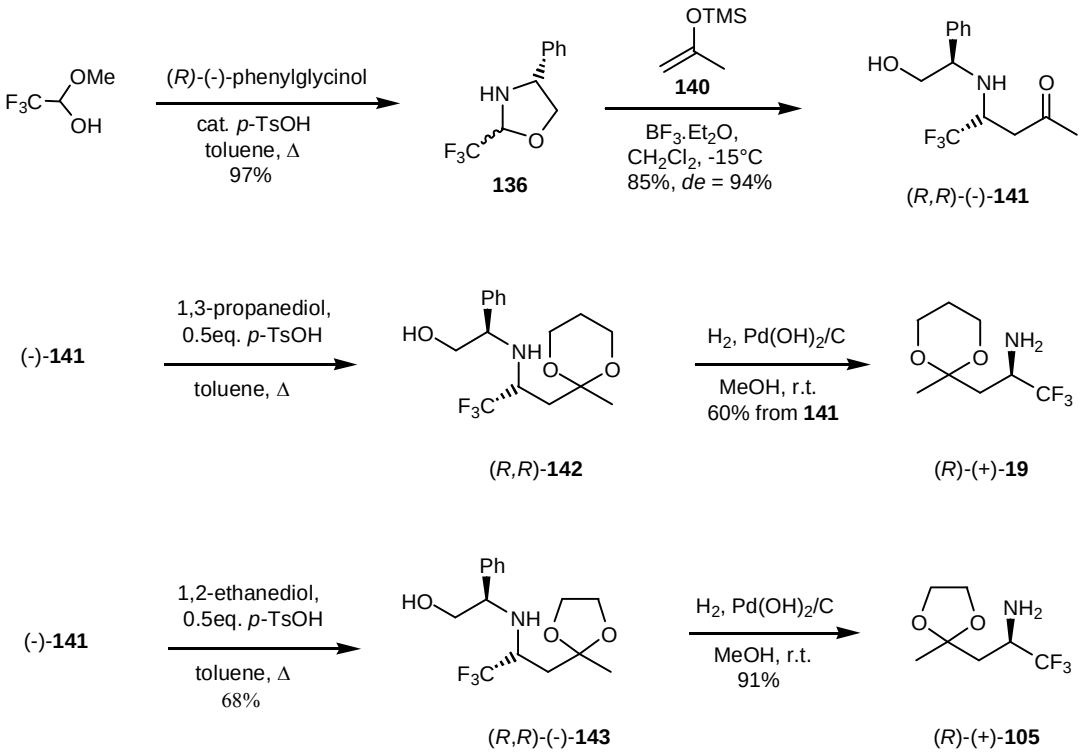


Scheme 42. Brigaud's approach to enantioenriched Tfm-aminoketones.

His Mukaiyama-Mannich-type methodology involved the diastereoselective addition of silyl enol ethers onto the stable oxazolidine **136**, very conveniently obtained from a fluoral hemiacetal and (*R*)-(-)-phenylglycinol. By the way, he has described a straightforward and highly selective (*de* up to 92%) synthesis of Tfm-aminoketones **137**, which were efficiently converted in enantiopure amines **138** after oxidative cleavage of the phenylglycinol side

chain then hydrolysis of imine intermediate. The high stereoselection degree was argued taking in consideration the iminium ion **139** as key intermediate (scheme 42) on which the nucleophilic attack at the much less hindered *re* face is largely favorized.

According to Brigaud, and as depicted in scheme 43, a 1:2 diastereomeric mixture of oxazolidines **136**[62] was treated with 2.2 equivalents of enoxysilane **140**[63], in the presence of boron trifluoride etherate at -15°C in dichloromethane.



Scheme 43.

Under these conditions, the wished β-aminoketone (-)-**141** was efficiently obtained (85% yield), in a few minutes and highly predominantly (94% *de* from GC/MS of the crude, diastereomers seperated by column chromatography).

Subsequently, a conventional keto protection afforded ketal **142**, which remained accompanied by an unidentified minor impurity. Removal of the phenyl glycinol appendage was then cleanly achieved by catalytic hydrogenolysis and furnished the desired amine (+)-**19** in 60% isolated yield from (-)-**141**. Once again ^{1}H-NMR analysis (*vide supra*) showed an excellent enantiomeric purity (> 95%) for compound (+)-**19**. At this moment, absolute configuration of trifluoromethyl amines (*R*)-(+)-**19**, (*S*)-(-)-**19** and intermediates (represented in schemes 41 and 43) were assigned, in respect with Brigaud's observations[61].

Applying the same synthetic scheme using ethylene glycol instead of 1,3-propanediol, optically pure Tfm-amine (*R*)-(+)-**105** was obtained in 62% overall yield starting from (-)-**141**, through dioxolane (-)-**143**.

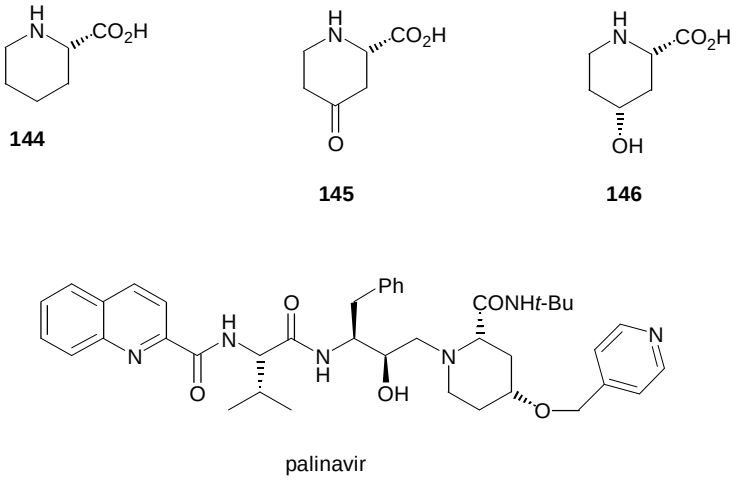
III. 2. Synthesis of enantio-enriched piperidines

Disposing of both homochiral antipodes of amines **19** and **105**, our next goal was to evaluate their potential towards the preparation of enantioenriched Tfm-piperidines. In order to not only reproduce the work already accomplished in racemic series (see chapter 2), we wished to select as application examples original structures of synthetic and/or biological interest.

III. 2. 1. Asymmetric synthesis of Tfm piperidine-based amino acids

In this aim, pipecolic acids were considered[64]. Effectively, examination of the literature data revealed that despite the numerous efforts devoted to fluorinated amino acids[65], compounds of relevant biological interest, none asymmetric synthesis of Tfm-homoprolines has been reported to date (for approaches to racemic α-Tfm and α'-Tfm pipecolic acids see chapter 1). The elaboration of α'-trifluoromethyl analogue of the simplest pipecolic acid **144** was thus envisaged, together with those of its 4-oxo and 4-hydroxy congeners **145** and **146**, interesting products for pharmaceutical research[66,67].

For instance, 4-oxo-pipecolic acid **145** has been employed as an intermediate for the synthesis of protein tyrosine phosphatase modulators[68], *N*-methyl-D-aspartate (NMDA) receptor antagonist[69] and thrombin inhibitors[70], constituent of cyclodepsipeptide antibiotics[71], 4-hydroxy pipecolic acid **146** has been included in skeleton of NMDA receptor antagonists[72] and HIV-protease inhibitors such as palinavir[73] (figure 11).

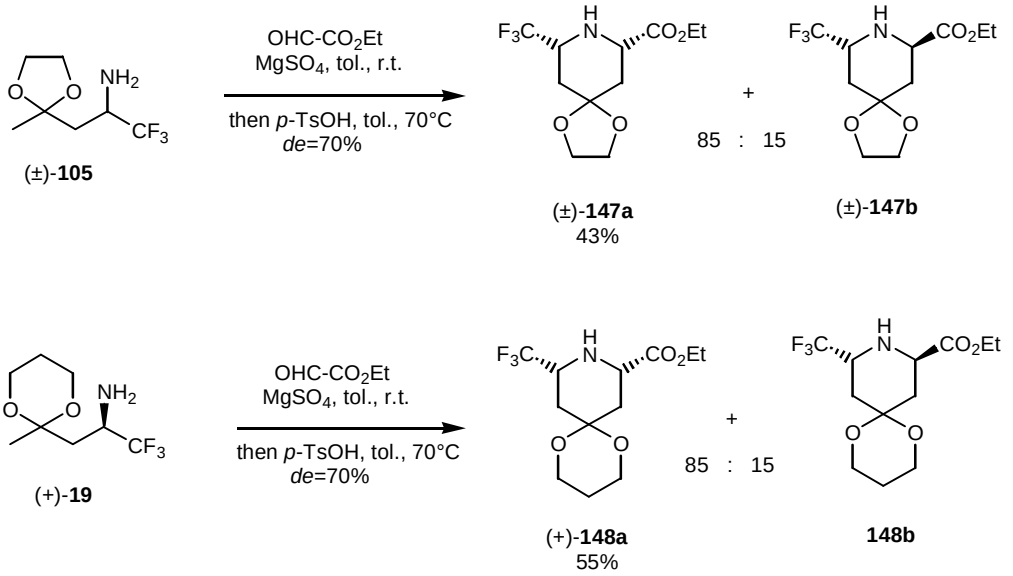


(potent HIV-1 and HIV-2 proteases inhibitor).

Figure 11.

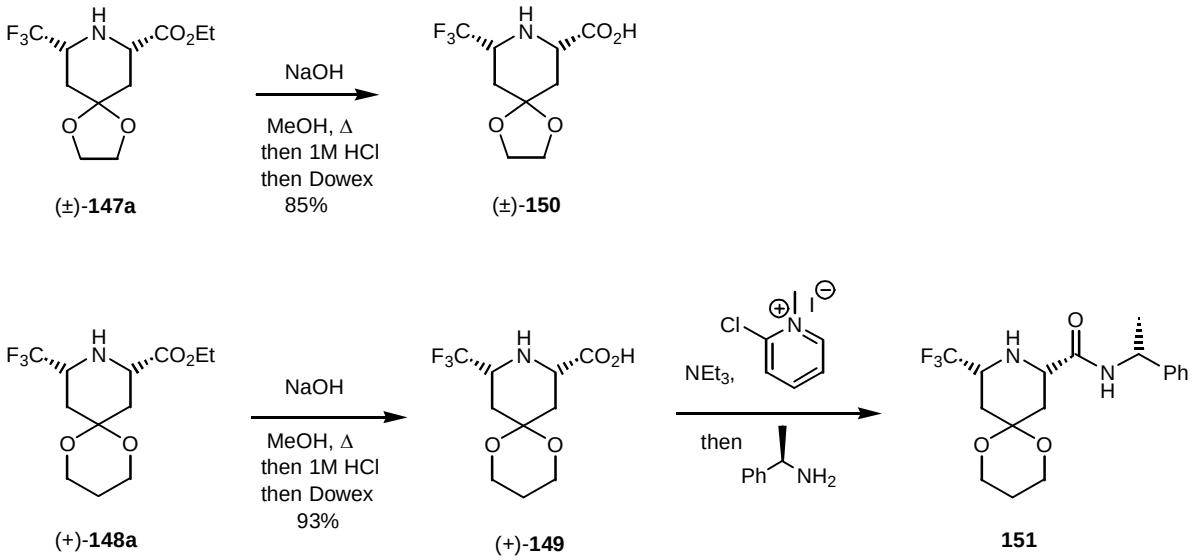
It has to be noticed that from this point, most of the following chemical reactions were performed in racemic and non-racemic series, for *ee* determination preoccupations and reactions optimization. Depending on temporary homochiral material stock shortage, some of the experiments were conducted only in racemic series. We assume results of these are nevertheless transposable in "asymmetric synthesis".

Thus, individual treatment of amines **(±)-105** and **(+)-19** with ethyl glyoxylate at room temperature led rapidly to the corresponding imines which, submitted to our standard acidic cyclizations, yielded in an appropriate 85 : 15 ratio, the 2,6-*cis* and 2,6-*trans*-ethyl Tfm-pipecolates **147a,b** and **148a,b** (scheme 44).



Scheme 44.

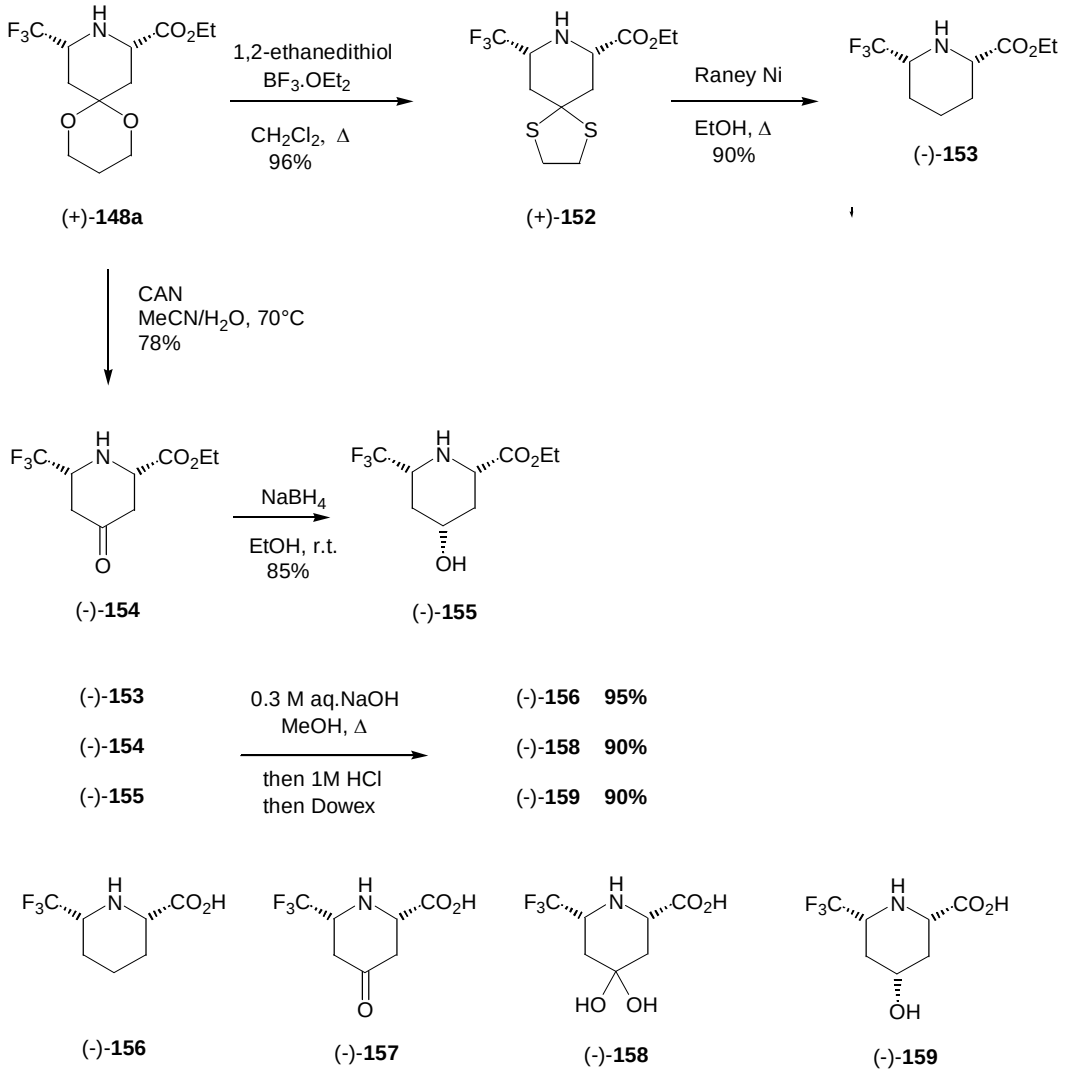
Major and less polar diastereomers **147a** and **148a** were easily purified by column chromatography (respectively 43% and 55% isolated yields). The crucial point to be checked here was the enantiomeric composition of the predominent compound (+)-**148a**. Unfortunately this couldn't be achieved directly by usual NMR or chromatographic technics, imposing therefore its derivation. Ester **148a** was so saponified into free aminoacid (+)-**149**, in the same time its companion **147a** underwent the same fate (scheme 45).



Scheme 45.

Reaction of Tfm-pipecolic acid **149** with (*R*)-(+)-α-methylbenzylamine in the presence of Mukaiyama's coupling reagent[74] gave the parent amide **151**, prepared from racemic **149** and from its dextrorotatory isomer. Comparison of both demonstrated an excellent stereoisomeric ratio (*de* > 95%), proving that no racemization occurred under the strong acidic and alkaline conditions used for cyclization and the saponification steps. This result confirmed in cascade the high optical purity of piperidines (+)-**149** and (+)-**148a**.

Asymmetric synthesis of α-Tfm analogues of **144**-**146** could then be serenely undertaken. As mentioned in scheme 46, transdithioketalization of (+)-**148a** led to dithiolane (+)-**152** which, after treatment with excess Raney nickel in refluxing ethanol furnished very cleanly the pipecolate (-)-**153** in 86% overall yield.



Scheme 46.

In contrast to previous observations on parent free Tfm-piperidines (chapter 2, page 40), direct keto-function regeneration of (+)-**148a** could be here realized by means of treatment with ceric ammonium nitrate at 70°C in acetonitrile-water for eight hours (78% yield, other acidic conditions being ineffective). The 4-piperidone (-)-**154** thus rapidly obtained was then reduced with sodium borohydride at room temperature in ethanol to afford in 85% yield (see chapter 2) the expected *all-cis*-piperidinol (-)-**155** as sole detectable isomer (^{1}H-NMR, GC/MS).

Finally, saponification of amino esters **153-155**, using 0.3M aqueous sodium hydroxide in refluxing methanol, followed by HCl acidification then migration through an ion exchange resin gave efficiently (90-95% yield) the trifluoromethylated analogues of free

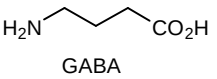
amino acids **144**, **145** and **146**, respectively (-)-**156**, **157** (which exists as its hydrate (-)-**158**) and (-)-**159**.

With this work dedicated to the synthesis of new constrained cyclic amino acids, we think we have shown that intramolecular Mannich reaction of β-aminoketals represents a worthwhile access strategy to homochiral α-trifuoromethyl piperidines.

III. 2. 2. Asymmetric synthesis of Tfm piperidine-based γ-amino acids

The preparation of non-racemic α'-Tfm-piperidine-based γ-amino acid was next considered.

γ-Aminobutyric acid (GABA, figure 12) is the main inhibitory neurotransmitter in the central nervous system and several important neurological or psychiatric pathologies are associated with its deficiency. Unfortunately, incapacity of GABA to cross the blood-brain barrier makes its oral or intravenous administration ineffective for the treatment of such diseases.



GABA

possible piperidine-based GABA analogues :

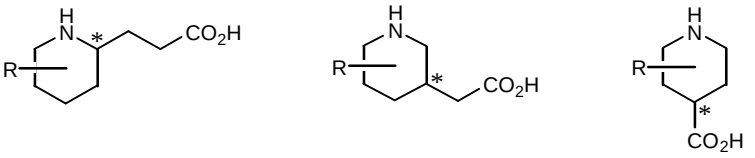


Figure 12.

As a consequence, research towards more lipophilic and active analogues knew a real boost. Meanwhile, among the multiple studies[75] directed to solve this problem, a very few described the enantioselective synthesis of structures possessing a piperidine backbone (figure 12). Furthermore and as far as we know, only one Tfm-piperidine bearing also a γ-aminoacid function has been reported in the literature[33] (figure 13, racemic; see also chapter 1 page 16).

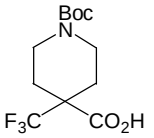
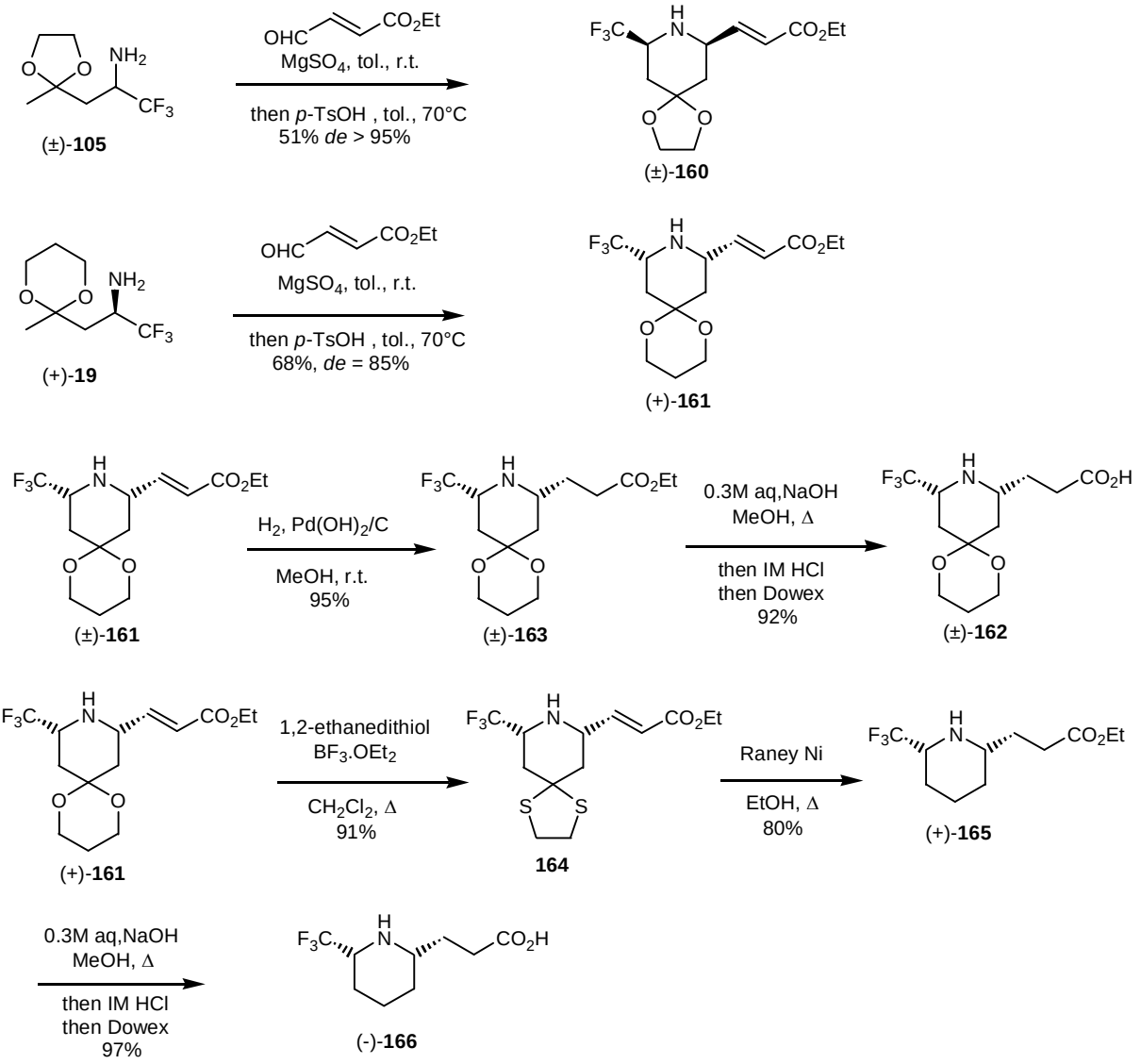


Figure 13.

Because our intramolecular Mannich strategy seemed appropriate for the stereoselective construction of piperidine-based γ-aminoacids possessing a lipophilic trifluoromethyl group, and because these compounds present patently a biological interest, their synthesis was examined.

Reaction of amine **(±)-105** with ethyl *E*-oxobutenoate under our classical cyclization conditions (scheme 47), afforded in 51% isolated yield *cis*-2,6-disubstituted piperidine



Scheme 47. Asymmetric synthesis of Tfm-piperidine-based γ-aminoacids.

(±)-160, as the sole detectable isomer (*de* > 95%, GC/MS of the crude). Identical treatment of aminoketal (+)-**19** then furnished highly majoritarly (*de* = 85%) the expected and presumed enantiopure Tfm-γ-aminoester (+)-**161** (68% yield, scheme 47).

Our first free azacyclic γ-aminoacid **(±)-162** was then easily obtained from **(±)-161**, by simple palladium hydroxyde catalyzed saturation of the olefinic bond, followed by saponification of the resulting ester **(±)-163** then migration through an ion-exchange resin (87% overall yield).

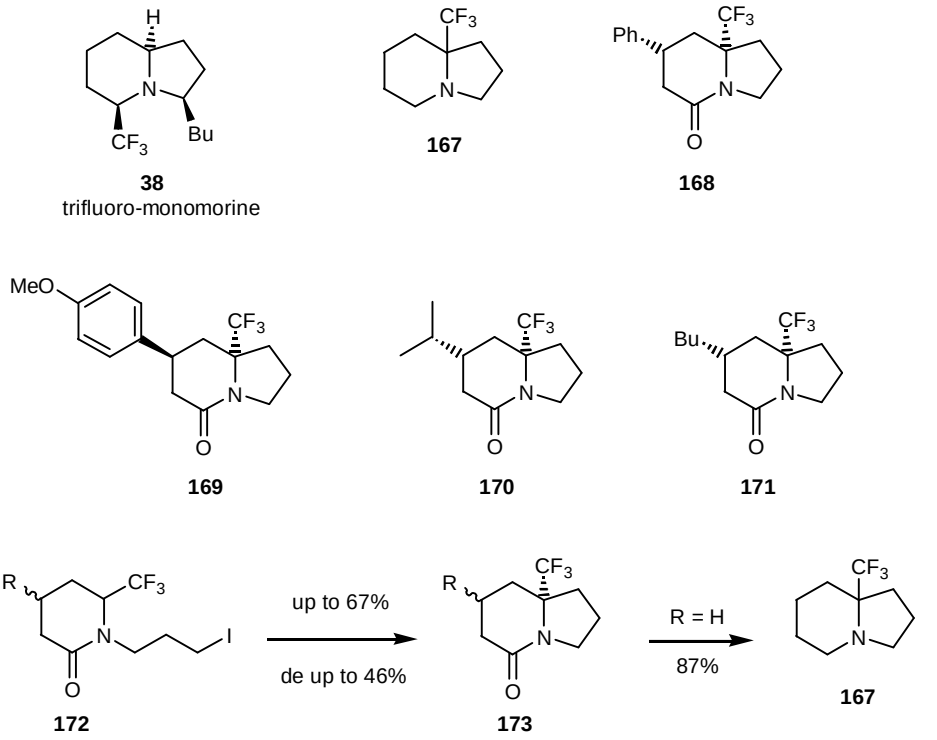
With enantioenriched piperidine (+)-**161** in hands we had the opportunity to propose, to our knowledge, the first asymmetric synthesis of trifluoromethyl piperidine-based GABA analogue. This was efficiently realized using a conventional three steps sequence (scheme 47). Ketal appendage of (+)-**161** was transferred into dithiolane **164** which upon hydrogenation/hydrogenolysis using Raney nickel in ethanol at reflux, furnished cyclic γ-aminoester (+)-**165**. Finally, saponification of the latter followed by purification on a Dowex® resin liberated the targeted heterocycle (-)-**166** in a 71% global isolated yield.

As already proven with the pipecolic series that reactional conditions involved did not provoke any racemization, we assume that Tfm-azacyclic γ-aminoacid (-)-**166** such synthetized presents an excellent enantiomerical purity (> 95%).

III. 2. 3. Asymmetric synthesis of Tfm-indolizidines

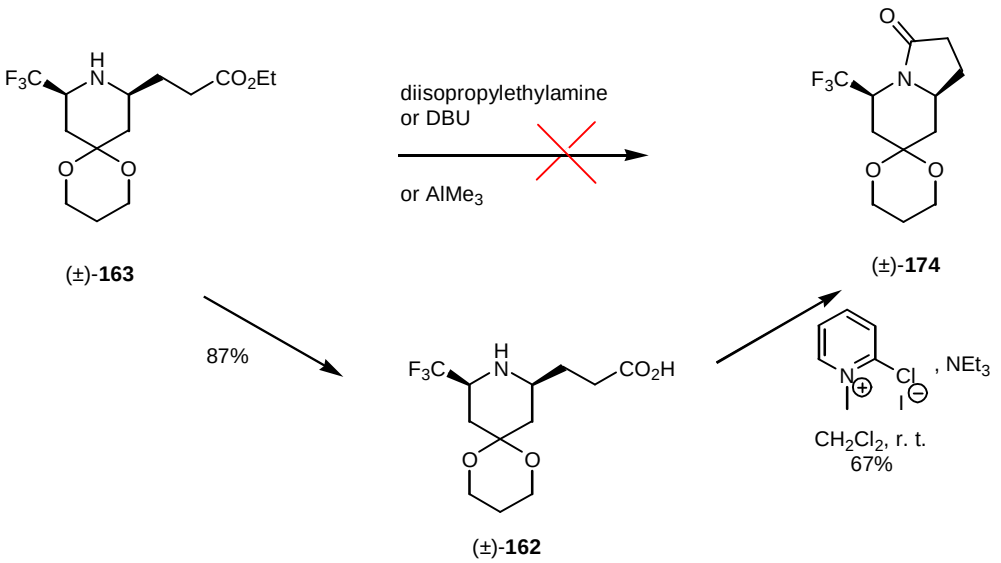
As last illustration examples of the synthetic potential of our intramolecular Mannich methodology, indolizidine-type bicyclic systems were selected.

Indeed, although this framework is commonly encountered in nature and even if it has been reported[39a] that "*the introduction of a trifluoromethyl group into the alkaloid-related heterocycle is a hopeful modification procedure to develop new biologically active compounds*", the selective synthesis of mono Tfm indolizidines remains a poorly investigated area. And effectively, we were able to find in the literature only two Tfm indolizidines, Tfm monomorine **38** (see chapter 1, page 14) and compound **167**, and with products **168**-**171** only four Tfm indolizidinones (scheme 48).



Scheme 48 Inventory of known Tfm indolizidines and Tfm indolizidinones.

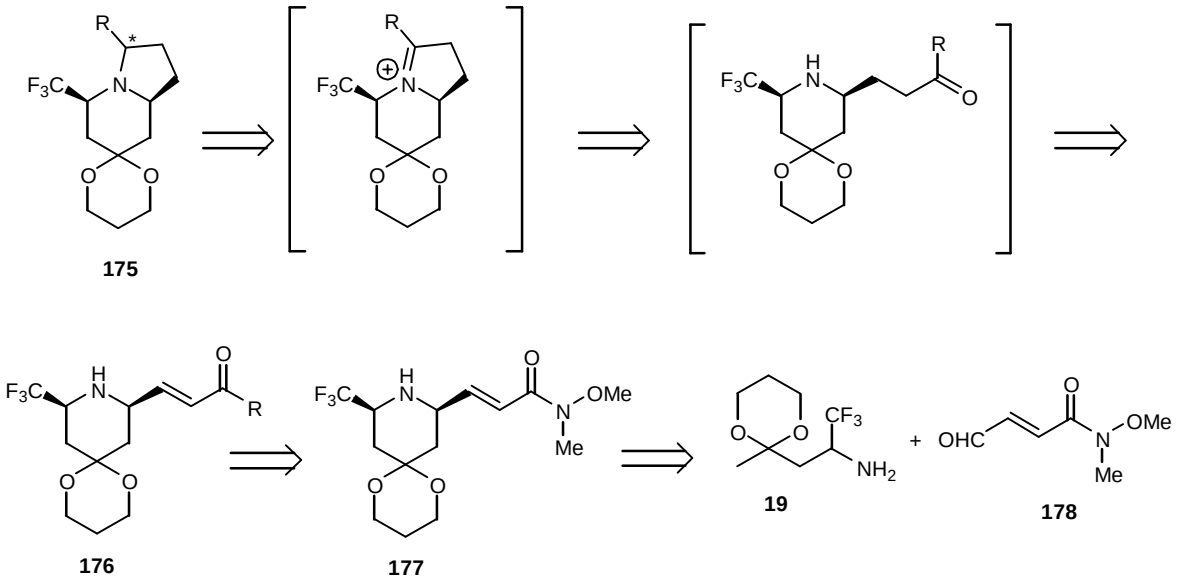
From our own, we thought that homochiral indolizidin(on)es would be quite rapidly accessible from our piperidine-based γ-aminoesters. First cyclization attempts concerned compound **(±)-163,** but gave disappointing results since, whatever the conditions involved (use of a base or of a Lewis acid) the formation of the expected heterobicycle **174** could not be observed (scheme 49).



Scheme 49. Synthesis of a Tfm-indolizidinone.

To circumvent this difficulty, the intramolecular amidification of aminoacid **(±)-162** was taken into account. Thus, treatment of **(±)-162** with Mukaiyama's reagent, at room temperature in dichloromethane in the presence of triethylamine, resulted this time in the clean formation of indolizidinone **(±)-174** (67% isolated yield, scheme 49), the first trifluoromethyl aza-bicyclic γ-lactam was synthetized.

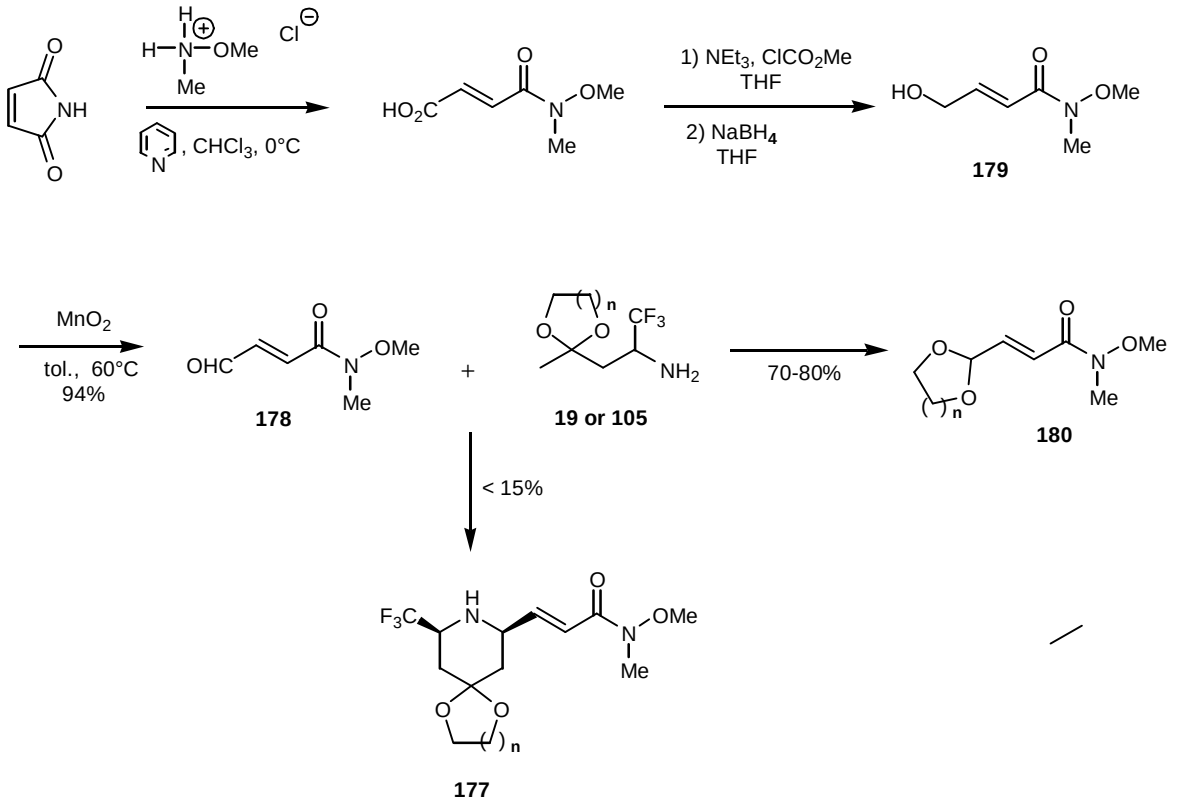
The corresponding indolizidine would be at this stage easily obtained from **174** by lithium aluminium hydride or borane mediated deoxygenation of the amido group. Anyway, as we wished to develop a more rapid and general access to this molecular skeleton, permitting the selective introduction of a supplementary stereogenic center, an alternative root was foreseen (scheme 50).



Scheme 50. Tfm-indolizidines: a retrosynthetical analysis.

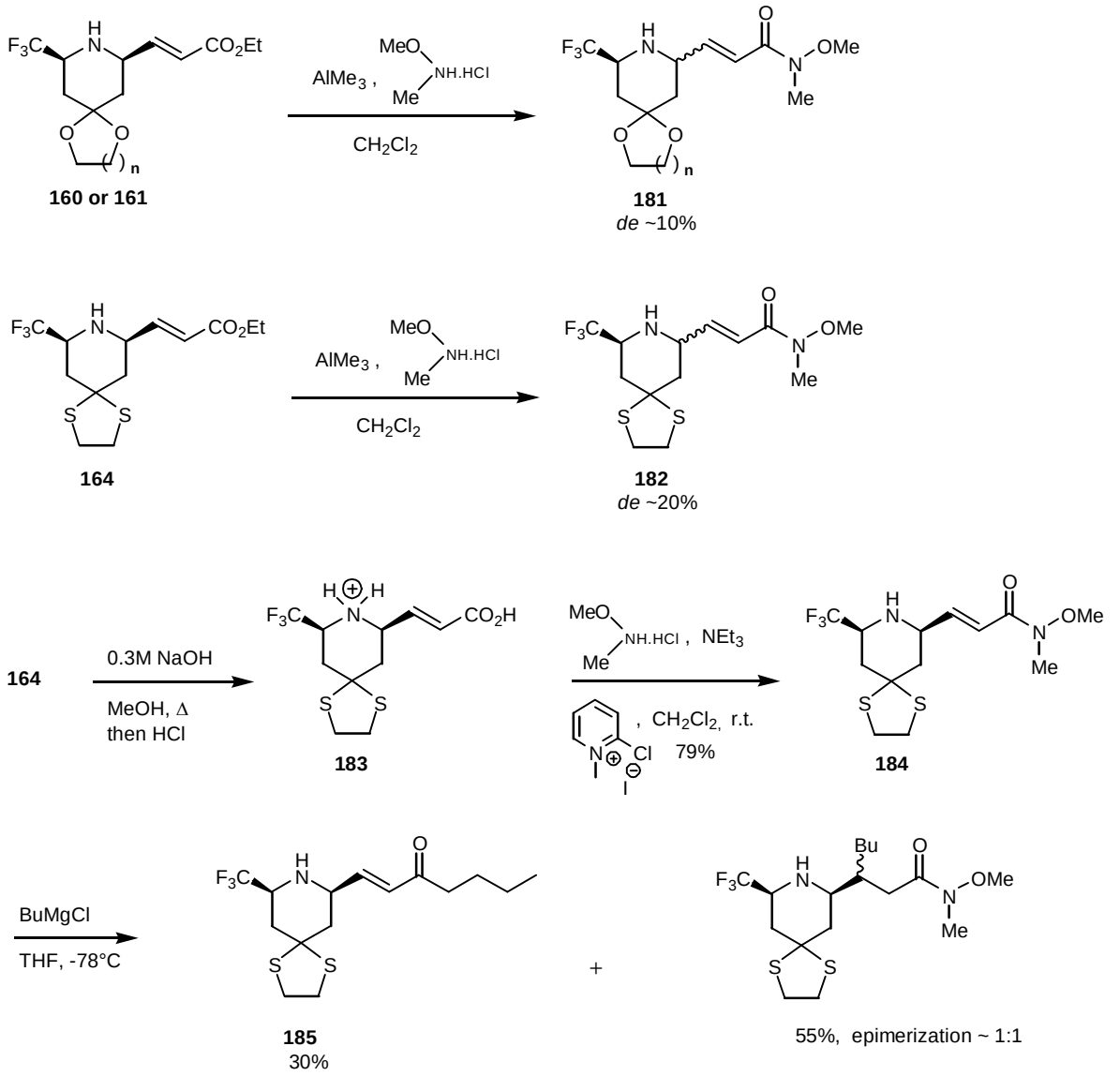
We reasonned that trifluoromethyl indolizidines **175** would directly arose from simple hydrogenation of enone **176** following an ethylenic saturation then intramolecular reductive amination cascade[71]. A wide access to key unsaturated ketones **176** seemed conceivable by Grignard reagents addition onto Weinreb amide **177**, intramolecular Mannich reaction adduct of amine **19** and functionalized aldehyde **178**.

Synthesis of enal **178** was envisaged by oxidation of allylic alcohol **179**, available in two steps from maleimide according to Jacobi's procedure[77] (scheme 51).



Scheme 51.

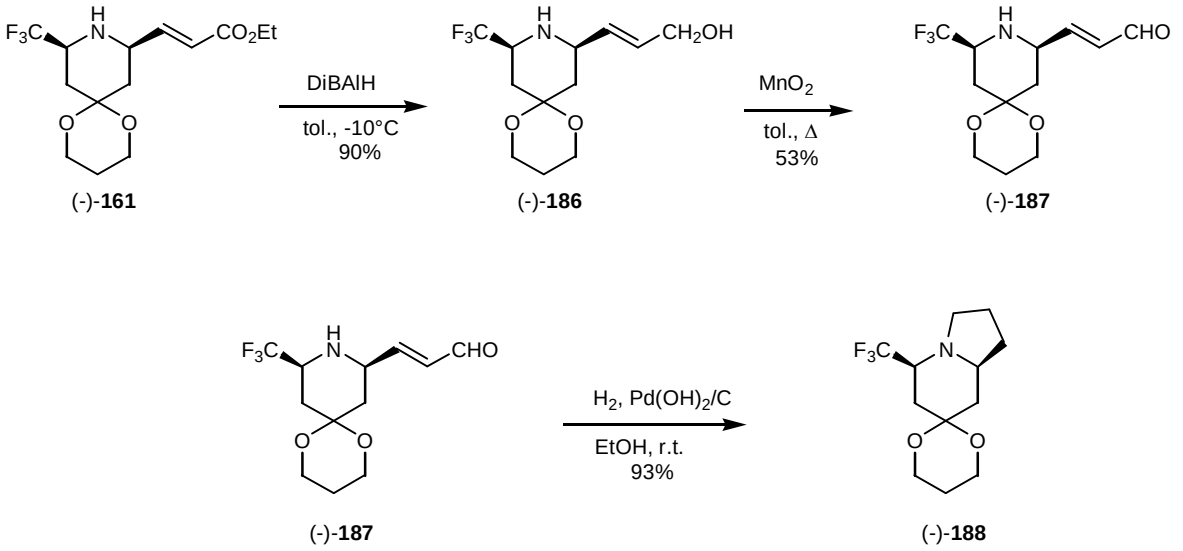
Treatment of alcohol **179** such prepared with manganese dioxide at 60°C in toluene furnished in a 94% yield the desired aldehyde **178**. Next was its employment in our Mannich-type process but, unexpectedly, all cyclization trials conducted either with amines **19** or **105**, failed to give efficiently piperidine **177** (< 15%) but trans-acetalation product **180**. These very disappointing results forced us to revisit our synthetic scheme. For this reason, piperidines **160**, **161** and **164** were submitted to Weinreb's procedure[78] (scheme 52). If the corresponding amides **181** and **182** could be thus prepared, the important epimerization degree noticed removed any interest to this approach. Finally, saponification of ester **164** followed by treatment of the resulting acid **183** with *N,O*-dimethyl hydroxylamine hydrochloride, in the presence of triethylamine and Mukaiyama's reagent, allowed us to get the piperidine based unsaturated Weinreb amide **184** (scheme 52). But unluckily, reaction of **184** with alkylmagnesium halides took place mainly in the β-position giving wished enone **185** in 30% yield at best. In our minds, these last and surprising failures condemned irremediably the "Weinreb route" to sink into oblivion.



Scheme 52.

Not decided to give up our indolizidines quest, and because transformation of an α,β-unsaturated ester into the corresponding enal or alkyl enone doesn't represent a major problem, we redefined a synthetic scheme starting from piperidine (-)-**161** (scheme 53).

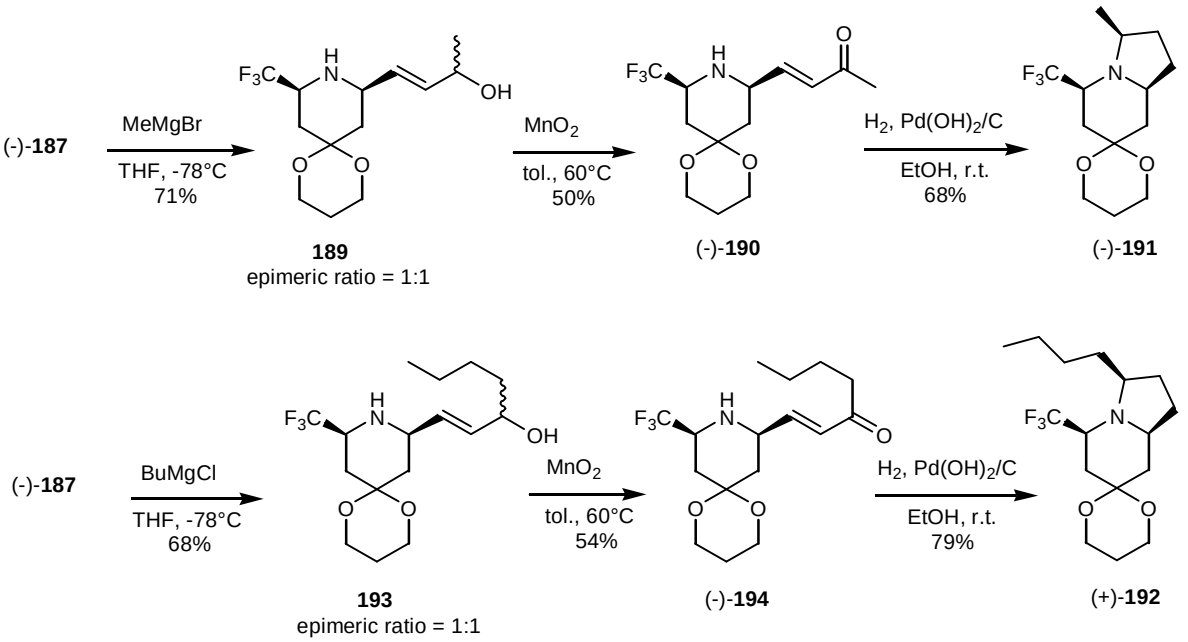
Reduction of (-)-**161** using one equivalent of diisobutyl aluminium hydride at low temperature (-78°C) led to a statistical mixture of unreacted ester, parent aldehyde (-)-**187** and alcohol (-)-**186**. It appeared so preferable to completely reduce the ester function with two equivalents of reducing agent. Allylic alcohol (-)-**186** thus conveniently prepared (90% yield) was subsequently converted into aldehyde (-)-**187** by MnO_2 mediated oxidation.



Scheme 53.

Catalytic hydrogenation of (-)-**187** then furnished very cleanly the expected indolizidine (-)-**188**, in a 40% overall yield from (-)-**161**.

In order to prepare related polycyclic systems but possessing a supplementary asymmetric center, a similar synthetic pathway was studied (scheme 54).



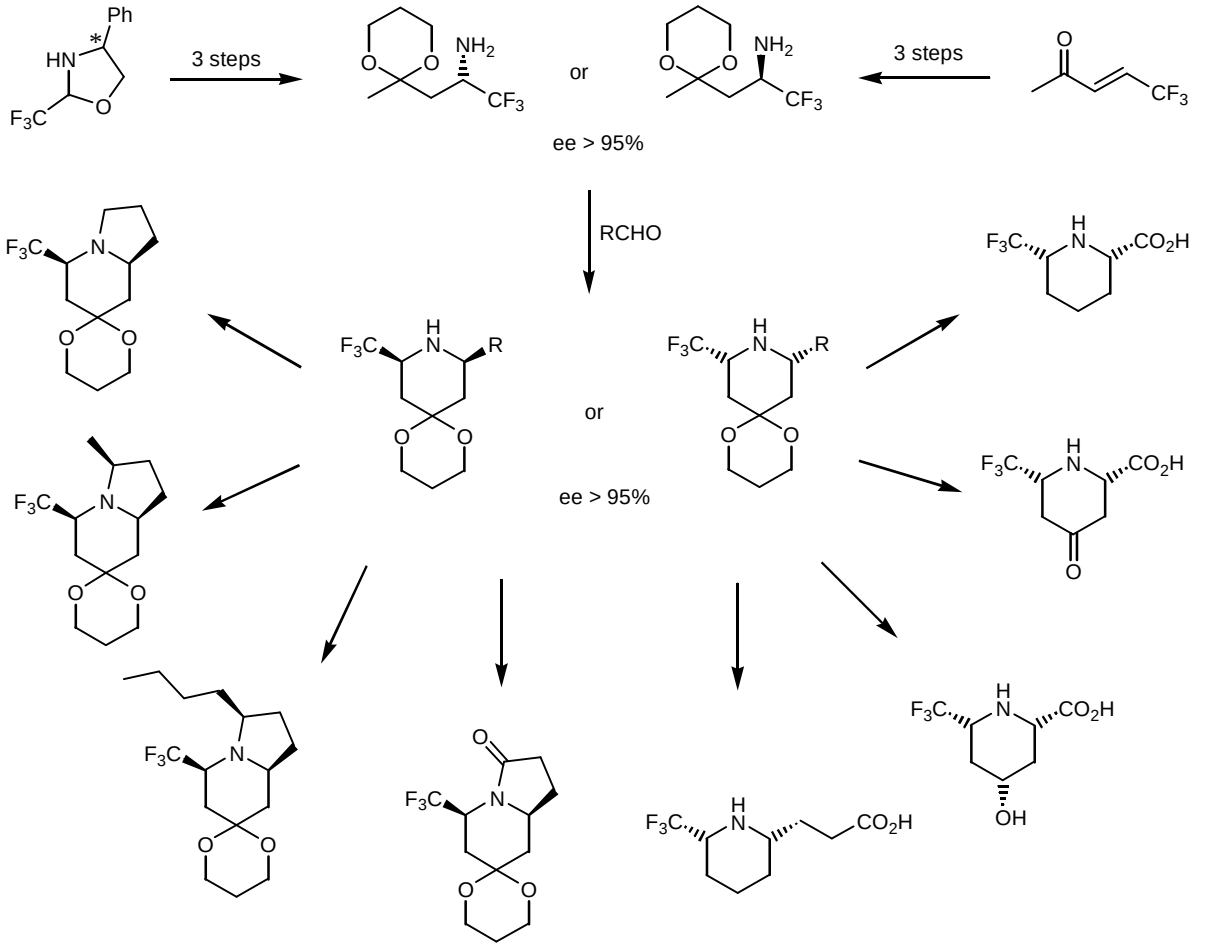
Scheme 54. Asymmetric synthesis of Tfm-indolizidines.

Addition of methyl magnesium bromide on aldehyde (-)-**187**, carried out at -78°C in tetrahydrofuran led in a 71% isolated yield to an inseparable mixture of epimers **189**, that was oxidized with MnO_2 to give the corresponding enone (-)-**190**. Palladium hydroxide catalysed hydrogenation of (-)-**190** then afforded stereospecifically (GC/MS and ^{1}H-NMR of the crude) substituted Tfm-indolizidine (-)-**191** (24% overall yield from (-)-**187**). Applying the same reactionnal sequence, using butyl magnesium chloride instead of methyl magnesium bromide, new Tfm-indolizidine (+)-**192** was obtained as the sole detectable stereoisomer, in three steps and in 29% overall yield from (-)-**187.**

Relative and therefore absolute configuration of the newly created stereogenic carbons, represented in scheme 54, was assigned in respect with unambiguous literature data[71].

III.3 Conclusion

In this chapter we have described concise accesses to highly enantioenriched α-trifluoromethyl-β-aminoketals. It is noteworthy that those implying a fluoral and phenylglycinol oxazolidine offers a highly stereoselective entry to both enantiomers, depending on the (*R*) or (*S*) nature of the chiral auxiliary. Involved in an intramolecular Mannich-type process, these chirons gave entry to homochiral (ee > 95%) Tfm-piperidines. The validation of this strategy was achieved through the first asymmetric synthesis of trifluoromethyl-bearing azacyclic α- and γ-aminoacids but also with the stereoselective preparation of original Tfm-indolizidines and indolizidinone (scheme 55).



Scheme 55. Asymmetric synthesis of Tfm-piperidines and Tfm-indolizidines.

With all the results disclosed herein, we hope we have proposed a pertinent tool for the enantioselective construction of molecular frameworks containing an α-Tfm-piperidine moiety.

CONCLUSION GENERALE

Depuis quelques années, les travaux de recherche menés au Laboratoire de Chimie des Hétérocycles et des Glucides ont permis de démontrer que la réaction de type Mannich intramoléculaire des β-aminocétals constituait un outil performant pour la synthèse asymétrique de pipéridines. Pour illustrer l'intérêt et les possibilités offertes par cet outil, il a été décidé de l'employer pour résoudre des problèmes de synthèse réputés assez difficiles.

L'objectif du présent travail de thèse était, dans ce cadre précis, de l'adapter à l'élaboration d'hétérocycles azotés saturés porteurs en position α d'un groupement trifluorométhyle.

Dans un premier temps, nous avons montré que cette stratégie « Mannich intra » ouvrait un accès simple et hautement stéréosélectif à de nouvelles Tfm-pipéridines *cis*-2,6-disubstituées, au départ d'un hémiacétal du fluoral ou, et de manière beaucoup plus générale, d'un trifluorométhyl aminocétal préformé (schéma 56).

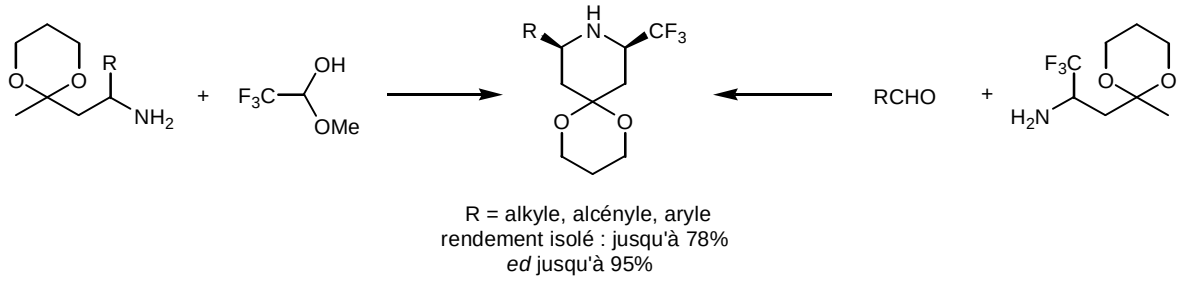


Schéma 56. Synthèse diastéréosélective de Tfm-piperidines par réaction de type Mannich intramoléculaire.

La validation de ce travail méthodologique réalisé en série racémique a été assurée par la préparation d'une famille originale de pipéridines fluorées fonctionnalisées, avec pour point d'orgue la synthèse totale de cinq analogues trifluorés d'alcaloïdes dont quatre inédits (schéma 57).

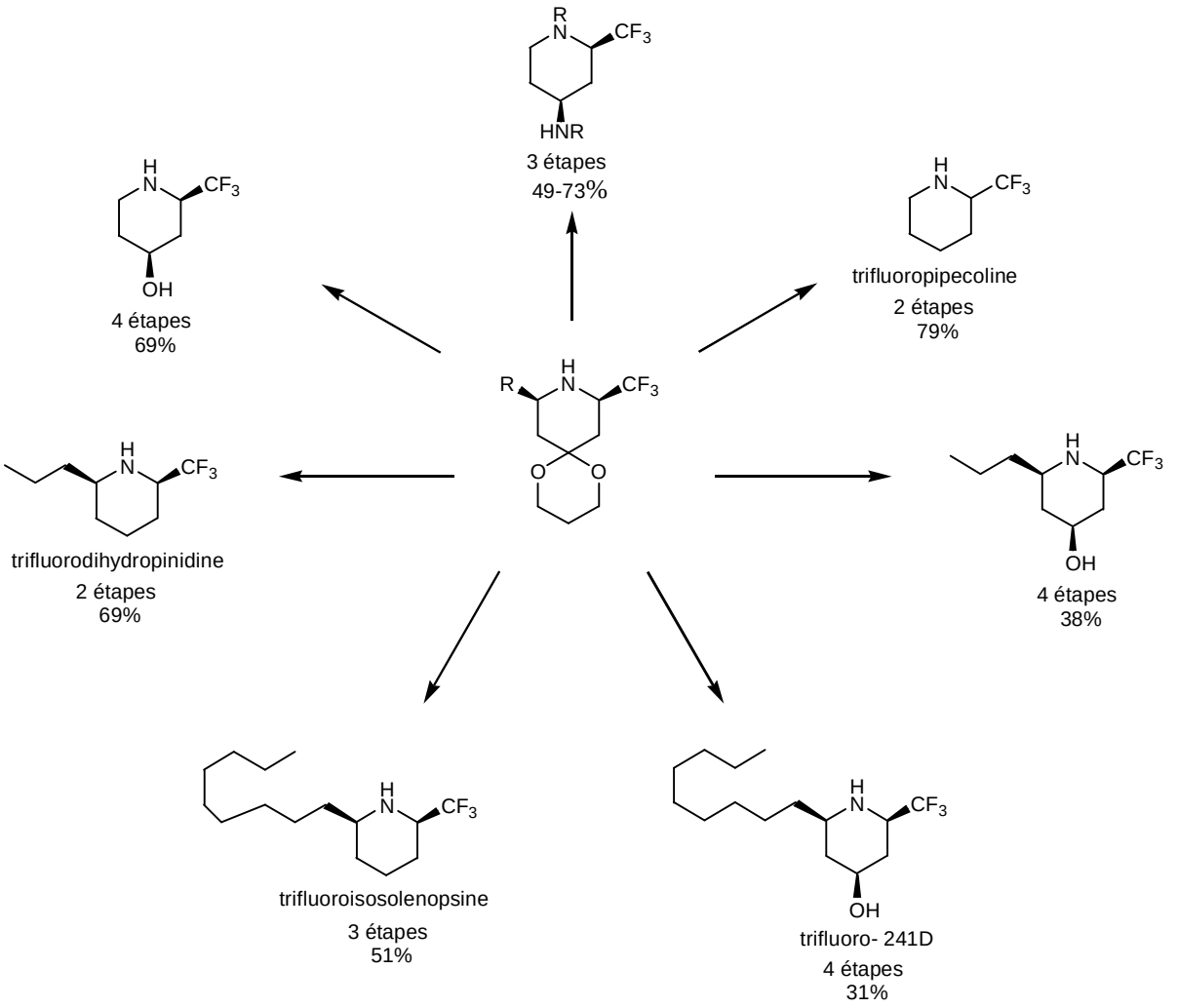


Schéma 57.

Ces premiers résultats très prometteurs nous ont rapidement conduit à réfléchir à leur extension en synthèse asymétrique proprement dite. C'est ainsi que nous avons pu proposer une synthèse concise et efficace du β-aminoacétal fluoré requis, reposant sur l'ouverture au moyen d'un énoxysilane d'une oxazolidine formée au départ du phénylglycinol et d'un équivalent synthétique du fluoral.

Cette approche hautement diastéréosélective inspirée de travaux récents de Brigaud *et coll*. nous a donné accès *in fine* à un chiron présentant une excellente pureté énantiomérique (schéma 58). Les réactions de Mannich intramoléculaire de ce dernier, réalisées en présence d'aldéhydes fonctionnalisés, ont alors fourni les pipéridines trifluorométhylées correspondantes, et ce sans perte d'information chirale.

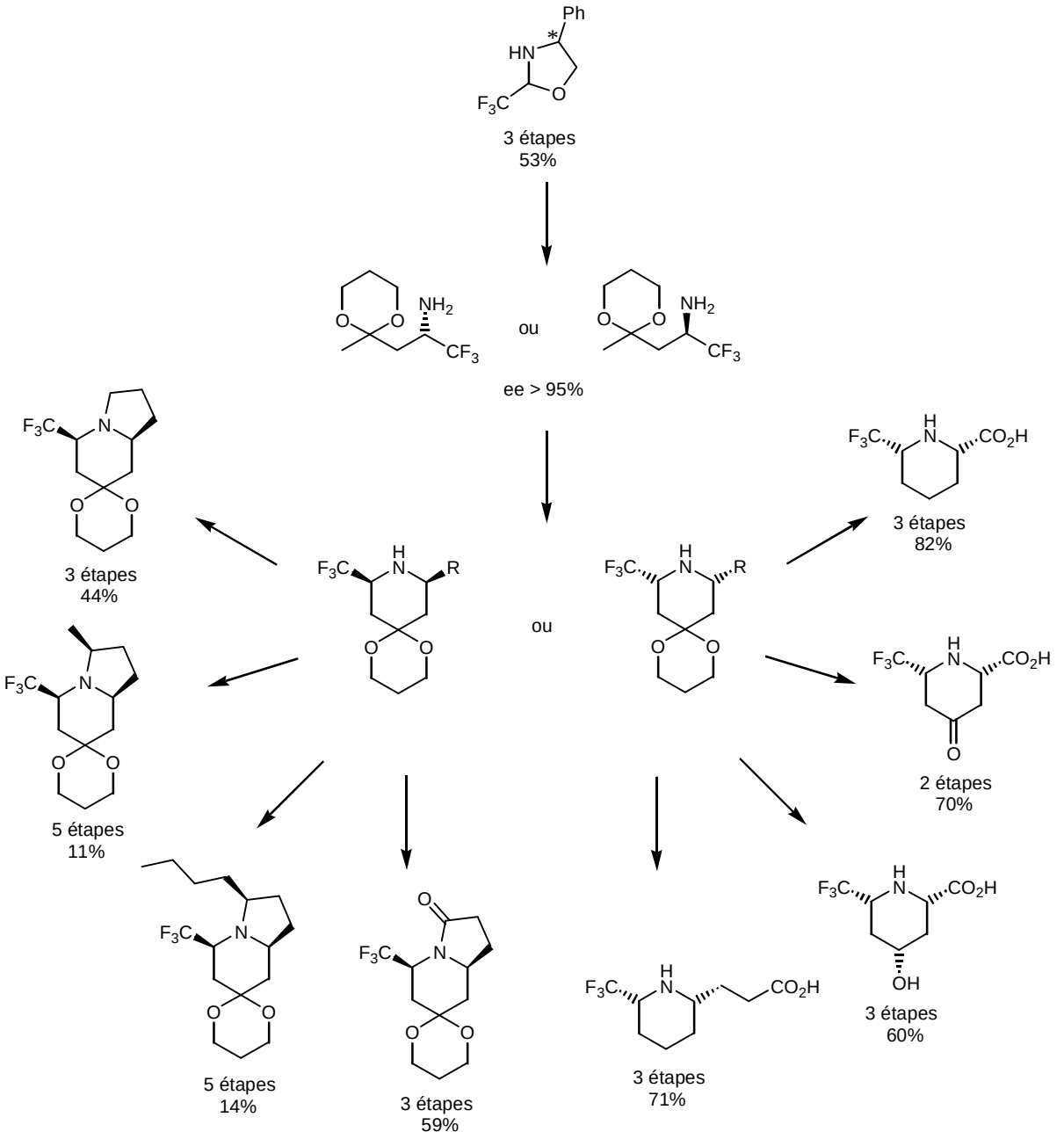


Schéma 58.

L’intérêt de cette nouvelle méthode de construction de tels hétérocycles a ensuite été illustré par :

- la première synthèse énantiosélective d’acides pipécoliques trifluorométhylés,
- la première synthèse énantiosélective d’un analogue du GABA à base de Tfm-pipéridine,

mais également par la synthèse énantiosélective de squelettes N-hétéro-polycycliques de type Tfm-indolizidine ou Tfm-indolizidinone, composés par ailleurs très rarement décrits.

Forts de l'ensemble des résultats rassemblés dans ce mémoire, nous pouvons estimer que notre objectif initial de mise au point d'une voie d'accès sélective et générale aux pipéridines trifluorométhylées, a été atteint.

Adaptation aux organofluorés d'une réaction bien connue et développée au Laboratoire en série « conventionnelle », la méthode ici proposée ne présente peut-être pas un caractère extrêmement novateur. Nous espérons néanmoins avoir convaincu l'examinateur et le lecteur qu'elle pouvait maintenant être considérée comme un nouvel outil, simple mais pertinent, autorisant la construction asymétrique de quantités de nouveaux aza-hétérocycles saturés trifluorométhylés.

Plusieurs suites à ce travail peuvent être imaginées. En ce qui concerne les aspects « synthèse » tout d'abord, si nous avons concentré nos efforts sur la préparation de pipéridines trifluorométhylées en position C-2 ou C-6, l'accès sélectif selon la même stratégie à des analogues porteurs de ce groupement en position C-3 ou C-5 semble tout à fait envisageable (schéma 59).

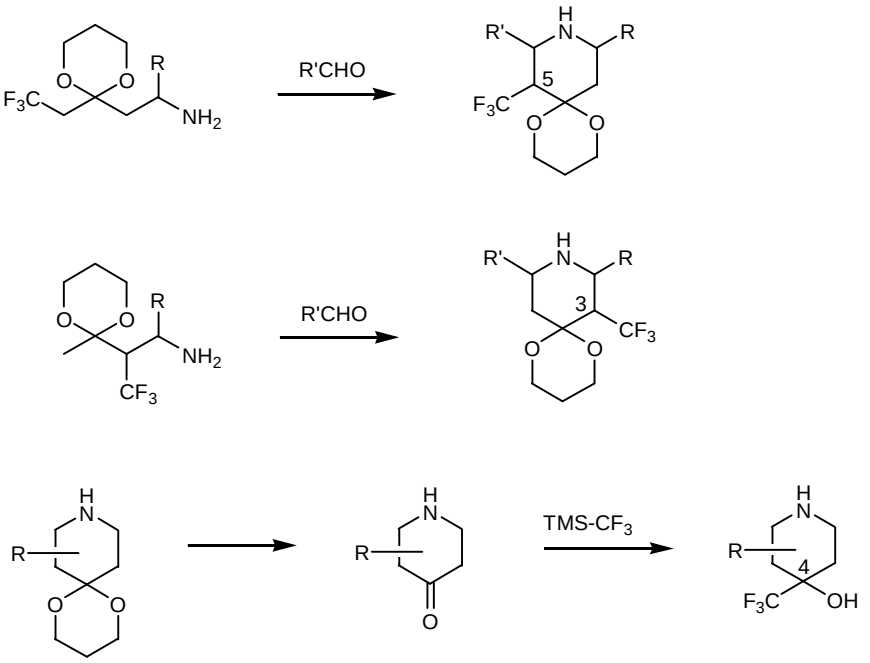


Schéma 59.

Ceci nécessitera la mise au point de synthèses efficaces de nouveaux aminocétals β-ou ω-trifluorométhylés (schéma 59), mais ce problème ne paraît pas, a priori, insurmontable.

De même, la réaction de Mannich intramoléculaire conduisant à des 4-pipéridinones, le simple traitement de ces dernières par un réactif de trifluorométhylation nucléophile tel

celui de Ruppert devrait fournir rapidement les 4-Tfm-pipéridines originales correspondantes (schéma 59).

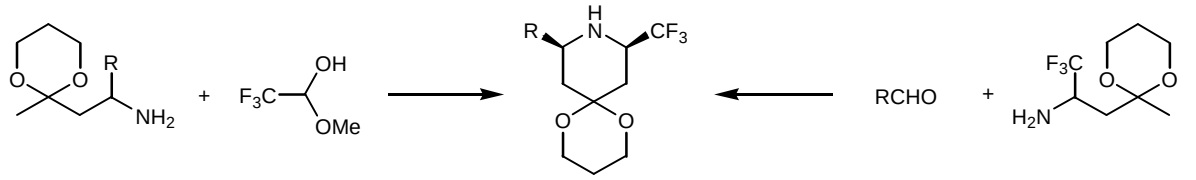
Enfin, disposant désormais d'un outil de synthèse bien au point et d'une belle collection d'α-Tfm-pipéridines, il nous apparaît indispensable d'évaluer leurs potentialités biologiques intrinsèques, qui demeurent inconnues. La détermination des cibles et la réalisation des tests d'activité ne pourront se faire sans la collaboration de spécialistes du domaine.

D'éventuelles réponses biologiques positives donneraient alors certainement d'autres perspectives, plus appliquées, à ce travail de thèse de doctorat.

GENERAL CONCLUSION

Since last few years, the research work carried out at the Laboratoire de Chimie des Hétérocycles et des Glucides have made it possible to show that an intramolecular Mannich type reaction of the β- aminoketals represents a powerful tool for the asymmetric synthesis of piperidines. To illustrate the interest and the possibilities offered by this method, it was decided to employ it to solve rather difficult problems of synthesis. The objective of this work of thesis was, within this precise framework, to adapt it to the development of saturated N-heterocycles carrying a trifluoromethyl group at α position

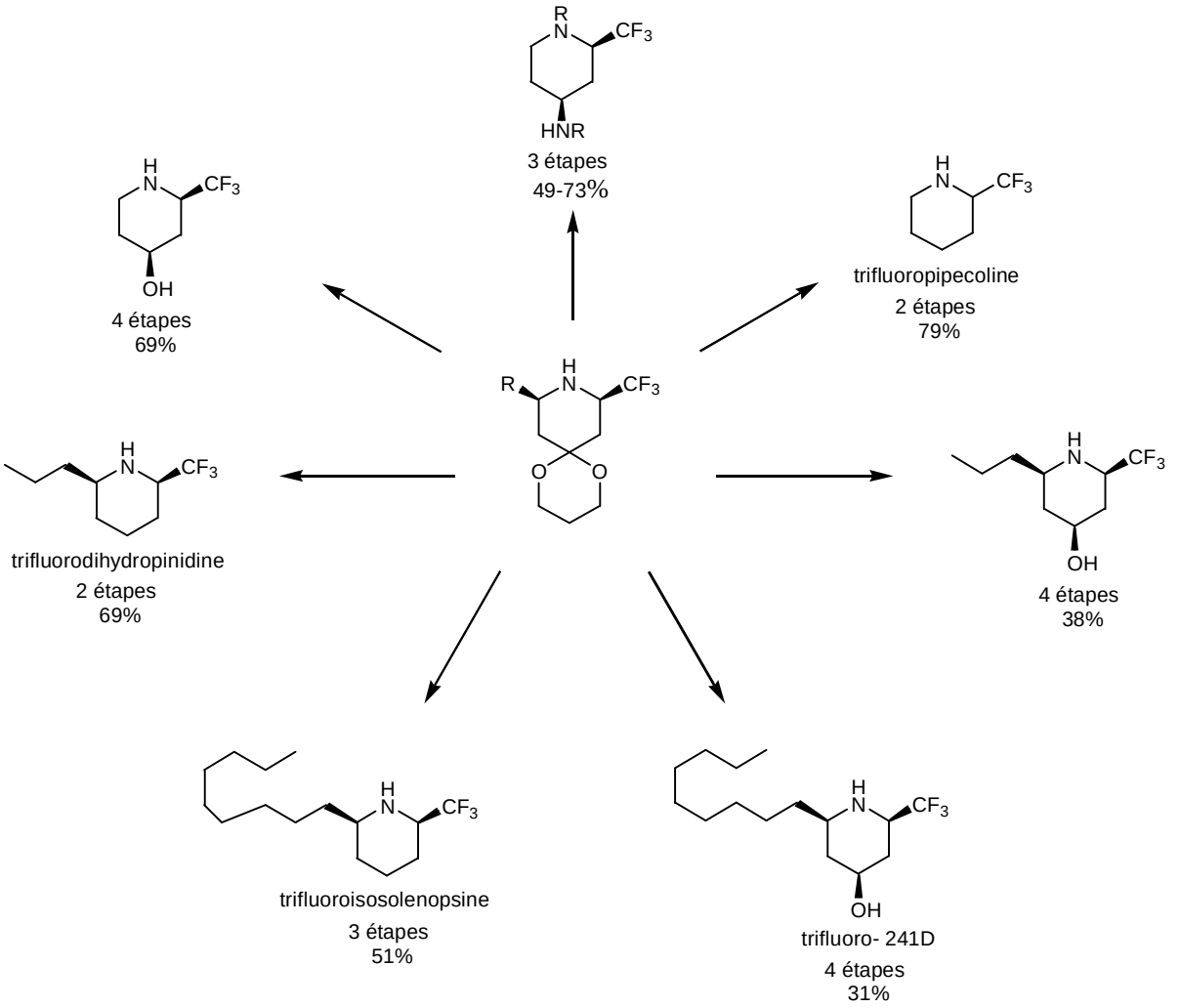
Initially, we showed that this strategy "Mannich intra" opened a simple and highly stereoselective access to new *cis*-2,6-disubstituted Tfm-piperidines, starting from a hemi-acetal of the fluoral or, and in a much more general way, from a preformed trifluoromethyl aminoketal (diagram 56).



R = alkyl, alkenyl, aryl
isolated yield : upto 78%
ed upto 95%

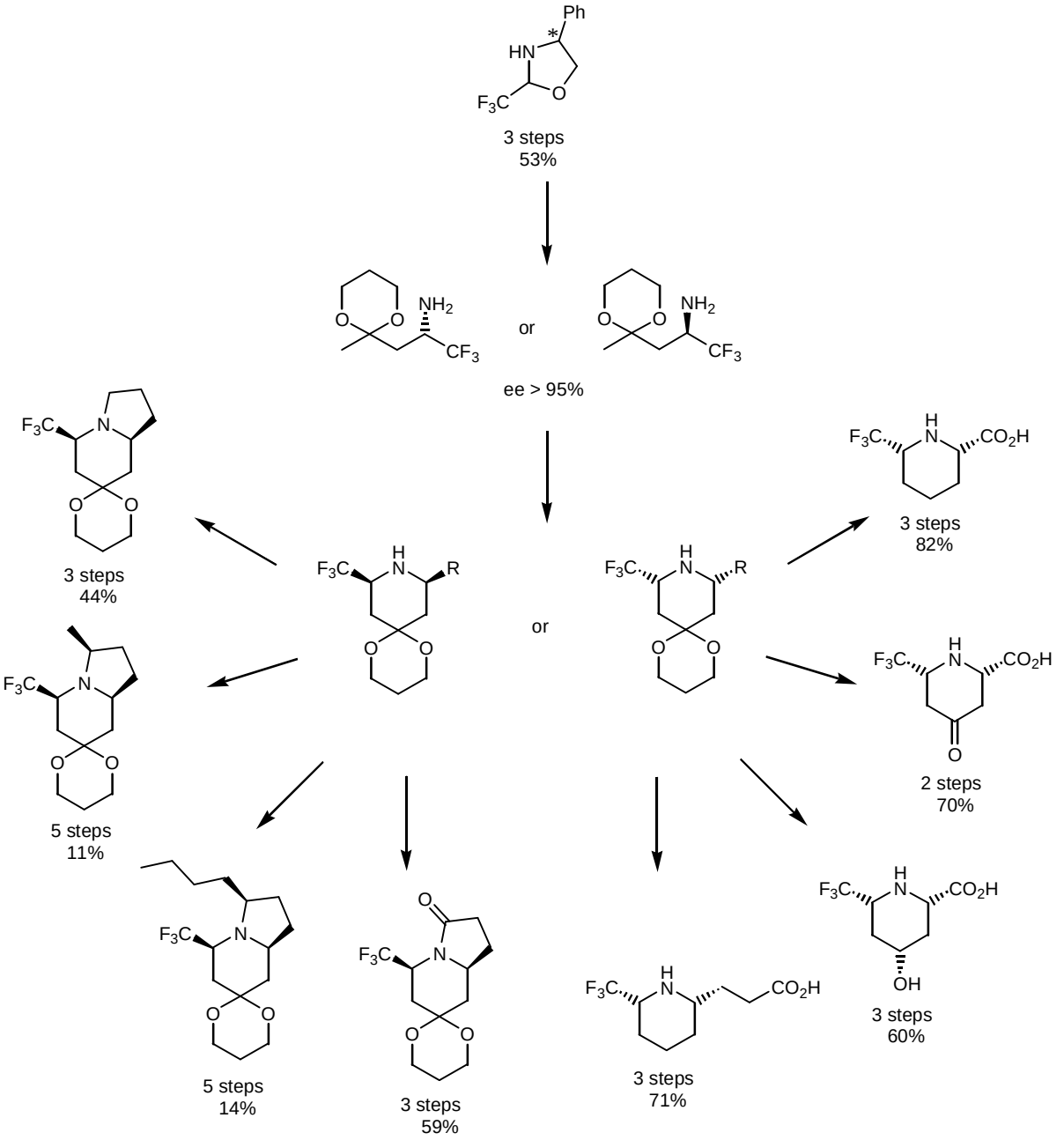
Scheme 56. Diastereoselective synthesis of Tfm-piperidines by intramolecular Mannich reaction.

The validation of this methodological work carried out in racemic series was ensured by the preparation of an original family of functionalized fluorinated piperidines, with the total synthesis of five trifluoro analogues of alkaloids including four original ones (scheme 57).



Scheme 57.

These very promising results quickly led us to think of their extension in asymmetric synthesis. Thus we could propose a concise and efficient synthesis of required fluorinated β-aminoketals, lying on the opening, by means of an enoxysilane, of an oxazolidine formed from phenylglycinol and a synthetic equivalent of fluoral. This highly diastereoselective approach inspired from recent work of Brigaud and *coll*., gave an access to a chiron having an excellent enantiomeric purity (scheme 58).



Scheme 58.

The intramolecular Mannich reaction of the latter, carried out in the presence of functionalized aldehydes, then provided corresponding trifluoromethylated piperidines, without loss of chiral information.

The interest of this new method of construction of such heterocycles was then illustrated by:

- the first enantioselective synthesis of trifluoromethylated pipecolic acids,

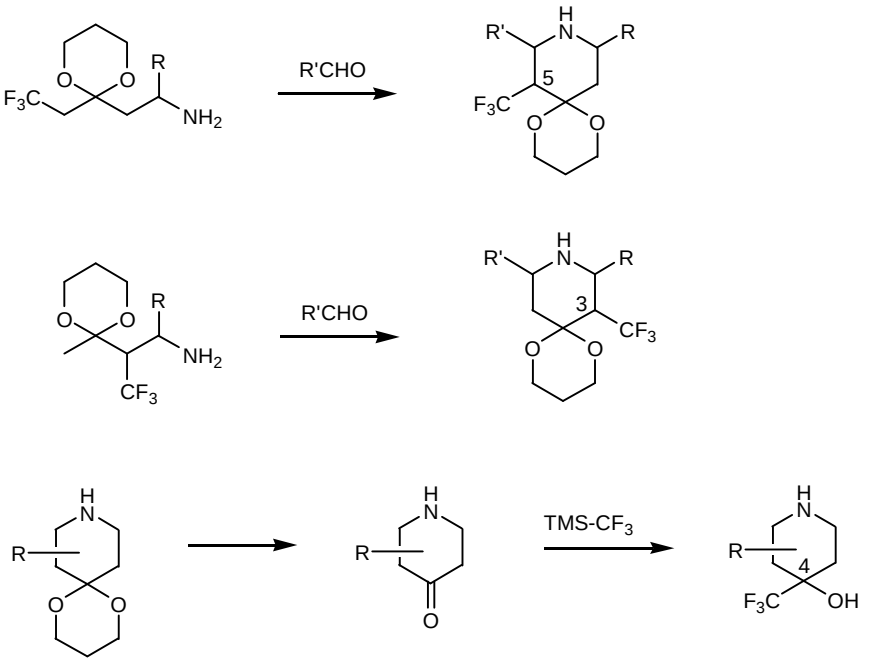
- the first enantioselective synthesis of an analogue of the GABA containing a Tfm-piperidine,

but also by the enantioselective synthesis of N-hetero-polycyclic skeletons of type Tfm-indolizidine or Tfm-indolizidinone, compounds rarely described..

With all the results summarized in this thesis, we can estimate that our initial objective of development of an access towards a selective and general route to trifluoromethylated piperidines, was achieved.

Adaptation to fluoro-organics of a well-known reaction developed at the Laboratory in “conventional” series, the suggested method may does not present an extremely innovative character. We hope nevertheless we could convince the examiner and the reader that it could now be regarded as a new tool, simple but relevant, allowing the asymmetric construction of quantities of new trifluoromethylated saturated aza-heterocycles.

Several perspectives of this work can be imagined. With regard to the “synthesis” aspects first of all, if we concentrated our efforts on the preparation of piperidines possessing trifluoromethyl group at position C-2 or C-6, the direct access according to the same strategy to their analogues carrying this group at C-3 or C-5 position seems completely possible (scheme 59).



Scheme 59.

This will require the effective synthesis of new ω or β-trifluoromethylated aminoketals (scheme 59), but this problem does not appear insurmountable.

In the same way, intramolecular Mannich reaction leading to 4-piperidinones, simple treatment of these latter by a nucleophilic trifluoromethylation reagent such that of Ruppert reagent, should readily provide the corresponding original 4-Tfm-piperidines (scheme 59).

Lastly, having a well developped tool of synthesis and an important collection of Tfm-piperidines, it appears essential for us to evaluate their intrinsic biological activities, which remains unknown. The determination of the targets and the realization of the tests of activity will can not be done without the collaboration of specialists of the field.

Possible positive biological response would then give certainly other prospects, more applied, of this work of thesis of doctorate.

EXPERIMENTAL PART

General remarks

Solvents were distilled prior to use. Other reagents were used as received. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotatory evaporator.

Thin layer chromatography were performed on TLC pre-coated aluminium backed silica plates Kieselgel 60 F_{254} (Merck) or glass backed silica Duracil 25 UV_{254} (Macherey nagel). Spots were visualized using UV light (254 nm) before using an ethanolic solution of phosphomolybdic acid (heating).

Purifications by column chromatography were carried out on silica gel (70-230 mesh).

Purifications on resin were carried out on an ion-exchange resin Dowex 50WX8-100 (Aldrich), regenerated with a solution of 1N HCl and washed with distilled water.

Melting points were measured by a Reichert plate-heating microscope.

Optical rotations were measured on a Jasco DIP-370 polarimeter at the wavelength of sodium D ray (λ = 589 nm).

The Infra-Red spectra were recorded on a Perkin Elmer Paragon 500 spectrophotometer in the form of film in between NaCl plates (liquids), or in the form of pellets of KBr (solids). The characteristic band positions are expressed in cm^{-1}.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometer at 400.13, 100.61 and 376.50 MHz respectively. Chemical shifts δ are reported in ppm relative to solvent residual signals (^{1}H and ^{13}C) or to hexafluorobenzene (^{19}F, δ = -164.9 ppm). The coupling constants J are given in Hertz (Hz). The abbreviations used for signal descriptions are as:

- s : singlet
- br s : broad singlet
- d : doublet
- t : triplet
- q : quartet
- Q : quintet
- m : multiplet
- dd: doublet of doublets
- dt: doublet of triplets
- dq : doublet of quartets
- tt : triplet of triplets
- ddd : doublet of doublets of doublets
- ax : axial
- eq : equatorial

Electron Impact Mass Spectra (EI-MS) were obtained on a spectrometer Hewlett Packard 5989B at 70 eV.

High Resolution Electro-Spray Ionisation Mass Spectra (HR-ESI-MS) were obtained from the “Centre Régional de Mesures Physiques de l'Université Blaise Pascal (Clermont II)”.

GC/MS analysis conditions used for diastereomeric excess determination were as follows; column: UB 1701 (14% cyanopropylphenyl)-methylpolysiloxane; injector temperature : 250°C ; oven temperature : 50°C for 2min then heating 50°C/min until 290°C.

Numbers placed in figures refer to NMR attributions, and were given independantly from IUPAC nomenclature.

General procedures

Intramolecular Mannich-type cyclization with amines

To a stirred solution of amine **19** or **105** (1 mmol) in dichloromethane (10 mL) was added $MgSO_4$ (*ca*. 1 g), followed by the aldehyde (1.1 mmol) then a catalytic amount of *p*-TsOH. The resulting mixture was heated at gentle reflux until complete disappearance (TLC monitoring) of the amine (1-4h), then cooled to room temperature and transferred to a solution of dry *p*-TsOH (2 mmol) in toluene (40 mL). The resulting mixture was heated (70-110°C) during 3-12h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added and the keto-protected piperidone was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-cyclohexane as eluent.

Dithioketalization

To a stirred solution of keto-protected piperidone (1 mmol) in dichloromethane (10 mL) was added dropwise, at room temperature, 1,2-ethanedithiol (5 mmol) then $BF_3.Et_2O$ (5 mmol). The resulting solution was refluxed until complete disappearance (TLC monitoring) of the starting material, then cooled to room temperature and treated with an excess of 2M aqueous NaOH. The layers were separated, and the aqueous phase was extracted (3 × 30 mL) with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by column chromatography using ethyl acetate-cyclohexane as eluent.

Reduction with W2 Raney nickel

To a stirred solution of dithioketal (100 mg) in absolute ethanol (5 mL), was added freshly prepared W2 Raney nickel[42] (*ca* 1.0 g). The resulting suspension was heated at reflux for 30 min then cooled to room temperature. The solution was filtered through Celite®,

washed with ethanol and H_2O. Concentrated HCl (1 mL) was then added to the filtrate. Evaporation of the solvent afforded the attempted piperidine hydrochloride salt.

Reductive amination of piperidone.

To a stirred solution of piperidone **93** (301 mg, 1 mmol) and amine (1 mmol) in CH_2Cl_2 (4 mL), was added sodium triacetoxyborohydride (300 mg, 1.4 mmol) then AcOH (60 µL, 1 mmol). The resulting solution was stirred at room temperature until completion of the reaction (TLC or GC analysis). The reaction was quenched by addition of 1N aqueous NaOH and the product extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated before purification of the product by column chromatography (ethyl acetate/cyclohexane).

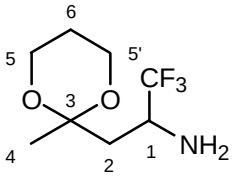
Saponification of esters.

To a stirred solution of ester **(**1 mmol) in methanol (15 mL) was added 0.3M aqueous NaOH (4 ml, 1.2 mmol). The resulting mixture was heated at reflux for 1h, then cooled to room temperature and treated with a solution of 1N HCl (2 mL). After evaporation of solvent, the acid was obtained in its sodium salt form, which was then passed through an ion exchange resin to afford free amino acid.

Preparation of ion-exchange resin.

A chromatography column was charged with an ion-exchange resin (Dowex® 50 w X 8-100) which was regenerated with a solution of 1N HCl and then washed with distilled water untill the obtention of a neutral pH. The sodium salt of the acid (dissolved in the minimum of distilled water) deposited on the resin and a sufficient volume of distilled water was passed through to eliminate the salts. After the salts were passed, a solution of ammonium hydroxide (10%) was used as eluent to get passed the aminoacid (at pH >7). The test tubes containing product were collected and concentrated under reduced pressure to afford free amino acid.

(±)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-amine 19.



To a solution of phthalimido-compound **(±)-104** (5.3 g, 15.5 mmol) in methanol (150 mL) was added hydrazine monohydrate (3.7 mL, 77 mmol). The resulting mixture was heated at reflux for 3h, then was allowed to cool to room temperature and cautiously concentrated under reduced pressure. The residue, diluted with dichloromethane (100 mL), was then treated with a 2M aqueous KOH solution (80 mL; vigorous stirring for 30 min.). The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. Amine **(±)-19** was obtained as a pale yellow liquid and was pure enough to be used without further purification. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) afforded pure amine **(±)-19 (**2.99 g, yield : 91%) as a colorless liquid.

R_f : 0.15 (ethyl acetate/cyclohexane = 1/2).

IR (neat) σ (cm^{-1}): 3402 (NH) ; 3338 (NH) ; 2973 ; 2877 ; 1617 ; 137 6; 1246 ; 1152 ; 1108 ; 1081 (C-O) ; 966 ; 804.

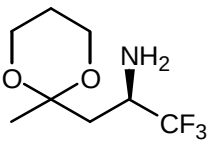
^{1}H NMR ($CDCl_3$) δ : 4.00 (m, 2H, H-5 and H-5') ; 3.85 (m, 2H, H-5 and H-5') ; 3.76 (m, 1H, H-1) ; 2.11 (br s, 2H, NH_2) ; 1.98 (dd, 1H, J = 14.5 and 1.5 Hz, H-2) ; 1.92 (m, 1H, H-6) ; 1.79 (dd, 1H, J = 14.5 and 10 Hz, H-2) ; 1.49 (s, 3H, Me) ; 1.30 (m, 1H, H-6).

^{13}C NMR ($CDCl_3$) δ : 126.5 (q, J_{C-F} = 280 Hz, CF_3) ; 98.2 (C-3) ; 59.7 (C-5) ; 59.6 (C-5') ; 49.6 (q, J_{C-F} = 29 Hz, C-1) ; 40.3 (C-2) ; 25.2 (C-6) ; 19.5 (C-4).

EI-MS (70eV) m/z : 213 (M^+, 1) ; 198 (40) ; <u>101</u> (100) ; 73 (40) ; 43 (90).

HR-ESI-MS calculated for $C_8H_{15}F_3NO_2$ $(M+H)^+$: 214.1055, found 214.1050.

(*R*)-(+)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-amine 19.



Method A :

In an hydrogenation vessel (Parr apparatus) was placed a solution of diastereoisomer (2*R*)-(+) **135** (2.20g, 6.94 mmol) in methanol (80 mL), then was added 20% Pd $(OH)_2$/C (500 mg). The mixture was stirred at room temperature under hydrogen pressure (50 Psi) for 3h, then was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford very clean amine (*S*)-(+) **19** (1.29 g, yield: 95%) as a pale yellow liquid.

$[\alpha]_D^{25}$ = +16.0 (c 1.30, $CHCl_3$).

Note : other analytical data are identical to those given for the racemic form **(±)-19** (*vide supra*).

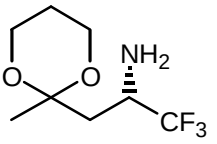
Method B :

Following the same procedure but starting from amino-alcohol (2*R*)-**142**, trifluoromethyl amine (*R*)-(+)-**19** was obtained in 80 % yield, after silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3).

$[\alpha]_D^{25}$ = +16.1 (c 1.22, $CHCl_3$).

Note : other analytical data are identical to those given for the racemic form **(±)-19** (*vide supra*).

(*S*)-(-)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-amine 19.

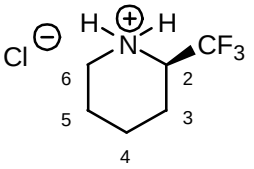


In an hydrogenation vessel (Parr apparatus) was placed a solution of diastereoisomer (2*S*)-(-)-**134** (2.20g, 6.94 mmol) in methanol (80 mL), then was added 20% Pd $(OH)_2$/C (500 mg). The mixture was stirred at room temperature under hydrogen pressure (50 Psi) for 3h, then was filtered through celite®. The filtrate was concentrated under reduced pressure to afford very clean amine (*S*)-(-) **19** (1.30g, yield : 95%) as a pale yellow liquid.

$[\alpha]_D^{25}$ = -16.5 (c 1.15, $CHCl_3$).

Note : other analytical data are identical to those given for the racemic form **(±)-19**(*vide supra*).

(±)-2-(Trifluoromethyl)piperidine (trifluoropipecoline) **24**·HCl salt.



Following the hydrogenolysis with Raney nickel general procedure, treatment of dithioketal **(±)-91** (100 mg, 0.41 mmol) afforded, trifluoropipecoline **(±)-24** hydrochloride salt (70 mg, yield : 90%).

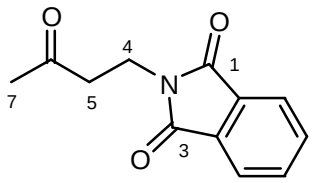
M.p. : 218°C (dec.), lit.[36] 220°C (dec.).

^{1}H NMR (D_2O) δ : 4.02 (m, 1H, H-2) ; 3.50 (m, 1H, H-6eq) ; 3.07 (td, 1H, J = 13 and 3.5 Hz, H-6ax) ; 2.15 (m, 1H, H-5eq) ; 2.08-1.90 (m ,2H) ; 1.80-1.55 (m, 3H).

EI-MS (70eV) (free base) m/z: 153 (M^+, 8) ; 152 (7) ; 84 (100) ; 56 (20).

Note: Data are identical with those already reported.[36]

2-(3-Oxobutyl)isoindoline-1,3-dione 78.



To a stirred solution of methyl vinyl ketone (10.4 mL, 128 mmol) in ethyl acetate (150 mL) was added phthalimide (15.0 g, 102 mmol) and 3 mL of a 40% solution of benzyl trimethyl ammonium hydroxyde (Triton B®) in methanol. The resulting solution was refluxed for 3h, then cooled to room temperature and the solvent was eliminated under reduced pressure. Recrystallisation from ethanol afforded pure phthalimido compound **78** (19.9 g, yield : 90%) as a white solid.

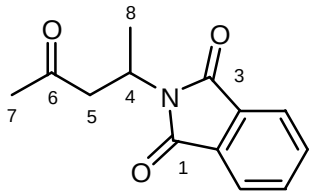
M.p : 110°C. (Lit.[79] 110-112°C).

R_f : 0.45 (ethyl acetate/cyclohexane = 1/2).

^{1}H NMR ($CDCl_3$) δ : 7.65-7.85 (m, 4H, H-Ar) ; 3.93 (t, J = 8 Hz, 2H, H-4) ; 2.87 (t, J = 8 Hz, 2H, H-5) ; 2.15 (s, 3H, H-7).

^{13}C NMR ($CDCl_3$) δ : 205.8 (C=O) ; 168.1 (C-1 and C-3) ; 134.0 (2C*ipso*) ; 123.3 (C-Ar) ; 41.6 (C-4) ; 33.0 (C-5) ; 29.4 (Me).

(±)-2-(4-Oxopentan-2-yl)isoindoline-1,3-dione 79.



To a stirred solution of 3-penten-2-one (12.0 mL, 142 mmol) in ethyl acetate (250 mL) was added phthalimide (17.6 g, 120 mmol) and 3 mL of a 40% methanolic solution of Triton B®. The resulting mixture was refluxed for 3h, then cooled to room temperature and the solvent was eliminated under reduced pressure. Recrystallisation from ethanol afforded pure phthalimido compound **(±)-79** (14.6 g, yield : 67%) as a white solid.

M.p : 60-62 °C.
R_f : 0.45 (ethyl acetate/cyclohexane = 1/2).

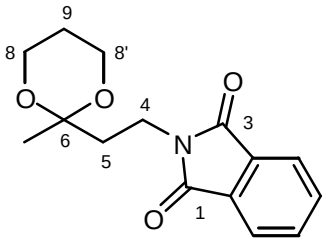
IR (KBr) σ (cm^{-1}) : 1772 (C=O, phthal) ; 1700 (C=O) ; 1608 (C=C) ; 1467 ; 1371.

^{1}H NMR ($CDCl_3$) δ : 7.77 (dd, J = 6 and 3 Hz, 2H, H-Ar) ; 7.66 (dd, J = 6 and 3 Hz, 2H, H-Ar) ; 4.80 (m, H-4) ; 3.28 (dd, J = 18 and 8 Hz, 1H, H-5) ; 3.02 (dd, J = 18 and 6 Hz, 1H, H-5) ; 2.11 (s, 3H, H-7) ; 1.41 (d, J = 7 Hz, 3H, H-8).

^{13}C NMR ($CDCl_3$) δ : 205.8 (C-6) ; 168.2 (C-1 and C-3) ; 133.9 (C-Ar) ; 131.9 (C-Ar) ; 123.2, (C-Ar) ; 46.7 (C-4) ; 42.5 (C-5) ; 30.2 (C-7) ; 18.8 (C-8).

EI-MS (70eV) m/z : 231 (M^+, 25) ; 188 (50) ; 174 (100) ; 147 (25) ; 130 (50) ; 76 (30) ; 43 (40).

2-[2-(2-Methyl-1,3-dioxan-2-yl)ethyl]isoindoline-1,3-dione 80.



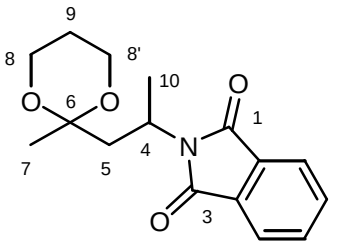
In a flask fitted with a Dean-Stark apparatus, was added to a solution of **78** (10.5 g, 48.6 mmol) in toluene (100 mL), propane-1,3-diol (7 mL, 97.1 mmol). The resulting mixture was heated at reflux for 3h, then was allowed to cool to room temperature and treated with a saturated $NaHCO_3$ solution (20 mL). The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Recrystallisation from EtOH, afforded pure phthalimido-compound **(±)-80** (11.4 g, yield : 85%) as a white solid.

M.p : 69-70°C.

^{1}H NMR ($CDCl_3$) δ : 7.95 (m, 2H, H-Ar) ; 7.70 (m, 2H, H-Ar) ; 3.92-3.82 (m, 6H, H-4, H-8 and H-8') ; 2.11 (t, J = 6 Hz, 2H, H-5) ; 1.76 (m, 1H, H-9) ; 1.61 (m, 1H, H-9) ; 1.45 (s, 3H, Me).

^{13}C NMR ($CDCl_3$) δ : 168.4 (C-1 and C-3) ; 133.0 (C-Ar) ; 123.5 (C-Ar) ; 98.1 (C-6) ; 59.8 (C-8) ; 59.7 (C-8') ; 35.6 (C-4) ; 33.3 (C-5) ; 25.2 (C-9) ; 21.7 (Me).

(±)-2-[1-(2-Methyl-1,3-dioxan-2-yl)-propan-2-yl]isoindoline-1,3-dione 81.



In a flask fitted with a Dean-Stark apparatus, was added to a solution of **(±)-79** (10.00 g, 43.3 mmol) in toluene (200 mL), propane-1,3-diol (3.79 mL, 49.8 mmol) and *p*-TsOH (50 mg, 0.236 mmol). The resulting mixture was heated at reflux for 5h and was cooled to room temperature then concentrated *in vacuo*. The residue, diluted with 200 mL of ethyl acetate, was then treated with a saturated $NaHCO_3$ solution (50 mL). The two layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Recrystallisation from ethanol afforded pure phthalimido-compound **81** (8.46 g, yield : 81%) as a white solid.

M.p. 78-80 °C.

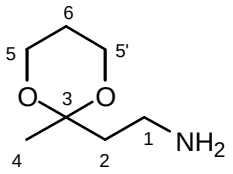
R_f : 0.51 (ethyl acetate/cyclohexane = 1/3).

IR (KBr) σ (cm^{-1}) : 2986 ; 1774 (C=O) ; 1702 (C=O) ; 1381 ; 1091 (C-O) ; 716.

^{1}H NMR ($CDCl_3$) δ : 7.80 (m, 2H, H-Ar) ; 7.68 (m, 2H, H-Ar) ; 4.79 (m, 1H, H-4) ; 3.86-3.69 (m, 3H, 2H-8 and 1H-8') ; 3.45 (m, 1H, H-8') ; 2.74 (dd, J = 15.5 and 10 Hz, 1H, H-5) ; 1.80 (dd, J = 15.5 and 3 Hz, 1H, H-5) ; 1.72 (m, 1H, H-9) ; 1.47 (d, J = 7 Hz, 3H, H-10) ; 1.36 (s, 3H, H-7) ; 1.28 (m, 1H, H-9).

^{13}C NMR ($CDCl_3$) δ: 168.7 (C=O) ; 133.5 (C-Ar) ; 132.3 (C-Ar) ; 122.9 (C-Ar) ; 98.4 (C-6) ; 59.8 (C-8) ; 59.7 (C-8') ; 42.5 (C-4) ; 42.2 (C-5) ; 25.0 (C-9) ; 20.0 (C-7) ; 19.9 (C-10).

2-(2-Methyl-1,3-dioxan-2-yl)ethanamine 82.



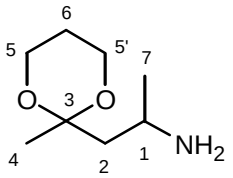
To a solution of **80** (5 g, 18 mmol) in methanol (50 mL) was added hydrazine monohydrate (9 mL, 178 mmol). The resulting mixture was heated at reflux for 4h and was allowed to cool to room temperature, then cautiously concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and 80 mL of a 2M aqueous KOH solution were added. After 15 min of stirring, the two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 30 mL) . The combined organic extracts were dried over Na_2SO_4, filtered and evaporated, affording amine **82 (**2.1 g, yield : 80%) as a yellow oil. The compound thus obtained, was enough pure to be directly engaged in the next step.

R_f : 0.10 (ethyl acetate).

^{1}H NMR ($CDCl_3$) δ : 4.90-4.55 (m, 4H, H-5 and H-5') ; 2.75 (m, 2H, H-1) ; 1.80 (br s, 2H, NH_2) ; 1.67 (m, 1H, H-6) ; 1.50 (m, 1H, H-6) ; 1.65 (s, 3H, H-4).

^{13}C NMR ($CDCl_3$) δ : 99.0 (C-3) ; 59.8 (C-5) ; 59.3 (C-5') ; 46.0 (C-1) ; 37.4 (C-2) ; 25.6 (C-6) ; 20.9 (C-4).

(±)-1-(2-Methyl-1,3-dioxan-2-yl)propan-2-amine 83.



To a solution of **(±)-81** (8.0 g, 27.7 mmol) in methanol (100 mL) was added hydrazine monohydrate (5.0 mL, 100 mmol). The resulting mixture was heated at reflux for 4h then allowed to cool to room temperature and cautiously concentrated under reduced pressure. The residue, diluted with dichloromethane (100 mL), was then treated with a 2M aqueous KOH solution (76 mL, 152 mmol ; vigorous stirring for 30min.). The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 70 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated, affording amine **(±)-83 (**5.8 g, yield : 95%) as a pale yellow liquid.

R_f : 0.10 (ethyl acetate).

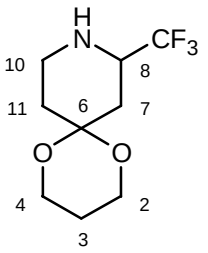
IR (neat) σ (cm^{-1}) : 3374 (NH) ; 2957 ; 2869 ; 1593 ; 1453 ; 1372 ; 1246 ; 1145 (C-O); 1100.

^{1}H NMR ($CDCl_3$) δ : 3.91 (m, 4H, H-5 and H-5') ; 3.25 (m, 1H, H-1) ; 2.08 (br s, 2H, NH_2) ; 1.88 (m, 1H, H-6), 1.80 (dd, J = 14 and 7 Hz, 1H, H-2) ; 1.63 (dd, J = 14 and 2 Hz, 1H, H-2) ; 1.54 (m, 1H, H-6) ; 1.45 (s, 3H, H-4) ; 1.10 (d, J = 7 Hz, 3H, H-7).

^{13}C NMR ($CDCl_3$) δ : 98.9 (C-3) ; 59.5 (C-5) ; 59.3 (C-5') ; 47.8 (C-1) ; 42.7 (C-2) ; 25.2 (C-6) ; 23.6 (C-7) ; 19.9 (C-4).

EI-MS (70 eV) m/z : 159 (M^+,1) ; 101 (100) ; 100 (55) ; 73 (25) ; 59 (40) ; 58 (35) ; 44 (98) ; 43 (80).

(±)-8-(Trifluoromethyl)-9-aza-1,5-dioxaspiro[5.5]undecane 86.



To a stirred solution of amine **(±)-82** (2.5 g, 17.2 mmol) in 25 mL of dichloromethane was added trifluoroacetaldehyde methylhemiacetal (3.4 g, 27.9 mmol) in CH_2Cl_2 (3 mL), $MgSO_4$ (*ca.* 1 g) and a catalytic amount of *para*-toluenesulfonic acid. The resulting mixture was heated at gentle reflux for 4h, cooled to room temperature then transferred into a solution of *p*-TsOH (4.5 g, 23.7 mmol; previously dried under Dean-Stark conditions) in 250 mL of toluene. The resulting mixture was heated at 80°C for 1.5h, then allowed to cool to room temperature, diluted with 100 mL of ethyl acetate before addition of saturated $NaHCO_3$ (35 mL). After separation, the aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were dried over Na_2SO_4, filtered then concentrated under reduced pressure to afford piperidine **(±)-86** as a pale brown oil (2.75 g, 71%) which solidified upon standing in freezer, and which could be engaged in the next step without purification. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/1) gave pure piperidine **(±)-86 (**1.90 mg, yield : 49%) as a pale yellow solid.

M.p. : 44-45°C.
R_f: : 0.60 (ethyl acetate).

IR (neat) σ (cm^{-1}) : 3300 (NH) ; 1283 ;1173 ; 1095 (C-O).

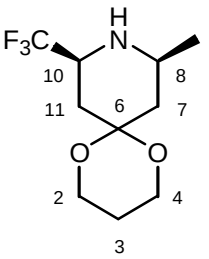
^{1}H NMR ($CDCl_3$) δ : 3.94 (t, 2H, J = 5 Hz, H-2) ; 3.88 (t, 2H, J = 5 Hz, H-4) ; 3.37 (m, 1H, H-8) ; 3.12 (m, 1H, H-10eq) ; 2.85 (td, 1H, J = 12 and 2 Hz, H-10ax) ; 2.44 (dt, 1H, J = 12 and 1.5 Hz, H-7eq) ; 2.30 (br s, 1H, NH) ; 2.28 (dq, 1H, J = 12 and 1.5 Hz, H-11eq) ; 1.75 (m, 2H, H-3) ; 1.50 (td, 1H, J = 12 and 2 Hz, H-11 ax) ; 1.44 (t, 1H, J = 12, H-7ax).

^{13}C NMR ($CDCl_3$) δ : 125.5 (q, J_{C-F} = 265 Hz, CF_3) ; 95.7 (C-6) ; 59.1 (C-2 and C-4) ; 55.0 (q, J_{C-F} = 29 Hz, C-8) ; 41.7 (C-10) ; 31.1 (C-3) ; 30.1 (C-11) ; 25.2 (C-7).

EI-MS (70eV) m/z : 225 (M^+, 10) ; 224 (12) ; 166 (90) ; <u>156</u> (100) ; 124 (60) ; 113 (55) ; 101 (80) ; 100 (80) ; 98 (90) ; 56 (70) ; 43 (60) .

HR-ESI-MS calculated for $C_9H_{15}F_3NO_2$ $(M+H)^+$: 226.1055, found 226.1060.

(±)-(8*S, 10*S**)-8-Methyl-10-(trifluoromethyl)-9-aza-1,5-dioxaspiro[5.5]undecane 89**.



To a stirred solution of amine **(±)-83** (800 mg, 5 mmol) in 25 mL of dichloromethane was added trifluoroacetaldehyde methylhemiacetal (987 mg, 7.6 mmol) in CH_2Cl_2 (3 mL), $MgSO_4$ (*ca.*1 g) and a catalytic amount of *para*-toluenesulfonic acid. The resulting mixture was heated at gentle reflux for 4h, cooled to room temperature then transferred into a solution of *p*-TsOH (2 g, 10.5 mmol; previously dried under Dean-Stark conditions) in 250 mL of toluene. The resulting mixture was heated at 80°C for 1.5h, then allowed to cool to room temperature, diluted with 100 mL of ethyl acetate before addition of saturated $NaHCO_3$ (35 mL). After separation, the aqueous layer was extracted with ethyl acetate (3 x 60 mL) and the combined organic extracts were dried over Na_2SO_4, filtered then concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/1) gave pure piperidine **(±)-89** (620 mg, yield : 51%) as a pale yellow oil.

R_f: : 0.65 (ethyl acetate).

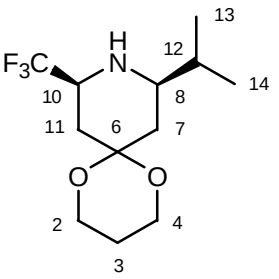
^{1}H NMR ($CDCl_3$) δ : 3.86 (t, 2H, J = 5 Hz, H-2) ; 3.83 (t, 2H, J = 5 Hz, H-4) ; 3.40 (m, 1H, H-10) ; 2.88 (m, 1H, H-8) ; 2.37 (dt, 1H, J = 12 and 1.5 Hz, H-11eq) ; 2.16 (dt, 1H, J = 12 and 2 Hz, H-7eq) ; 1.75 (br s, 1H, NH) ; 1.67 (m, 2H, H-3) ; 1.35 (t, 1H, J = 12 Hz, 1H, H-11 ax) ; 1.14 (t, 1H, J = 12 Hz, H-7ax) ; 1.13 (d, J = 7 Hz, 3H, Me).

^{13}C NMR ($CDCl_3$) δ : 125.5 (q, J_{C-F} = 280 Hz, CF_3) ; 96.0 (C-6) ; 59.1 (C-2 and C-4) ; 55.0 (q, J_{C-F} = 29 Hz, C-10) ; 47.9 (C-8) ; 41.7 (C-3) ; 32.0 (C-11) ; 25.5 (C-7) ; 22 .0 (Me).

EI-MS (70eV) m/z : 239 (M^+, 10) ; 224 (20) ; <u>180</u> (100) ; 170 (45) ; 138 (40) ; 124 (50) ; 101 (60) ; 70 (40) ; 43 (45).

HR-ESI-MS calculated for $C_{10}H_{17}F_3NO_2$ $(M+H)^+$: 240.1211, found 240.1217.

(±)-(8*R, 10*S**)-8-(1-Methylethyl)-10-(trifluoromethyl)-9-aza-1,5-dioxaspiro[5.5] undecane 90.**



To a stirred solution of amine **(±)-84** (500 mg, 2.68 mmol) in 20 mL of dichloromethane was added trifluoroacetaldehyde methylhemiacetal (516 mg, 4 mmol) in CH_2Cl_2 (3 mL), $MgSO_4$ (*ca.*1 g) and a catalytic amount of *para*-toluenesulfonic acid. The resulting mixture was heated at gentle reflux for 4h, cooled to room temperature then transferred into a solution of *p*-TsOH (1 g, 5.4 mmol; previously dried under Dean-Stark conditions) in 100 mL of toluene. The resulting mixture was heated at 80°C for 2h, then allowed to cool to room temperature, diluted with 100 mL of ethyl acetate before addition of saturated $NaHCO_3$ (20 mL). After separation, the aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered then concentrated under reduced pressure. Crude piperidine was purified by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/1) to give pure compound **(±)-90** (250 mg, yield : 34%, pale yellow oil).

R_f : 0.65 (ethyl acetate).

IR (neat) σ (cm^{-1}) : 3308 (NH) ; 2963 ; 2872 ; 1272 ; 1180 ; 1143 ; 1106 (C-O) ; 910 ; 734.

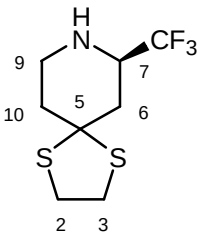
^{1}H NMR ($CDCl_3$) δ: 3.95 (m, 2H, H-2) ; 3.89 (m, 2H, H-4) ; 3.33 (m, 1H, H-10) ; 2.55 (m, 1H, H-8) ; 2.47 (dt, 1H, J = 12 and 2 Hz, H-11eq) ; 2.21 (dt, 1H, J = 12 and 2 Hz, H-7eq) ; 1.84-1.56 (m, 3H, H-3 and H-12) ; 1.48 (br s, 1H, NH) ; 1.36 (t, 1H, J = 12 Hz, H-11ax) ; 1.15 (t, 1H, J = 12 Hz, , H-7ax) ; 0.95 (d, 3H, J = 7 Hz , H-13) ; 0.92 (d, 3H, J = 7 Hz , H-14).

^{13}C NMR ($CDCl_3$) δ : 125.5 (q, J_{C-F} = 277 Hz, CF_3) ; 96.7 (C-6) ; 59.3 (C-2) ; 59.1 (C-4) ; 57.4 (C-8) ; 55.0 (q, J_{C-F} = 28 Hz, C-10) ; 36.1 (C-3) ; 32.6 (C-12) ; 31.7 (C-11) ; 25.3 (C-7) ; 18.7 (C-13) ; 18.3 (C-14).

EI-MS (70eV) m/z : 267 (M^+, 1) , 224 (50) ; <u>181</u> (100) ; 166 (20) ; 124 (20) ; 101 (25) ; 43 (15).

HR-ESI-MS calculated for $C_{12}H_{21}F_3NO_2$ $(M+H)^+$: 268.1524, found 268.1513.

(±)-7-(Trifluoromethyl)-8-aza-1,4-dithiaspiro[4.5]decane 91



Following the dithioketalization general procedure, treatment of piperidine **(±)-86** (225 mg, 1 mmol) furnished after silica-gel column chromatography (ethyl acetate/cyclohexane = 1/6) dithioketal **(±)-91** (214 mg, yield : 83%) as a colorless oil.

R_f : 0.68 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3308 (NH) ; 1277 ; 1162 ; 1133 ; 1097.

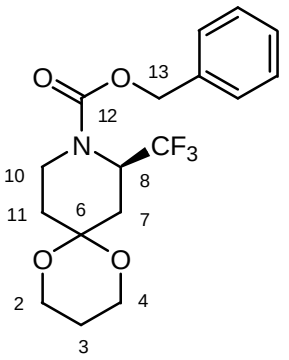
^{1}H NMR ($CDCl_3$) δ : 3.36 (m, 5H, H-2, H-3 and H-7) ; 3.20 (dt, 1H, J = 12 and 3 Hz, H-9eq) 2.87 (m, 1H, H-9ax) ; 2.24 (dt, 1H, J = 12 and 1.5 Hz, H-10eq) ; 2.09 (m, 2H, H-6eq and H-10ax) ; 2.00 (dd, 1H, J = 11.5 and 11 Hz, H-6ax) ; 1.67 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) δ : 125.3 (q, J_{C-F} = 279 Hz, CF_3) ; 65.0 (C-5) ; 57.4 (q, J_{C-F} = 29 Hz, C-7); 45.2 (C-9) ; 41.5 (C-2) ; 41.45 (C-3) ; 39.0 (C-6) ; 38.0 (C-10).

EI-MS (70eV) m/z : 243 (M^+, 15) ; 182 (20) ; <u>150</u> (100) ; 124 (10) ; 110 (12).

HR-ESI-MS calculated for $C_8H_{13}F_3NS_2$ $(M+H)^+$: 244.0442, found 244.0450.

(±)-Benzyl [8-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-9-yl]carboxylate 92.



To a stirred solution of piperidine **(±)-86** (1.0 g, 4.4 mmol) in dichloromethane (20 mL) was added 20 mL of a 0,44M sodium carbonate aqueous solution then, at 0°C, benzylchloroformate (1.3 mL, 8.8 mmol). The resulting mixture was stirred overnight at room temperature before addition of 50 mL of dichloromethane. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. Purification by silica gel column chromatography (ethyl acetate/cyclohexane = 1/5) gave carbamate **(±)-92** (1.51 g, yield : 95%) as a white solid.

M.p. : 97-98°C.

R_f : 0.48 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 1698 (C=O) ; 1429 ; 1362 ; 1142 ; 1109.

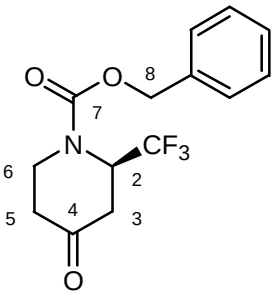
^{1}H NMR ($CDCl_3$) δ : 7.36 (m, 5H, H-Ar) ; 5.19 (d, 1H, J = 12 Hz, H-13) ; 5.16 (d, 1H, J = 12 Hz, H-13) ; 4.83 (br s, 1H, H-8) ; 4.15 (m, 1H, H-10eq) ; 3.88 (m, 4H, H-2 and H-4) ; 3.25 (td, 1H, J = 12 and 3 Hz, H-10ax) ; 2.48 (dd, 1H, J = 12 and 3 Hz, H-11eq) ; 2.10-1.60 (m, 5H, H-11ax, 2H-7, and 2H-3).

^{13}C NMR ($CDCl_3$) δ : 155.5 (C-12) ; 136.1 (C*ipso*) ; 128.5 (C-Ar) ; 128.1 (C-Ar) ; 127.8 (C-Ar) ; 125.4 (q, J_{C-F} = 285 Hz, CF_3) ; 95.2 (C-6) ; 67.8 (C-13) ; 59.5 (C-2 and C-4) ; 51.6 (q, J_{C-F} = 32 Hz, C-8) ; 38.2 (C-3) ; 25.1 (C-11 and C-7).

EI-MS (70eV) m/z : 359 (M^+, 5) ; 268 (30) ; 248 (32) ; 224 (30) ; 166 (20) ; 91 (100).

HR-ESI-MS calculated for $C_{17}H_{20}F_3NNaO_4$ $(M+Na)^+$: 382.1242, found 382.1247.

(±)-Benzyl 4-oxo-2-(trifluoromethyl)piperidin-1-yl carboxylate 93.



To a stirred solution of piperidine (±)-**92** (1.0 g, 2.8 mmol) in dichloromethane (10 mL), was added 6 mL of a 50% trifluoroacetic acid aqueous solution. The resulting mixture was kept under vigorous stirring for 3 days then neutralized by adding 4N aqueous NaOH (8 mL). The deprotected product was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/5) furnished piperidone (±)-**93** (796 mg, yield : 95%) as a white solid.

M.p. : 67-68°C.

R_f : 0.62 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 1713 (C=O) ; 1423 ; 1271 ; 1169 ; 1135.

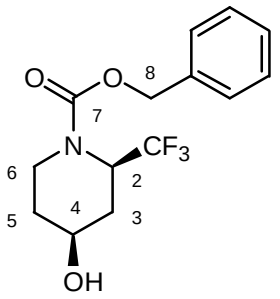
^{1}H NMR ($CDCl_3$, low resolution spectrum due to the coexistence of carbamate rotamers) δ : 7.36 (m, 5H, H-Ar) ; 5.40-5.05 (m, 3H, H-2 and 2H-8) ; 4.47 (m 1H) ; 3.45 (m, 1H, H-6ax) ; 2.69 (m, 2H) ; 2.50 (m, 2H).

^{13}C NMR ($CDCl_3$) δ : 203.5 (C-4) ; 155.4 (C-7) ; 135.4 (C*ipso*) ; 128.6 (C-Ar) ; 128.5 (C-Ar) 128.1 (C-Ar) ; 125.0 (q, J_{C-F} = 267 Hz, CF_3) ; 68.2 (C-8) ; 53.3 (q, J_{C-F} = 32 Hz, C-2) ; 40.1 (C-6) ; 39.3 (C-3) ; 37.7 (C-5).

EI-MS (70eV) m/z : 301 (M^+, 15) ; 210 (15) ; 166 (10) ; 91 (100) ; 65 (17).

HR-ESI-MS calculated for $C_{14}H_{14}F_3NNaO_3$ $(M+Na)^+$: 324.0823, found 324.0828.

(±)-Benzyl [(2*R, 4*S**)- 4-hydroxy-oxy-2-(trifluoromethyl)piperidin-1-yl]carboxylate 94.**



To a stirred solution of piperidone **(±)-93** (301 mg, 1 mmol) in methanol (8 mL) was added at –10°C sodium borohydride (76 mg, 2 mmol). The resulting mixture was stirred for 1h before adding 3 mL of saturated NH_4Cl, then warmed to room temperature. The methanol was eliminated under reduced pressure and the piperidinol extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvent followed by column chromatography (ethyl acetate/cyclohexane = 1/3) gave piperidinol **(±)-94** (267 mg, yield : 88%) as a colorless oil.

R_f : 0.20 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 3457 (OH) ; 1710 (C=O) ; 1424 ; 1283 ; 1141 ; 1051 (C-O).

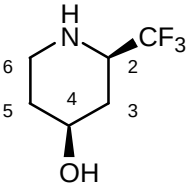
^{1}H NMR ($CDCl_3$, low resolution spectrum due to the coexistence of carbamate rotamers) δ : 7.35 (m, 5H, H-Ar) ; 5.19 (d, 1H, J = 12 Hz, H-8) ; 5.15 (d, 1H, J = 12 Hz, H-8) ; 4.82 (m, 1H, H-2) ; 4.11 (m, 2H, H-6eq and H-4) ; 3.40 (m, 1H, H-6ax) ; 2.06 (m, 2H) ; 1.77 (m, 2H) ; 1.60 (br s, 1H, OH).

^{13}C NMR ($CDCl_3$) δ : 155.5 (C-7) ; 135.9 (*Cipso*) ; 128.5 (C-Ar) ; 128.2 (C-Ar) ; 127.9 (C-Ar) ; 125.5 (q, J_{C-F} = 285 Hz, CF_3) ; 68.0 (C-8) ; 62.0 (C-4) ; 50.4 (q, J_{C-F} = 31 Hz, C-2) ; 35.7 (C-6) ; 31.2 (C-5) ; 29.1 (C-3).

EI-MS (70eV) m/z : 303 (M^+, 5) ; 212 (10) ; 190 (15) ; 91 (100) ; 65 (10).

HR-ESI-MS calculated for $C_{14}H_{16}F_3NNaO_3$ $(M+Na)^+$: 326.0980, found 326.0996.

(±)-(2*R, 4*S**)-2-(Trifluoromethyl)piperidin-4-ol 95**.



To a stirred solution of compound **(±)-94** (200 mg, 0.66 mmol) in methanol (10 mL) was added $Pd(OH)_2/C$ 20% (50 mg) and ammonium formate (208 mg, 3.30 mmol). The mixture was heated at 60°C for 2h. After cooling to room temperature, the solution was filtered through Celite®, and the filtrate was concentrated under reduced pressure to give a residue which was diluted with saturated aqueous $NaHCO_3$ (5 mL) before extraction with dichloromethane (5 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered. Evaporation of the solvent followed by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) gave piperidinol **(±)-95** (102 mg, yield: 92%) as a colorless oil.

R_f : 0.15 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 3279 (OH) ; 1273 ; 1182 ; 1070.

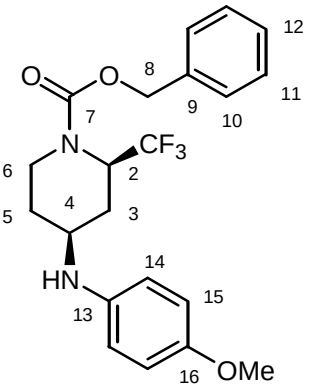
^{1}H NMR ($CDCl_3$) δ : 3.70 (m, 1H, H-4) ; 3.22 (dt, 1H, J = 12.5 and 1.5 Hz, H-6eq) ; 3.14 (m, 1H, H-2) ; 2.65 (td, 1H, J = 12 and 1.5 Hz, H-6ax) ; 2.17 (m, 1H, H-5eq) ; 1.98 (m, 1H, H-3eq) ; 1.70 (br s, 2H, OH and NH) ; 1.42 (qd, 1H, J = 12 and 3 Hz, H-5ax) ; 1.38 (q, 1H, J = 12 Hz, H-3ax).

^{13}C NMR ($CDCl_3$) δ : 124.8 (q, J_{C-F} = 279 Hz, CF_3) ; 67.6 (C-4) ; 56.9 (q, J_{C-F} = 29 Hz, C-2) 43.8 (C-6) ; 34.7 (C-5) ; 34.1 (C-3).

EI-MS (70eV) m/z : 169 (M^+, 5) ; 150 (15) ; 124 (20) ; 110 (30) ; <u>100</u> (100) ; 82 (50) ; 56 (50).

HR-ESI-MS calculated for $C_6H_{11}F_3NO$ $(M+H)^+$: 170.093, found 170.091.

(±)-Benzyl {(2*R, 4*S**)-4-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)piperidine-1-yl}carboxylate 97**.



Following the reductive amination general procedure, treatment of piperidone **(±)-93** (1.0 g, 3.3 mmol) by 4-methoxyaniline afforded, after silica-gel column chromatography (ethyl acetate/cyclohexane 1/3), 4-aminopiperidine **(±)-97** (1.17 g, yield : 85%) as a brown oil.

R_f : 0.55 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 3379 (NH) ; 1706 (C=O) ; 1513 ; 1422 ; 1270 ; 1234 ; 1150 ; 1036.

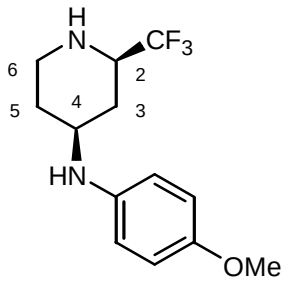
^{1}H NMR ($CDCl_3$, low resolution spectrum due to the coexistence of carbamate rotamers) δ : 7.37 (m, 5H, H-Ar) ; 6.80 (dd, 2H, J = 9 and 1.5 Hz, H-Ar) ; 6.57 (dd, 2H, J = 9 and 1.5, H-Ar) ; 5.21 (d, 2H, J = 14 Hz, H-8) ; 5.17 (d, 2H, J = 14 Hz, H-8) ; 4.70 (m, 1H,) ; 4.14 (m, 1H,) ; 3.75 (s, 3H) ; 3.54 (m, 1H,) ; 3.40 (br s, 1H, NH) ; 3.27 (m, 1H) ; 2.25 (m, 1H) ; 2.14 (m, 1H) ; 1.86 (m, 1H) ; 1.58 (m, 1H) .

^{13}C NMR ($CDCl_3$) δ : 155.7 (C-7) ; 152.5 (C-16) ; 135.9 (C-9) ; 128.5 (C-13) ; 128.2 (C-10) ; 127.9 (C-11 and C-12) ; 125.5 (q, J_{C-F} = 281 Hz, CF_3) ; 115.0 (C-14) ; 114.9 (C-15) ; 67.9 (C-8) 55.6 (OMe) ; 51.6 (q, J_{C-F} = 31 Hz, C-2) ; 45.2 (C-4) ; 37.2 (C-6) ; 29.1 (C-3) ; 26.1 (C-5).

EI-MS (70eV) m/z : 408 (M^+, 60) ; 273 (15) ; 134 (25) ; 91 (100) ; 65 (10) .

HR-ESI-MS calculated for $C_{21}H_{24}F_3N_2O_3$ $(M+H)^+$: 409.1739, found 409.1728.

(±)-(2*R, 4*S**)-4-[(4-Methoxyphenyl)amino]-2-trifluoromethylpiperidine 98**.



To a stirred solution of protected compound **(±)-97** (500 mg, 1.2 mmol) in methanol (20 mL) was added $Pd(OH)_2$/C 20% (100 mg) and ammonium formate (386 mg, 6.1 mmol). The mixture was heated at 60°C for 2h. After cooling to room temperature, the solution was filtered through Celite®, and the filtrate was concentrated under reduced pressure to give a residue which was diluted with saturated aqueous $NaHCO_3$ (8 mL). The two layers were seperated and aqueous phase extracted with dichloromethane (5 x 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered. Evaporation of the solvent followed by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) afforded compound **(±)-98** (235 mg, yield : 70%) as a dark red oil.

$\mathbf{R_f}$: 0.15 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}): 3333 (NH) ; 2953 ; 1518 ; 1228 ; 1138 ; 1036 ; 821.

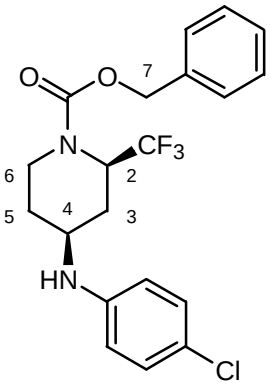
^{1}H NMR ($CDCl_3$) δ : 6.79 (m, 2H, H-Ar) ; 6.59 (m, 2H, H-Ar) ; 3.75 (s, 3H, Me) ; 3.25 (m, 3H, H-4, H-2 and H-6eq) ; 2.76 (td, 1H, J = 13 and 2.5 Hz, H-6ax) ; 2.40 (br s, 2H, NH) ; 2.30 (m, 1H, H-5eq) ; 2.09 (m, 1H, H-3eq) ; 1.29 (qd, 1H, J = 12.5 and 4 Hz, H-5ax) ; 1.21 (q, 1H, J = 11.5 Hz, H-3ax) .

^{13}C NMR ($CDCl_3$) δ : 152.4 (C*ipso*) ; 140.6 (C*ipso*) ; 125.3 (q, J_{C-F} = 280 Hz, CF_3) ; 115.2 (C-Ar) ; 114.9 (C-Ar) ; 57.5 (q, J_{C-F} = 29 Hz, C-2) ; 55.6 (OMe) ; 50.8 (C-4) ; 44.8 (C-6) ; 33.1 (C-5) ; 32.2 (C-3).

EI-MS (70eV) m/z : 274 (M^+, 100) ; 229 (10) ; 205 (10) ; 160 (15) ; 149 (30) ; 134 (40) ; 123 (50) ; 108 (25) ; 82 (30) ; 56 (15).

HR-ESI-MS calculated for $C_{13}H_{17}F_3N_2O$ $(M+H)^+$: 275.1371, found 275.1382.

(±)-Benzyl {(2*R, 4*S**)-4-[(4-chlorophenyl)amino]-2-(trifluoromethyl) piperidin-1-yl}carboxylate 99**.



Following the reductive amination general procedure, treatment of piperidone **(±)-93** (301 mg, 1 mmol) by 4-chloroaniline afforded after column chromatography on silica-gel (ethyl acetate/cyclohexane = 1/5) 4-aminopiperidine **(±)-99** (235 mg, yield : 60%) as a brown oil.

R_f : 0.60 (ethyl acetate/cyclohexane = 1/1).

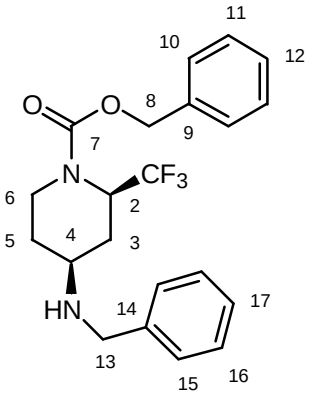
IR (neat) σ (cm^{-1}): 3383 (NH) ; 1704 (C=O) ; 1599 ; 1499 ; 1422 ; 1276 ; 1150 ; 1118 ; 817 ; 698.

^{1}H NMR ($CDCl_3$): low resolution spectrum due to the coexistence of carbamate rotamers) δ : 7.38 (m, 5H); 7.12 (m, 2H, H-Ar) ; 6.50 (m, 2H, H-Ar) ; 5.21 (d, 1H, J = 12.5 Hz, H-7) ; 5.18 (d, 1H, J = 12.5 Hz, H-7) ; 4.82 (m, 1H) ; 4.15 (m, 1H) ; 3.60 (m, 1H) ; 3.26 (m, 1H) ; 2.23 (m, 1H) ; 2.11 (m, 1H) ; 1.91 (m, 1H) ; 1.62 (m, 1H).

EI-MS (70eV) m/z : 414 (M^+, ^{37}Cl, 5) ; 412 (M^+, ^{35}Cl, 15) ; 277 (10) ; 140 (10) ; 91 (100) ; 65 (10) .

HR-ESI-MS calculated for $C_{20}H_{21}ClF_3N_2O_2$ $(M+H)^+$: 413.1244, found 413.1259.

(±)-Benzyl {(2*R, 4*S**)-4-[(4-benzyl)amino]-2-(trifluoromethyl) piperidin-1-yl}carboxylate 100**.



Following the reductive amination general procedure, treatment of piperidone **(±)-93** (301 mg, 1 mmol) by benzylamine afforded after silica-gel column chromatography (ethyl acetate/cyclohexane 1/3) compound **(±)-100 (**251 mg, yield : 64%) as a pale yellow oil.

R_f : 0.25 (ethyl acetate/cyclohexane = 1/1).

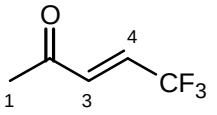
IR (neat) σ (cm^{-1}) : 3314 (NH) ; 1713 (C=O) ; 1422 ; 1274 ; 1151 ; 698.

^{1}H NMR ($CDCl_3$) δ : 7.32 (m, 10H, H-Ar) ; 5.18 (d, 1H, J = 12 Hz, H-8) ; 5.14 (d, 1H, J = 12 Hz, H-8) ; 4.61 (m, 1H, H-2) ; 4.06 (m, 1H, H-6) ; 3.82 (d, 1H, J = 12 Hz, H-13) ; 3.75 (d, 1H, J = 12 Hz, H-13) ; 3.27 (m, 1H, H-6) ; 2.83 (m, 1H, H-4) ; 2.08 (m, 2H, H-3eq and H-5eq) ; 1.81 (m, 1H, H-5ax) ; 1.47 (m, 1H, H-3ax) ; 1.33 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) δ : 155.8 (C-7) ; 139.9 (C*ipso*) ; 136.0 (C*ipso*) ; 128.5 (C-Ar) ; 128.4 (C-Ar) ; 128.1 (C-Ar) ; 127.9 (C-Ar) ; 127.8 (C-Ar) ; 127.0 (C-Ar) ; 125.5 (q, J_{C-F} = 284 Hz, CF_3) 67.9 (C-8) ; 52.0 (q, J_{C-F} = 31 Hz, C-2) ; 51.1 (C-13) ; 48.6 (C-4) ; 37.3 (C-6) ; 29.3 (C-3) ; 26.5 (C-5).

EI-MS (70eV) m/z : 392 (M^+, 1) ; 301 (20) ; 257 (15) ; 106 (15) ; 91 (100).

(*E*)-5,5,5-Trifluoropent-3-en-2-one 101.



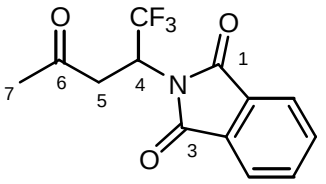
Sodium dithionite (32.0 g, 160 mmol) and sodium hydrogen carbonate (12.0 g, 144 mmol) were suspended in aqueous acetonitrile (1:1, 240 mL). The suspension was vigorously stirred and cooled to 10°C, then 2-methoxypropene (18.4 mL, 97%, 255 mmol) and $CF_3CHClBr$ (16.9 mL, 86 mmol) were added one by one. The cooling bath was removed and the reaction mixture, while stirring, was allowed to warm up slowly. At about 20°C a noticeable exothermic effect occurred, the temperature reached 28–30°C and most inorganic salts dissolved. Stirring was continued for 1h (altogether about 2h from the beginning of the reaction) during which time the temperature of the reaction mixture returned to ambient. Water (240 mL) was added and the reaction mixture was extracted with diethyl ether (240 mL), the organic layer was separated, washed with water (4×120 mL) and dried over Na_2SO_4. After filtration, triethylamine (24 mL, 17.2 mmol) was added to the etheral solution. A precipitate of $Et_3N{\cdot}HCl$ began to form almost immediately. The reaction mixture was left overnight and washed with water (100 mL) then with dilute hydrochloric acid (*ca*. 1%, 200 mL) followed by water until neutral. Organic layer was separated and dried over Na_2SO_4. Careful evaporation of the solvent gave enone **101** (18 g, yield : 80%) as a colourless liquid. This material was pure enough to be directly engaged in the next step. Careful distillation afforded 11.5 g (yield : 51%) of pure enone.

B.p. : 97°C (Lit[50]. : B.p. : 98-102°C).

^{1}H NMR ($CDCl_3$) δ : 6.69 (dq, J_{HH} = 16 Hz, $^4J_{HF}$ = 2 Hz, 1H, H-3) ; 6.58 (dq, J_{HH} = 16 Hz, $^3J_{HF}$ = 6 Hz, 1H, H-4) ; 2.37 (s, 3H, H-1).

Note: Data are identical with those already described.[50]

(±)-2-(1,1,1-Trifluoro-4-oxo-pentan-2-yl)isoindoline-1,3-dione 102.



To a stirred solution of enone **101** (8.0 g, 58 mmol) in ethyl acetate (230 mL) was added phthalimide (8.53 g, 58 mmol) and 2 mL of a 40% solution of Triton B® in methanol. The resulting mixture was heated at reflux for 5h, then cooled to room temperature and treated with 50 mL of a 1M aqueous NaOH solution. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford very cleanly 15.94 g (96%) of compound **(±)-102** as a pale yellow solid and that could be engaged directly in the next step. Recrystallisation from ethanol afforded pure phthalimido compound **(±)-102** (10.74 g, yield: 65%) as a white solid.

M.p: 100-101°C.

R_f: 0.35 (ethyl acetate/cyclohexane = 1/3).

IR (KBr) σ (cm^{-1}) : 2966 ; 1775 (C=O phtal) ; 1722 (C=O) ; 1386 ; 1284 ;1174 ; 1105 ; 729.

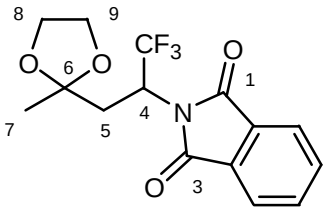
^{1}H NMR ($CDCl_3$) δ : 7.85 (m, 2H, H-Ar) ; 7.74 (m, 2H, H-Ar) ; 5.27 (m, 1H, H-4) ; 4.03 (dd, 1H, J = 19 and 11 Hz, H-5) ; 3.08 (dd, 1H, J = 19 and 4 Hz, H-5) ; 2.18 (s, 3H, Me).

^{13}C NMR ($CDCl_3$) δ : 202.8 (C-6) ; 167.1 (C-1 and C-3) ; 134.5 (C-Ar) ; 134.3 (C-Ar) ; 127.0 (q, J_{C-F} = 282 Hz, CF_3) ; 123.7 (C-Ar) ; 123.5 (C-Ar) ; 122.9 (2 C*ipso*) ; 47.8 (q, J_{C-F} = 33 Hz, C-4) ; 37.6 (C-7) ; 29.8 (C-5).

EI-MS (70eV) m/z : 285 (M^+, 5) ; 265 (80) ; 222 (50) ; 174 (90) ; 76 (50) ; 43 (100).

HR-ESI-MS calculated for $C_{13}H_{10}F_3NNaO_3$ $(M+Na)^+$: 308.0510, found 308.0516.

(±)-2-[1,1,1-Trifluoro-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-yl] isoindoline-1,3-dione 103.



In a flask fitted with a Dean-Stark apparatus, was added, to a solution of compound **(±)-102** (10.4 g, 36.5 mmol) in toluene (140 mL), ethane-1,2-diol (4.1 mL, 73 mmol) and *p*-TsOH (200 mg). The resulting mixture was heated at reflux for 4h and was then cooled to room temperature and concentrated under reduced pressure. The residue, diluted with 100 mL of ethyl acetate, was treated with 30 mL of a satured $NaHCO_3$ solution. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Simple washing of the solid residue with cold cyclohexane, afforded pure phthalimido-compound **(±)-103 (**9.60 g, yield : 80%) as a white solid.

M.p. : 94-95°C.

R_f : 0.60 (ethyl acetate/cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}) : 2980 ; 2894 ; 1774 (C=O) ; 1727 (C=O) ; 1382 ; 1289 ; 1186 ; 1119 ; 1079 ; 1067 (C-O) ; 1036 ; 909 ; 890 ; 735 ; 720.

^{1}H NMR ($CDCl_3$) δ : 7.86 (m, 2H, H-Ar) ; 7.74 (m, 2H, H-Ar) ; 5.03 (m, 1H, H-4) ; 3.88 (m, 2H, H-8 and H-9) ; 3.76 (m, 1H, H-8 or H-9) ; 3.65 (m, 1H, H-8 or H-9) ; 3.20 (dd, 1H, *J* = 15 and 11.5 Hz, H-5) ; 2.14 (dd, 1H, *J* = 15 and 1.5 Hz, H-5) ; 1.28 (s, 3H, Me).

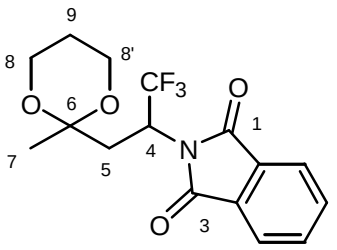
^{13}C NMR ($CDCl_3$) δ : 167.1 (C-1 and C-3) ; 134.5 (C-Ar) ; 134.1 (C-Ar) ; 132.0 (C*ipso*) ; 131.0 (C*ipso*) ; 124.4 (q, J_{C-F} = 232 Hz, CF_3) ; 123.6 (2 C-Ar) ; 108.1 (C-6) ; 64.6 (C-8) ; 64.3 (C-9) ; 48.2 (q, J_{C-F} = 33 Hz, C-4) ; 31.4 (C-5) ; 23.8 (C-7).

^{19}F NMR ($CDCl_3$) δ : -76.5.

EI-MS (70eV) m/z : 314 ($(M-Me)^+$, 25) ; 269 (15) ;167 (75) ; 123 (15) ; 87 (100) ; 43 (25).

HR-ESI-MS calculated for $C_{15}H_{14}F_3NNaO_4$ $(M+Na)^+$: 352.0773, found 352.0785.

(±)-2-[1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-yl]isoindoline-1,3-dione 104.



Starting from **(±)-102** (9.2 g, 32.4 mmol), 1,3-propanediol (4.7 mL, 64.8 mmol) and *p*-TsOH (200 mg), as described in the previous procedure, compound **(±)-104** (10.78 g, yield : 97%) was obtained as a white solid.

M.p: 124°C.

$\mathbf{R_f}$: 0.75 (ethyl acetate/cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}): 2959 ; 2888 ; 1778 (C=O) ; 1725 (C=O) ; 1383; 1290 ; 1247 ; 1186 ; 1118; 1086 (C-O) ; 1068 (C-O) ; 889 ; 729.

^{1}H NMR ($CDCl_3$) δ : 7.87 (m, 2H, H-Ar) ; 7.73 (2H, m, H-Ar) ; 5.35 (m, 1H, H-4) ; 3.91 (dt, 1H, J = 12 and 3 Hz, H-8) ; 3.71-4.00 (m, 2H, H-8 and H-8') ; 3.27 (m, 1H, H-8') ; 3.08 (dd, 1H, J = 15 and 11 Hz, H-5) ; 2.01 (dd, 1H, J = 15 and 1.5 Hz, H-5) ; 1.80 (m, 1H, H-9) ; 1.42 (s, 3H, Me) ; 1.19 (m, 1H, H-9).

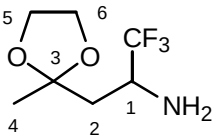
^{13}C NMR ($CDCl_3$) δ : 167.5 (C-1 and C-3) ; 134.2 (C-Ar) ; 134.0 (C-Ar) ; 132.2 (C*ipso*); 131.3 (C*ipso*) ; 124.7 (q, J_{C-F} = 282 Hz, CF_3) ; 123.5 (C-Ar) ; 123.4 (C-Ar) ; 97.6 (C-6) ; 60.0 (C-8) ; 59.9 (C-8') ; 47.7 (q, J_{C-F} = 33 Hz, C-4) ; 34.6 (C-5) ; 24.8 (C-9) ; 19.0 (C-7).

^{19}F NMR ($CDCl_3$) δ : -75.7

EI-MS (70eV) m/z : 328 ($(M-Me)^+$, 85) ; 181 (95) ; 123 (45) ; <u>101</u> (100) ; 43 (60).

HR-ESI-MS calculated for $C_{16}H_{16}F_3NNaO_4$ $(M+Na)^+$: 366.0929, found 366.0947.

(±)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-amine 105.



To a solution of phthalimido-compound **(±)-103** (6.2 g, 19 mmol) in methanol (100 mL) was added hydrazine monohydrate (4.60 mL, 95 mmol). The resulting mixture was heated at reflux for 3h, then was allowed to cool to room temperature and cautiously concentrated under reduced pressure. The residue, diluted with dichloromethane (100 mL), was then treated with a 2M aqueous KOH solution (76 mL, 152 mmol ; vigorous stirring for 30 min.). The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. Amine **(±)-105** was obtained as a pale yellow liquid and was pure enough to be used without further purification. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) afforded pure amine **(±)-105 (**3.21 g, yield : 85%) as a colorless liquid.

R_f : 0.10 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3405 (NH) ; 3340 (NH) ; 2988 ; 2892 ; 1618 ; 1381 ; 1307 ; 1249 ; 1219 ; 1148 ; 1112 ; 1045 (C-O) ; 949 ; 813.

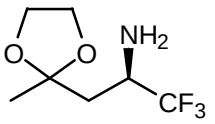
^{1}H NMR ($CDCl_3$) δ : 3.98 (m, 4H, H-5 and H-6) ; 3.50 (m, 1H, H-1) ; 2.05 (br d, 1H, J = 14.5 Hz, H-2) ; 1.63 (dd, 1H, J = 14.5 and 10 Hz, H-2) ; 1.65 (br s, 2H, NH_2) ; 1.38 (s, 3H, Me).

^{13}C NMR ($CDCl_3$) δ : 126.3 (q, J_{C-F} = 280 Hz, CF_3) ; 108.7 (C-3) ; 64.6 (C-5) ; 64.2 (C-6) ; 50.3 (q, J_{C-F} = 29 Hz, C-1) ; 38.1 (C-2) ; 24.0 (C-4).

EI-MS (70eV) m/z : 184 ($(M-Me)^+$, 20) ; 98 (25) ; 87 (100) ; 43 (70).

HR-ESI-MS calculated for $C_7H_{13}F_3NO_2(M+H)^+$: 200.0898, found 200.0903.

(*R*)-(+)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-amine 105.

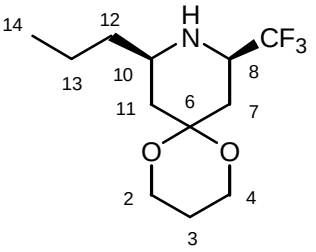


In an hydrogenation vessel (Parr apparatus) was placed a solution of diastereoisomer (2*R*)-(-)-**143** (500 mg, 1.57 mmol) in methanol (30 mL), then was added 20% Pd $(OH)_2$/C (100 mg). The mixture was stirred at room temperature under hydrogen pressure (50 Psi) for 5h, then was filtered through Celite®. The filtrate was concentrated under reduced pressure. Silica gel column chromatography (ethyl acetate/cyclohexane = 1/3) afforded 284 mg (91%) of trifluoromethylamine(*R*)-(+) 105 (colorless liquid).

$\mathbf{[\alpha]_D^{25}}$ = +13.0 (c 1.07, $CHCl_3$).

Note : other analytical data are identical to those given for the racemic form (*vide supra*).

(±)-(8*R, 10*R**)-10-Propyl-8-(trifluoromethyl)-9-aza-1,5-dioxaspiro[5.5]undecane 106.**



Following the general procedure for the intramolecular Mannich-type reaction (reaction temperature = 72°C), amine **(±)-19** (400 mg, 1.9 mmol), butanal (186 µL, 2.1 mmol) and *p*-TsOH (711 mg, 3.7 mmol) gave, after chromatography on silica gel column (ethyl acetate/cyclohexane = 1/6), *cis*-piperidine **(±)-106** (161 mg, yield : 32%) as yellow oil.

R_f : 0.48 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3316 (NH) ; 2961 ; 2933 ; 2873 ; 1337 ; 1268 ; 1180 ; 1142 ; 1092 (C-O) ; 1023 (C-O) ; 934 ; 793.

^{1}H NMR ($CDCl_3$) δ : 3.94 (t, 2H, J = 5.5 Hz, H-2) ; 3.88 (t, 2H, J = 5.5 Hz, H-4) ; 3.38 (m, 1H, H-8) ; 2.81 (m, 1H, H-10) ; 2.47 (br d, 1H, J = 13 Hz, H-7eq) ; 2.26 (br d, 1H, J = 13 Hz, H-11eq) ; 1.81-1.67 (m, 3H) ; 1.52-1.31 (m, 5H) ; 1.18 (m, 1H, H-3) ; 0.92 (t, 3H, J = 6.5 Hz, H-14).

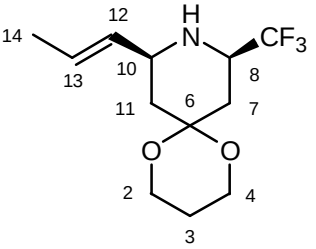
^{13}C NMR ($CDCl_3$) δ : 125.6 (q, J_{C-F} = 279 Hz, CF_3) ; 96.4 (C-6) ; 59.3 (C-2) ; 59.2 (C-4) ; 55.0 (q, J_{C-F} = 29 Hz, C-8) ; 51.9 (C-10) ; 39.2 (C-3) ; 38.4 (C-7) ; 32.0 (C-11) ; 25.3 (C-12) ; 18.9 (C-13) ; 14.1 (C-14).

^{19}F NMR ($CDCl_3$) δ : -81.1.

EI-MS (70eV) m/z : 267 (M^+, 1) ; 224 (60) ; 208 (25) ; <u>181</u> (100) ; 166 (30) ; 124 (25) ; 101 (40) ; 43 (25).

HR-ESI-MS calculated for $C_{12}H_{21}F_3NO_2$ $(M+H)^+$: 268.1524, found 268.1534.

(±)-(8*R, 10*S**)-10-(Prop-1-enyl)-8-(trifluoromethyl)-9-aza 1,5-dioxaspiro[5.5]undecane 107**



Following the general procedure for the intramolecular Mannich-type reaction (reaction temperature = 76°C), amine **(±)-19** (2.00 g, 9.4 mmol), crotonaldehyde (842 µL, 10.4 mmol) and *p*-TsOH (3.58 g, 18.8 mmol) gave, after silica-gel column chromatography (ethyl acetate/cyclohexane = 1/9), piperidine **(±)-107** (1.94 g, yield : 78%) as a pale yellow oil.

R_f : 0.52 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3310 (NH) ; 2969 ; 2868 ; 1336 ; 1279 ; 1267 ; 1176 ; 1137 (C-O) ; 1020 (C-O) ; 971.

^{1}H NMR ($CDCl_3$) δ : 5.67 (dq, 1H, J = 15 and 6.5 Hz, H-13) ; 5.45 (dd, 1H, J = 15 and 7 Hz, H-12) ; 3.94 (br t, 2H, J = 5.5 Hz, H-2) ; 3.89 (t, 2H, J = 5.5 Hz, H-4) ; 3.41 (m, 1H, H-8) ; 3.33 (m, 1H, H-10) ; 2.40 (dt, 1H, J = 13 and 3 Hz, H-11eq) ; 2.26 (dd, 1H, J = 13.5 and 3 Hz, H-7eq) ; 1.74 (m, 2H, H-3) ; 1.68 (d, 3H, J = 7 Hz, H-14) ; 1.50 (bs s, NH) ; 1.45 (t, 1H, J = 12.5 Hz, H-11ax) ; 1.30 (t, 1H, J = 13 Hz, H-7ax).

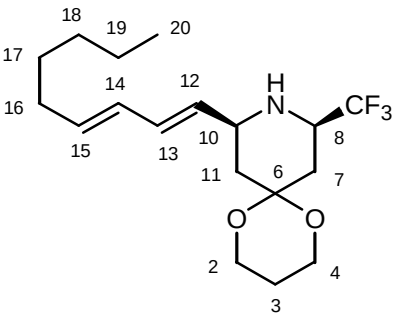
^{13}C NMR ($CDCl_3$) δ : 132.6 (C-13) ; 127.0 (C-14) ; 125.6 (q, J_{C-F} = 279 Hz, CF_3) ; 96.2 (C-6) 59.3 (C-2) ; 59.2 (C-4) ; 54.6 (q, J_{C-F} = 29 Hz, C-8) ; 54.3 (C-10) ; 38.7 (C-3) ; 32.0 (C-11) ; 25.3 (C-7) ; 17.7 (C-14).

^{19}F NMR ($CDCl_3$) δ : -79.5.

EI-MS (70eV) m/z : 265 (M^+, 5) ; <u>206</u> (100) ; 181 (30) ; 101 (25).

HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_2$ $(M+H)^+$: 266.1368, found 266.1362.

(±)-(8*R, 10*S**)-10-[(1*E*, 3*E*)-Nona-1,3-dienyl]-8-(trifluoromethyl)-9-aza-1,5-dioxaspiro [5.5]undecane 108**



Following the general procedure for the intramolecular Mannich-type reaction (reaction temperature = 70°C), amine **(±)-19** (2.88 g, 13.5 mmol), *trans*,*trans*-deca-2,4-dienal (2.60 mL, 14.9 mmol) and *p*-TsOH (5.15 g, 27.1 mmol) gave, after column chromatography (ethyl acetate/cyclohexane = 1/19), piperidine **(±)-108** (3.33 g, yield : 71%) as a yellow oil.

R_f : 0.58 (ethyl acetate/cyclohexane = 1/1).
IR (neat) σ (cm^{-1}) : 3321 (NH) ; 2958 ; 2930 ; 2861 ; 1728 ; 1459 (C=C) ; 1429 (C=C) ; 1400 (C=C) ; 1379 ; 1337 ; 1280 ; 1175 (C-O) ; 1135 (C-O) ; 1018 ; 990.

^{1}H NMR ($CDCl_3$) δ : 6.18 (dd, 1H, *J* = 15 and 10.5 Hz, H-13) ; 5.99 (dd, 1H, *J* = 15 and 10.5 Hz, H-14) ; 5.68 (m, 1H, H-15) ; 5.53 (dd, 1H, *J* = 15 and 7 Hz, H-12) ; 3.90 (m, 4H, H-2 and H-4) ; 3.41 (m, 2H, H-8 and H-10) ; 2.38 (dt, 1H, *J* = 13 and 3 Hz, H-11eq) ; 2.29 (dt, 1H, *J* = 13 and 3 Hz, H-7eq) ; 2.06 (q, 2H, *J* = 7 Hz, H-16) ; 1.73 (m, 3H, H-3 and NH) ; 1.44 (t, 1H, J = 13 Hz, H-11ax) ; 1.48-1.21 (m, 7H, H-7ax, H-17, H-18 and H-19) ; 0.88 (t, 3H, J = 7 Hz, H-20).

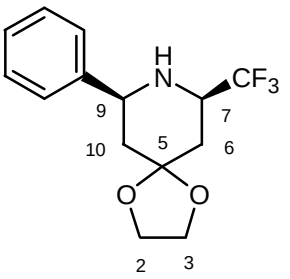
^{13}C NMR ($CDCl_3$) δ : 135.7 (C-13) ; 131.7 (C-14) ; 131.5 (C-15) ; 129.3 (C-2) ; 125.6 (q, J_{C-F} = 279 Hz, CF_3) ; 96.1 (C-6) ; 59.3 (C-2) ; 59.2 (C-4) ; 54.7 (q, J_{C-F} = 29 Hz, C-8) ; 54.3 (C-10) 38.6 (C-3) ; 32.5 (C-11) ; 33.1 (C-7) ; 31.3 (C-16) ; 28.8 (C-17) ; 25.4 (C-18) ; 22.5 (C-19) ; 13.9 (C-20).

^{19}F NMR ($CDCl_3$) δ : -81.4.

EI-MS (70eV) m/z : 347 (M^+, 20) ; 290 (20) ; 276 (20) ; <u>181</u> (100) ; 150 (25) ; 123 (20) ; 101 (20).

HR-ESI-MS calculated for $C_{18}H_{29}F_3NO_2$ $(M+H)^+$: 348.2150, found 348.2157.

(±)-(7*R, 9*S**)-9-Phenyl-7-(trifluoromethyl)-8-aza-1,4-dioxaspiro[4.5]decane 109.**



Following the general procedure for the intramolecular Mannich-type reaction (reaction temperature = 110°C), amine **(±)-105** (200 mg, 1 mmol), benzaldehyde (112 µL, 1.1 mmol) and *p*-TsOH (382 mg, 2 mmol) gave, after chromatography on silica-gel (ethyl acetate/cyclohexane = 1/6), piperidine **(±)-109** (191 mg, yield : 66%) as a pale yellow oil.

R_f : 0.50 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3313 (NH) ; 3032 ; 2977 ; 2887 ; 1455 ; 1401 ; 1337 ; 1280 ; 1247 ; 1174; 1124 ; 1077 ; 1058 ; 1015 ; 948 ; 761 ; 701.

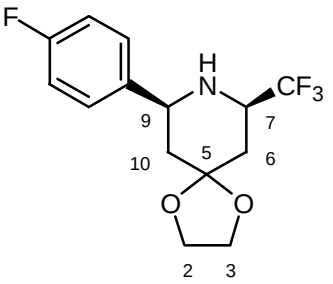
^{1}H NMR ($CDCl_3$) δ : 7.35 (m, 5H, H-Ar) ; 4.01 (m, 4H, H-2 and H-3) ; 3.95 (dd, 1H, J = 12 and 3 Hz, H-9) ; 3.56 (m, 1H, H-7) ; 1.93 (dt, 1H, J = 12.5 and 3 Hz, H-10eq) ; 1.85 (dt, 1H, J = 13 and 3 Hz, H-6eq) ; 1.77 (t, 1H, J = 12 Hz, H-10ax) ; 1.75 (t, 1H, J = 12 Hz, H-6ax) ; 1.60 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) δ : 142.9 (C*ipso*) ; 128.6 (C-Ar) ; 127.7 (C-Ar) ; 126.8 (C-Ar) ; 125.6 (q, J_{C-F} = 278 Hz, CF_3) ; 107.0 (C-5) ; 64.6 (C-2) ; 64.5 (C-3) ; 58.1 (C-9) ; 56.4 (q, J_{C-F} = 29.0 Hz, C-7) ; 43.3 (C-10) ; 34.0 (C-6).

EI-MS (70eV) m/z : 287 (M^+, 10) ; <u>242</u> (100) ; 266 (20) ; 132 (20) ; 104 (40) ; 86 (35).

HR-ESI-MS calculated for $C_{14}H_{17}F_3NO_2$ $(M+H)^+$: 288.1211, found 288.1207.

(±)-(7*R, 9*S**)-9-(4-Fluorophenyl)-7-(trifluoromethyl)-8-aza 1,4-dioxaspiro[4.5]decane 110**.



Following the general procedure for the intramolecular Mannich-type reaction (reaction temperature = 70°C), amine **(±)-105** (200 mg, 1 mmol), 4-fluorobenzaldehyde (117 µL, 1.1 mmol) and *p*-TsOH (382 mg, 2 mmol) gave, after column chromatography on silica-gel (ethyl acetate/cyclohexane 1/6), piperidine **(±)-110** (215 mg, yield: 70%) as a white solid.

M.p. : 85-89 °C.

R_f : 0.72 (ethyl acetate/cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}) : 3305 (NH) ; 1605 ; 1509 ; 1276 ; 1180 ; 1135 ; 1013 ; 840.

^{1}H NMR ($CDCl_3$) δ : 7.38 (m, 2H, H-Ar) ; 7.02 (m, 2H, H-Ar) ; 3.99 (m, 5H, H2, H-3 and H-9) ; 3.55 (m, 1H, H-7) ; 1.93 (br s, 1H, NH) ; 1.92 (dt, 1H, J = 12.5 and 3 Hz, H-10eq) ; 1.82 (dt, 1H, J = 13 and 3 Hz, H-6eq) ; 1.76 (t, 1H, J = 12.5 Hz, H-10ax) ; 1.73 (t, 1H, J = 13 Hz, H-6ax).

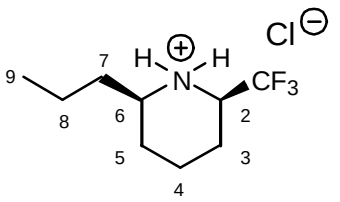
^{13}C NMR ($CDCl_3$) δ : 163.4 (d, $^1J_{C\text{-}F}$ = 246 Hz, C_{Ar}-F) ; 138.6 (C*ipso*) ; 128.4 (d, $^3J_{C\text{-}F}$ = 8 Hz, C-Ar) ; 125.5 (q, $J_{C\text{-}F}$ = 279 Hz, CF_3) ; 115.3 (d, $^2J_{C\text{-}F}$ = 21 Hz, C-Ar) ; 106.8 (C-5) ; 64.6 (C-2) ; 64.5 (C-3) ; 57.4 (C-9) ; 56.3 (q, $J_{C\text{-}F}$ = 30 Hz, C-7) ; 43.4 (C-10) ; 33.8 (C-6).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 305 (M^+, 10) ; 260 (100) ; 150 (40) ; 122 (60) ; 86 (50).

HR-ESI-MS calculated for $C_{14}H_{16}F_4NO_2$ $(M+H)^+$: 306.1117, found 306.1117.

(±)-(2*R, 6*R**)-6-Propyl-2-(trifluoromethyl)piperidine.HCl** (Trifluorodihydropinidine) **111**·HCl.



Following the general procedure for hydrogenolysis with Raney nickel, dithioketal **115** (70 mg, 0.24 mmol) in absolute ethanol (7 mL) treated with W2 Raney nickel (*ca* 700 mg), gave pure compound **111.**HCl (51 mg, yield: 90%) as a white solid.

M.p. 201°C (dec.).

IR (KBr) σ (cm^{-1}) : 2935 ; 1271 ; 1192 ; 1119.

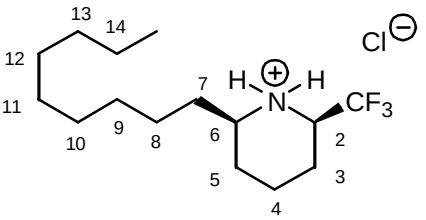
^{1}H NMR (CD_3OD) δ : 4.19 (m, 1H, H-2) ; 3.31 (m, 1H, H-6) ; 2.23-1.96 (m, 3H) ; 1.87-1.30 (m, 7H) ; 0.99 (t, 3H, J = 7.5 Hz, H-9).

^{13}C NMR (CD_3OD) δ : 124.6 (q, J_{C-F} = 280 Hz, CF_3) ; 60.3 (C-6) ; 58.6 (q, J_{C-F} = 32 Hz, C-2) 36.0 (C-3) ; 28.4 (C-5) ; 23.1 (C-7) ; 22.0 (C-4) ; 19.6 (C-8) ; 14.0 (C-9).

EI-MS (70eV, free base) m/z : 195 (M^+, 1) ; 194 (3) ; 152 (100) ; 55 (10).

HR-ESI-MS calculated for $C_9H_{17}ClF_3N$ $(M-Cl)^+$: 196.1313, found 196.1317.

(±)-(2*R, 6*R**)-6-Nonyl-2-(trifluoromethyl)piperidine.HCl** (Trifluoroisosolenopsin) **112.**HCl.



Following the general procedure, starting from thioketal **117** (200 mg, 0.5 mmol) in absolute ethanol (20 mL), and W2 Raney nickel (*ca* 2.0 g), trifluoroisosolenopsine HCl salt **112.**HCl (157 mg, yield: 92%) was obtained without purification as a white solid.

M.p : 165-166°C.

IR (KBr) σ (cm^{-1}) : 3420 ; 2023 ; 1468 ; 1270 ; 1190 ; 1135.

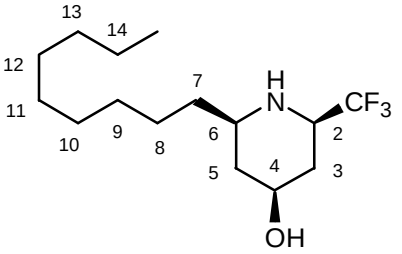
^{1}H NMR (CD_3OD) δ : 4.15 (m, 1H, H-2) ; 3.22 (m, 1H, H-6) ; 2.18-2.07 (m, 2H) ; 2.00 (m, 1H) ; 1.81 (m, 1H) ; 1.74-1.50 (m, 3H) ; 2.18-1.50 (m, 16H) ; 0.86 (t, 3H, J = 7 Hz, Me).

^{13}C NMR (CD_3OD) δ : 124.6 (q, J_{C-F} = 280 Hz, CF_3) ; 60.5 (C-6) ; 58.6 (q, J_{C-F} = 32 Hz, C-2) ; 34.0 (C-3) ; 33.0 (C-5) ; 30.6 (C-7) ; 30.5 (C-4) ; 30.4 (C-8) ; 28.4 (C-9) ; 26.3 (C-10) ; 23.7 (C-11) ; 23.2 (C-12) ; 23.1 (C-13) ; 22.6 (C-14) ; 14.5 (Me).

EI-MS (70eV, free base) m/z : 279 (M^+, 1) ; 278 (3) ; 152 (100) ; 55 (10).

HR-ESI-MS calculated for $C_{15}H_{29}F_3N$ $(M+H)^+$: 280.2252, found 280.2260.

(±)-(2*R, 4*S**, 6*R**)-6-Nonyl-2-(trifluoromethyl)piperidin-4-ol** (Trifluoro-241 D) **113**.



Following the procedure employed for the synthesis of compound **114** (see page 113) starting from compound **124** (65 mg, 0.22 mmol) in anhydrous methanol (10 mL), ammonium formate (70 mg, 1.1 mmol) and 20% $Pd(OH)_2/C$ (20 mg), compound **113** (61 mg, yield : 93%) was obtained without needed purification as a white solid.

M.p : 78-81°C.

R_f : 0.25 (ethyl acetate).

IR (KBr) σ (cm^{-1}) : 3269 (NH and OH) ; 2964 ; 1264 ; 1191 ; 1146 ; 1089 (C-O) ; 1043.

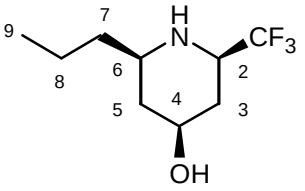
^{1}H NMR ($CDCl_3$) δ : 3.71 (m, 1H, H-4) ; 3.18 (m, 1H, H-2) ; 2.58 (m, 1H, H-6) ; 2.14 (dQ, 1H, J = 12 and 2.5 Hz, H-3eq) ; 2.00 (dQ, 1H, J = 12.5 and 2 Hz, H-5eq) ; 1.56 (br s, 2H, NH and OH) ; 1.49-1.26 (m, 17H, H-5ax and 8 CH_2 of the alkyl side chain) ; 1.07 (q, 1H, J = 12 Hz, H-3ax) ; 0.88 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 125.3 (q, J_{C-F} = 279 Hz, CF_3) ; 68.2 (C-4) ; 56.7 (q, J_{C-F} = 29 Hz, C-2) ; 54.4 (C-6) ; 41.2 (C-3) ; 36.5 (C-5) ; 34.2 (C-7) ; 31.9 (C-8) ; 29.6-29.3 (4C, C-9, C-10, C-11, C-12) ; 25.8 (C-13) ; 22.7 (C-14) ; 14.1 (Me).

EI-MS (70eV) m/z : 295 (M^+, 1) ; 168 (100) ; 150 (25) ; 124 (20).

HR-ESI-MS calculated for $C_{15}H_{29}F_3NO$ $(M+H)^+$: 296.2201, found 296.2195.

(±)-(2*R, 4*S**, 6*R**)-6-Propyl-2-(trifluoromethyl)piperidin-4-ol 114.**



To a stirred solution of compound **120** (82 mg, 0.39 mmol) in methanol (10 mL) was added $Pd(OH)_2/C$ 20% (30 mg) and ammonium formate (123 mg, 1.95 mmol). The mixture was heated at reflux for 2h. After cooling to room temperature, the solution was filtered through Celite® and the filtrate was concentrated under reduced pressure to give a residue which was diluted with saturated aqueous $NaHCO_3$ (5 mL) before extraction with dichloromethane (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated, to afford saturated piperidine **114** (70 mg, yield : 85%) as a white solid.

M.p. : 47-49°C.
R_f : 0.18 (ethyl acetate).

IR (KBr) σ (cm^{-1}) : 3415 (OH) ; 3331 (NH) ; 2956 ; 1267 ; 1150 ; 1111 ; 1086 ; 1046 ; 884.

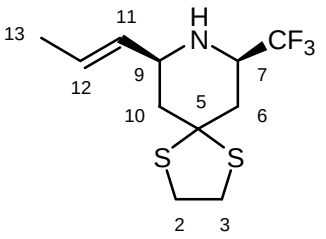
^{1}H NMR ($CDCl_3$) δ : 3.70 (tt, 1H, J = 11 and 4.5 Hz, H-4) ; 3.18 (m, 1H, H-2) ; 2.60 (m, 1H, H-6) ; 2.14 (dQ, 1H, J = 12 and 2 Hz, H-3eq) ; 2.00 (dQ, 1H, J = 12 and 2 Hz, H-5eq) ; 1.66 (br s, 2H, NH and OH) ; 1.50-1.31 (m, 5H, H-5ax, H-7 and H-8) ; 1.06 (q, 1H, J = 11.5 Hz, H-3ax) ; 0.92 (t, 3H, J = 7 Hz, H-9).

^{13}C NMR ($CDCl_3$) δ : 125.3 (q, J_{C-F} = 278 Hz, CF_3) ; 68.0 (C-4) ; 56.7 (q, J_{C-F} = 29 Hz, C-2) ; 54.1 (C-6) ; 41.1 (C-3) ; 38.6 (C-5) ; 34.1 (C-7) ; 18.9 (C-8) ; 14.0 (C-9).

EI-MS (70eV) m/z : 211 (M^+, 1) ; <u>168</u> (100) ; 150 (50) ; 124 (40) ; 98 (10).

HR-ESI-MS calculated for $C_9H_{17}F_3NO$ $(M+H)^+$: 212.1262, found 212.1279.

(±)-(7*R, 9*S**)-9-(1*E*-Prop-1-enyl)-7-(trifluoromethyl)-8-aza-1,4-dithiaspiro[4.5]decane 115.**



Following the general procedure for dithioketalization, protected piperidone **107** (200 mg, 0.75 mmol) in dichloromethane (10 mL), ethanedithiol (320 µL, 3.8 mmol) and $BF_3.Et_2O$ (481 µL, 3.8 mmol) gave, after purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/19), dithiolane **115** (164 mg, yield: 77%) as a pale yellow oil.

R_f : 0.60 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3308 (NH) ; 2957 ; 2926 ; 2837 ; 1275 ; 1173 ; 1139 ; 1125 ; 1060 ; 968 ; 815 ; 786.

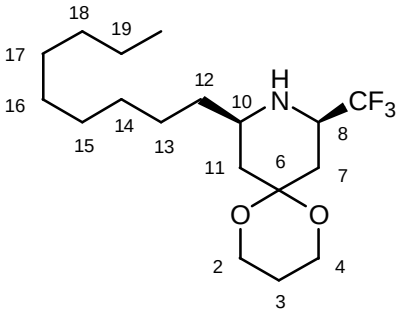
^{1}H NMR ($CDCl_3$) δ : 5.70 (dq, 1H, J = 15 and 6.5 Hz, H-12) ; 5.44 (dd, 1H, J = 15 and 7.0 Hz, H-11) ; 3.46 (m, 1H, H-7) ; 3.32 (m, 5H, H-2 , H-3 and H-9) ; 2.22 (ddd, 1H, J = 13, 4.5 and 2.5 Hz, H-10eq) ; 2.10 (ddd, 1H, J = 13.5, 5 and 2.5 Hz, H-6eq) ; 1.98 (t, 1H, J = 13 Hz, H-10ax) ; 1.85 (t, 1H, J = 13.5 Hz, H-6ax) ; 1.70 (br s, 1H, NH) ; 1.68 (d, 3H, J = 6.5 Hz, H-13).

^{13}C NMR ($CDCl_3$) δ : 132.2 (C-12) ; 127.4 (C-11) ; 125.3 (q, J_{C-F} = 279 Hz, CF_3) ; 64.8 (C-5); 52.7 (C-9) ; 57.3 (q, J_{C-F} = 29 Hz, C-7) ; 47.4 (C-2) ; 40.7 (C-3) ; 39.3 (C-10) ; 38.0 (C-6) ; 17.7 (C-13).

^{19}F NMR ($CDCl_3$) δ : -79.0.

HR-ESI-MS calculated for $C_{11}H_{17}F_3NS_2$ $(M+H)^+$: 284.0755, found 284.0750.

(±)-(8*R, 10*R**)-10-Nonyl-8-(trifluoromethyl)-9-aza-1,5-dioxaspiro[5.5]undecane 116**.



To a stirred solution of compound **108** (200 mg, 0.6 mmol) in methanol (10 mL) was added $Pd(OH)_2/C$ 20% (50 mg) and ammonium formate (182 mg, 2.9 mmol). The mixture was heated at reflux for 2h. After cooling to room temperature, the solution was filtered through Celite® and the filtrate was concentrated under reduced pressure to give a residue which was diluted with saturated aqueous $NaHCO_3$ (5 mL) before extraction with dichloromethane (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated, to afford saturated piperidine **116** (186 mg, yield : 92%) as a pale yellow oil.

$\mathbf{R_f}$: 0.50 (ethyl acetate/cyclohexane = 1/1).

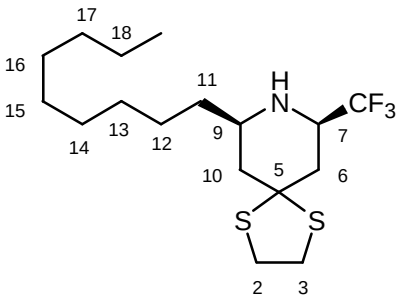
IR (neat) σ (cm^{-1}) : 3338 (NH) ; 2995 ; 2927 ; 1467 ; 1338 ; 1279 ; 1172 ; 1137 (C-O) ; 1091 (C-O) ; 1018 (C-O).

^{1}H NMR ($CDCl_3$) δ : 3.93 (t, 2H, J = 5.5 Hz, H-2) ; 3.87 (t, 2H, J = 5.5 Hz, H-4) ; 3.35 (m, 1H, H-8) ; 2.75 (m, 1H, H-10) ; 2.45 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.24 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 1.72 (m, 2H, H-3) ; 1.40 (t, 1H , J = 12.5 Hz, H-7ax) ; 1.34-1.18 (m, 17H, NH, H-12, H-13, H-14, H-15, H-16, H-17, H-18 and H-19) ; 1.12 (t, 1H, J = 13 Hz, H-11ax) ; 0.88 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 125.7 (q, J_{C-F} = 279 Hz, CF_3) ; 96.4 (C-6) ; 59.2 (C-2) ; 59.1 (C-4) ; 54.9 (q, J_{C-F} = 29 Hz, C-8) ; 52.0 (C-10) ; 39.2 (C-3) ; 36.4 (C-7) ; 32.0 (C-11) ; 31.8 (C-12) ; 29.6 (C-13) ; 29.5 (C-14) ; 29.4 (C-15) ; 29.2 (C-16) ; 25.7 (C-17) ; 25.3 (C-18) ; 22.6 (C-19); 14.0 (Me).

HR-ESI-MS calculated for $C_{18}H_{33}F_3NO_2$ $(M+H)^+$: 352.2463, found 352.2461.

(±)-(7*R, 9*R**)-9-Nonyl-7-(trifluoromethyl)-8-aza-1,4-dithiaspiro[4.5]decane 117**.



Following the general procedure for dithioketalization, starting from ketal **116** (378 mg, 1.1 mmol) in dichloromethane (12 mL), ethanedithiol (450 µL, 5.4 mmol) and $BF_3.Et_2O$ (700 µL, 5.4 mmol), dithiolane **117** (238 mg, yield : 60%) was obtained as a yellow oil after purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/19).

R_f : 0.60 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) : 3339 (NH) ; 2926 ; 2854 ; 1466 ; 1397 ; 1277 ; 1172 ; 1142.

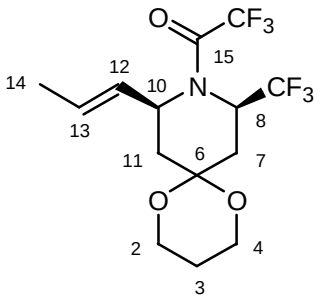
^{1}H NMR ($CDCl_3$) δ : 3.40 (m, 1H, H-7) ; 3.33 (s, 4H, H-2 and H-3) ; 2.76 (m, 1H, H-9) ; 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.13 (dt, 1H, J =13 and 2.5 Hz, H-10eq) ; 1.96 (t, 1H, J = 12 Hz, H-6ax) ; 1.72 (t, 1H, J = 12 Hz, H-10ax) ; 1.62 (br s, 1H, NH) ; 1.45-1.23 (m, 16H, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18) ; 0.90 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 125.4 (q, J_{C-F} = 279 Hz, CF_3) ; 65.2 (C-5) ; 57.5 (q, J_{C-F} = 29 Hz, C-7) ; 55.7 (C-9) ; 47.4 (C-2) ; 41.5 (C-3) ; 39.2 (C-6) ; 38.0 (C-10) ; 36.5 (C-11) ; 31.8 (C-12) ; 29.6 (C-13) ; 29.5 (C-14) ; 29.3 (C-15) ; 25.6 (C-16) ; 23.5 (C-17) ; 22.6 (C-18) ; 14.1 (Me).

EI-MS (70eV) m/z : 369 (M^+, 2) ; 308 (30) ; 276 (70) ; <u>242</u> (100) ; 199 (25) ; 182 (15) ; 138 (15) ; 119 (20).

HR-ESI-MS calculated for $C_{17}H_{31}F_3NS_2$ $(M+H)^+$: 370.1850, found 370.1840.

(±)-(8*R, 10*S**)-10-[(1*E*)-Prop-1-enyl]-8-(trifluoromethyl)-9-(trifluoromethylcarbonyl)-9-aza-1,5-dioxaspiro[5.5]undecane 118.**



To a stirred solution of compound **107** (1.0 g, 3.8 mmol) in dichloromethane (30 mL) was added triethylamine (4.2 mL, 30.1 mmol) and DMAP (139 mg, 1.1 mmol). To the resulting solution was added, at 0°C, trifluoroacetic anhydride (2.1 mL, 15.2 mmol). The resulting mixture was stirred at room temperature for 30min, and then concentrated *in vacuo*. The residue was purified by chromatography on silica-gel column (ethyl acetate/cyclohexane = 1/3) to afford compound **118** (1.27 g, yield : 93%) as a pale yellow oil.

R_f : 0.55 (ethyl acetate/cyclohexane = 1/3).

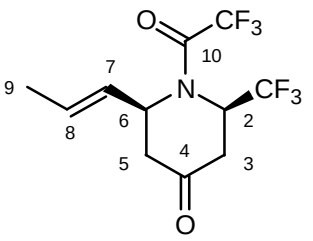
IR (neat) σ (cm^{-1}) : 2974 ; 2872 ; 1705 (C=O) ; 1433 ; 1360 ; 1287 ; 1254 ; 1212 ; 1182 ; 1150 ; 1119 ; 1016 (C-O) ; 964 ; 958.

^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers) δ : 5.90-5.36 (m, 2H) ; 5.15-5.04 (m, 1H) ; 4.82-4.55 (m, 1H) ; 4.02-3.81 (m, 4H) ; 2.71-2.42 (m, 2H); 2.19-1.53 (m, 7H).

^{13}C NMR ($CDCl_3$) δ : 158.0 (C-15) ; 129.9 (C-13) ; 128.7 (C-12) ; 124.5 (q, J_{C-F} = 282 Hz, CF_3) ; 116.3 (q, J_{C-F} = 287 Hz, $CO\underline{C}F_3$) ; 94.9 (C-6) ; 60.0 (C-2) ; 59.8 (C-4) ; 52.9 (C-10) ; 51.0 (q, J_{C-F} = 34 Hz, C-8) ; 36.1 (C-3) ; 27.5 (C-11) ; 24.9 (C-7) ; 17.5 (C-14).

HR-ESI-MS calculated for $C_{14}H_{17}F_6NNaO_3$ $(M+Na)^+$: 384.1010, found 384.1017.

(±)-(2*R, 6*S**)-6-[(1*E*)-Prop-1-enyl]-2-(trifluoromethyl)-1-(trifluoromethylcarbonyl) piperidin-4-one 119**.



To a stirred solution of ketal **118** (815 mg, 2.2 mmol) in CH_3CN (5 mL) was added, at 70°C, in one portion, a solution of CAN (3.08 g, 5.6 mmol) in H_2O (10 mL). The resulting mixture was stirred for 30min, then allowed to cool to room temperature and poured into H_2O (75 mL) before extraction with dichloromethane (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) to afford compound **119 (**513 mg, yield : 75%) as a pale yellow oil.

R_f : 0.42 (ethyl acetate/cyclohexane = 1/3).

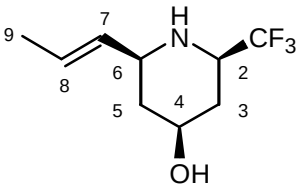
IR (neat) σ (cm^{-1}) : 3042 ; 2977 ; 2926 ; 2862 ; 1732 (C=O) ; 1708 (C=O) ; 1433 ; 1384 ; 1346 ; 1297 ; 1275 ; 1210 ; 1182 ; 1148 ; 1128 ; 1006 ; 972 ; 941 ; 760 ; 694.

^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers) δ : 8.80-5.07 (m, 4H) ; 2.96-2.71 (m, 4H) ; 1.72 (d, 3H, J = 6.5 Hz, H-9).

^{13}C NMR (100 MHz, $CDCl_3$) δ : 201.0 (C-4) ; 158.0 (C-10) ; 131.0 (C-8) ; 128.2 (C-7) ; 124.0 (q, J_{C-F} = 284 Hz, CF_3) ; 116.1 (q, J_{C-F} = 287 Hz, $CO\underline{C}F_3$) ; 54.3 (C-6) ; 42.5 (C-5) ; 36.4 (C-3) ; 17.6 (C-9).

HR-ESI-MS calculated for $C_{11}H_{14}F_6NNaO_2$ $(M+Na)^+$: 326.0592, found 326.0596.

(±)-(2*R, 4*S**, 6*S**)-6-[(1*E*)-Prop-1-enyl]-2-(trifluoromethyl)piperidin-4-ol 120.**



To a cooled (-30°C) stirred solution of piperidone **119** (298 mg, 0.98 mmol) in methanol (20 mL) was added sodium borohydride (74 mg, 1.97 mmol). The resulting mixture was stirred for 1h before addition of satured aqueous NH_4Cl (8 mL). After heating to room temperature, the methanol was removed *in vacuo*. The residue was then extracted with dichloromethane (5 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvent, followed by purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) afforded piperidinol **120** (132 mg, yield: 64%) as a white solid.

M.p : 77-80°C.

R_f : 0.20 (ethyl acetate/cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}): 3296 (OH) ; 1677 (C=C) ; 1268 ; 1185 ; 1153 ; 1089 ; 1046 (C-O) ; 879.

^{1}H NMR ($CDCl_3$) δ : 5.66 (dq, 1H, J = 15 and 6.5 Hz, H-8) ; 5.77 (ddq, 1H, J = 15, 7 and 1.5 Hz, H-7) ; 3.75 (m, 1H, H-4) ; 3.23 (m, 1H, H-2) ; 3.14 (m, 1H, H-6) ; 2.14 (m, 1H, H-5eq) ; 1.99 (m, 1H, H-3eq) ; 1.69 (d, 3H, J = 6.5 Hz, H-9) ; 1.58, (br s, 2H, NH and OH) ; 1.37 (q, 1H, J = 11.5 Hz, H-5ax) ; 1.24 (q, 1H, J = 11.5 Hz, H-3ax).

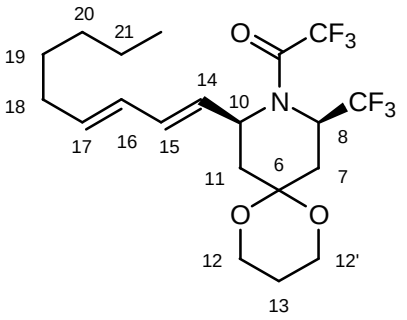
^{13}C NMR ($CDCl_3$) δ : 132.3 (C-8) ; 127.1 (C-7) ; 125.2 (q, J_{C-F} = 279 Hz, CF_3) ; 67.7 (C-4) ; 56.5 (C-6) ; 56.4 (q, J_{C-F} = 29 Hz, C-2) ; 41.0 (C-5) ; 38.4 (C-3) ; 17.6 (C-9).

^{19}F NMR ($CDCl_3$) δ : -80.4.

EI-MS (70eV) m/z : 209 (M^+, 25) ; 194 (100) ; 176 (50) ; 164 (40) ; 150 (60) ; 96 (70) ; 68 (80) ; 41 (50).

HR-ESI-MS calculated for $C_9H_{15}F_3NO$ $(M+H)^+$: 210.1106, found 210.1112.

(±)-(8*R, 10*S**)-10-[(1*E*, 3*E*)-Nona-1,3-dienyl]-8-(trifluoromethyl)-9-trifluoromethyl carbonyl-1,5-dioxa-9-azaspiro[5.5]undecane 122.**



Following the procedure employed for the synthesis of compound **118** (see page 117), starting from ketal **19** (500 mg, 1.44 mmol) in dichloromethane (12 mL), triethylamine (1.6 mL, 11.5 mmol), DMAP (53 mg, 0.43 mmol) and trifluoroacetic anhydride (0.8 mL, 5.8 mmol), compound **122** (447 mg, yield : 70%) was obtained after purification by column chromatography (ethyl acetate/cyclohexane = 1/19) as a dark yellow oil.

$\mathbf{R_f}$: 0.45 (ethyl acetate/cyclohexane = 1/5).

IR (neat) σ (cm^{-1}) : 2960 ; 2930 ; 2861 ; 1706 (C=O) ; 1656 (C=C) ; 1431 ; 1213 ; 1183 ; 1148 (C-O) ; 990.

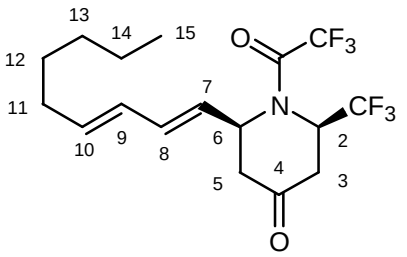
^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers) δ : 6.38-4.51 (m, 6H) ; 3.99-3.83 (m, 4H) ; 2.72-2.45 (m, 2H) ; 2.20-1.57 (m, 6H) ; 1.42-1.24 (m, 6H) 0.88 (t, 3H, J = 7.0 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 158.0 (C=O) ; 136.3 (C-14) ; 133.6 (C-15) ; 131.8 (C-16) ; 127.7 (C-17) ; 123.5 (q, J_{C-F} = 286 Hz, CF_3) ; 115.3 (q, J_{C-F} = 286 Hz, CO<u>C</u>F_3) ; 93.9 (C-6) ; 59.1 (C-12) ; 58.9 (C-12') ; 52.0 (C-10) ; 50.5 (q, J_{C-F} = 34.0 Hz, C-8) ; 35.4 (C-13) ; 31.6 (C-11) ; 30.4 (C-7) ; 27.8 (C-18) ; 26.5 (C-19) ; 24.0 (C-20) ; 21.5 (C-21) ; 13.0 (Me).

EI-MS (70eV) m/z : 443 (M^+, 15) ; 181 (100) ; 166 (25) ; <u>123</u> (100) ; 79 (50) ; 55 (25) ; 41 (65).

HR-ESI-MS calculated for $C_{20}H_{28}F_6NO_3$ $(M+H)^+$: 444.1973, found 444.1968.

(±)-(2*R, 6*S**)-6-[(1*E*, 3*E*)-Nona-1,3-dienyl]-2-(trifluoromethyl)-1-(trifluoromethyl)carbonyl piperidin-4-one 123**.



To a stirred solution of ketal **122** (593 mg, 1.3 mmol) in acetone (20 mL) was added 4M HCl solution (6 mL). The resulting mixture was stirred at room temperature for 4 days, then quenched with an excess of a 4M NaOH solution. Acetone was eliminated under reduced pressure and the residue was diluted with diethylether (50 mL). The two layers were separated, and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue, after purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/9), afforded compound **123** (335 mg, yield : 65%) as a yellow oil.

$\mathbf{R_f}$: 0.50 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3026 ; 2960 ; 2931 ; 2861 ; 1732 (C=O) ; 1709 (C=O) ; 1430 ; 1274 ; 1227 ; 1178 ; 1149 (C-O) ; 993.

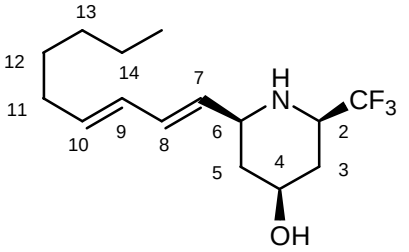
^{1}H NMR ($CDCl_3$, complex spectrum due to the coexistence of amide rotamers) δ : 6.29-5.06 (m, 4H) ; 2.88-2.72 (m, 4H) ; 2.18-2.05 (m, 2H) ; 1.59 (br s, 1H) ; 1.42-1.23 (m, 7H) ; 0.88 (t, 3H, J = 8 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 199.8 (C-4) ; 157.7 ($\underline{C}OCF_3$) ; 138.6 (C-7) ; 134.7 (C-8) ; 128.4 (C-9) ; 125.5 (C-10) ; 122.7 (q, J_{C-F} = 215.5 Hz, CF_3) ; 115.2 (q, J_{C-F} = 287 Hz, $CO\underline{C}F_3$) 54.4 (C-6) ; 54.1 (q, J_{C-F} = 29 Hz, C-2) ; 42.5 (C-5) ; 32.5 (C-3) ; 31.3 (C-11) ; 28.6 (C-12 and C-13) ; 22.4 (C-14) ; 13.9 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.2.

EI-MS (70eV) m/z : 385 (M^+, 30) ; 215 (30) ; 202 (30) ; 175 (30) ; <u>123</u> (100) ; 91 (70) ; 79 (70) ; 55 (30) ; 41 (40).

(±)-(2*R, 4*S**, 6*S**)-6-[(1*E*, 3*E*)-Nona-1,3-dienyl]-2-(trifluoromethyl)piperidin-4-ol 124**.



Following the procedure employed for the synthesis of compound **120** (see page 119), starting from compound **123** (150 mg, 0.39 mmol) in anhydrous methanol (10 mL) and sodium borohydride (29 mg, 0.78 mmol), compound **124** (84 mg, yield : 74%) was obtained, after purification by chromatography on silica gel column (ethyl acetate/cyclohexane = 1/4), as a white solid.

M.p : 93-95°C.

R_f : 0.20 (ethyl acetate/cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}) : 3263 (NH and OH) ; 1658 (C=C) ; 1266 ; 1190 ; 1157; 1086 ; 988 ; 886.

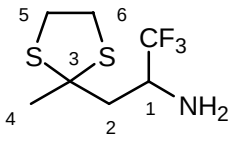
^{1}H NMR ($CDCl_3$) δ : 6.17 (dd, 1H, J = 15 and 10 Hz, H-8) ; 6.00 (dd, 1H, J = 15 and 10 Hz, H-9) ; 5.68 (m, 1H, H-10) ; 5.55 (dd, 1H, J = 15 and 7 Hz, H-7) ; 3.74 (m, 1H, H-4) ; 3.23 (m, 2H, H-2 and H-6) ; 2.07 (m, 4H, H-3eq, H-5eq, and H-11) ; 1.60 (br s, 2H, OH and NH) ; 1.43-1.20 (m, 8H, H-3ax, H-5ax, H-12, H-13 and H-14) ; 0.88 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 135.9 (C-8) ; 131.5 (C-9) ; 131.4 (C-10) ; 129.2 (C-7) ; 125.2 (q, J_{C-F} = 279 Hz, CF_3) ; 67.9 (C-4) ; 56.4 (q, J_{C-F} = 29 Hz, C-2) ; 56.3 (C-6) ; 41.1 (C-11) ; 33.6 (C-5); 32.6 (C-3) ; 31.4 (C-12) ; 28.9 (C-13) ; 22.5 (C-14) ; 14.0 (Me).

EI-MS (70eV) m/z : 291 (M^+, 35) ; 234 (75) ; 220 (85) ; 181 (100) ; 112 (40).

HR-ESI-MS calculated for $C_{15}H_{23}F_3N$ $(M-H_2O+H)^+$: 274.1783, found 274.1771.

(±)-1,1,1-Trifluoro-3-(2-methyl-1,3-dithiolan-2-yl)propan-2-amine 127.



To a solution of **128** (1.14 g, 3.18 mmol) in methanol (20 mL) was added hydrazine monohydrate (1.60 mL, 32 mmol). The resulting mixture was heated at reflux for 4h, then cooled to room temperature and concentrated under reduced pressure. The residue, diluted with dichloromethane (20 mL), was then treated with a 2M KOH solution (15 mL) and stirred vigorously for 30min. The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/1) afforded pure amine **127 (**382 mg, yield : 52 %) as a pale yellow liquid.

$\mathbf{R_f}$: 0.20 (ethyl acetate/cyclohexane = 1/2).

^{1}H NMR ($CDCl_3$) δ : 3.46 (m, 1H, H-1) ; 3.37-3.22 (m, 4H, H-5 and H-6) ; 2.31 (dd, 1H, J = 15 and 2 Hz, H-2) ; 1.95 (dd, 1H, J = 15 and 9 Hz, H-2) ; 1.78 (s, 3H, Me) ; 1.68 (br s, 2H, NH_2).

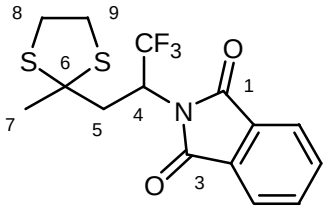
^{13}C NMR ($CDCl_3$) δ : 126.4 (q, J_{C-F} = 282 Hz, CF_3) ; 64.7 (C-3) ; 52.7 (q, J_{C-F} = 29 Hz, C-1) ; 44.2 (C-2) ; 40.2 (C-5) ; 39.4 (C-6) ; 33.1 (C-4).

^{19}F NMR ($CDCl_3$) δ : - 82.1.

EI-MS (70eV) m/z : 231 (M^+; 25) ; 172 (95) ; 138 (50) ; 119 (98) ; 98 (85) ; 75 (40) ; 59 (100) ; 45 (40).

HR-ESI-MS calculated for $C_7H_{13}F_3NS_2$ $(M+H)^+$: 232.0442, found 232.0447.

(±)-2-[1,1,1-Trifluoro-3-(2-methyl-1,3-dithiolan-2-yl]propan-2-yl)isoindoline-1,3-dione 128



To a solution of phthalimido compound **102** (1.0 g, 3.5 mmol) in dichloromethane (25 mL) was added 1,2-ethanedithiol (355 µL, 3.7 mmol) then, at 0°C, $BF_3.Et_2O$ (220 µL, 1.5 mmol). The resulting mixture was stirred for 1h at 0°C and then treated with a 2M aqueous solution of NaOH (5 mL). The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/7) afforded pure compound **128** (1.18 g, yield : 93 %) as a white solid.

M.p: 110°C.

$\mathbf{R_f}$: 0.60 (ethyl acetate/cyclohexane = 1/3).

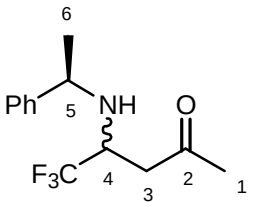
^{1}H NMR ($CDCl_3$) δ : 7.88 (m, 2H, H-Ar) ; 7.77 (m, 2H, H-Ar) ; 5.22 (m, 1H, H-4) ; 3.45 (dd, 1H, J = 16 and 10.5 Hz, H-5) ; 3.31 (m, 2H, H-8 and H-9) ; 3.25 (m, 2H, H-8 and H-9) ; 2.34 (dd, 1H, J = 16 and 1.5 Hz, H-5) ; 1.82 (s, 3H, H-7).

^{13}C NMR ($CDCl_3$) δ : 167.6 (C-1) ; 167.3 (C-3) ; 134.5 (C-Ar) ; 134.3 (C-Ar) ; 132.2 (C*ipso*) ; 131.1 (C*ipso*) ; 124.8 (q, J_{C-F} = 281 Hz, CF_3) ; 123.8 (C-Ar) ; 123.7 (C-Ar) ; 64.3 (C-6) ; 50.6 (q, J_{C-F} = 32 Hz, C-4) ; 40.5 (C-8) ; 40.2 (C-9) ; 36.0 (C-5) ; 34.2 (C-7).

EI-MS (70eV) m/z : 361 (M^+, 25) ; 302 (20) ; 261 (25) ; 199 (25) ; 148 (20) ; 130 (20) ; 119 (100) ; 104 (20) ; 76 (20) ; 59 (25).

HR-ESI-MS calculated for $C_{15}H_{14}F_3NNaO_2$ $(M+Na)^+$: 384.0316, found 384.0318.

(+)-5,5,5-Trifluoro-4-[(*R*)-1-phenylethylamino]pentan-2-one 131.



To a stirred solution of (*R*)-(+)-α-methylbenzylamine (11.07 mL, 91 mmol) and trifluoromethyl sulfonic acid (514 µL, 3.4 mmol) in acetonitrile (150 mL) was added, *trans*-5,5,5-trifluoropent-3-en-2-one (8 g, 58 mmol) and the reaction mixture was stirred at room temperature for 1h. Saturated $NaHCO_3$ (25 mL) was added before extraction with ethyl acetate (3 x 150 mL) and the combined organic extracts were dried over Na_2SO4, filtered then concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave compound **131** (1/1 unseparable mixture of diastereoisomers, 12g, yield : 80%) as a pale yellow oil.

R_f : 0.65 (ethyl acetate/cyclohexane = 1/3).

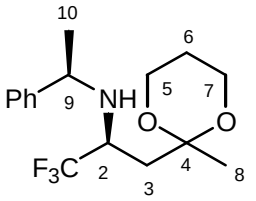
^{1}H NMR ($CDCl_3$) δ : 7.30 (m, 5H, H-Ar) ; 4.08 (q, J = 6.5 Hz, 0.5H, H-5, 1st dia) ; 4.00 (q, J = 6.5 Hz, 0.5H, H-5, 2nd dia) ; 3.68 (m, 0.5H, H-4, 1st dia) ; 3.42 (m, 0.5H, H-4, 2nd dia) ; 2.76-2.44 (m, 2H, H-3) ; 2.16 (s, 1.5H, H-1, 1st dia) ; 2.02 (s, 1.5H, H-1, 2nd dia) ; 1.60 (br s, 1H, NH) ; 1.34 (d, J = 6.5 Hz, 1.5H, H-6, 1st dia) ; 1.32 (d, J = 6.5 Hz, 1.5H, H-6, 2nd dia).

^{13}C NMR ($CDCl_3$) δ : 205.7 (C-2) ; 140.3 (C*ipso*) ; 128.6 (C-Ar) ; 128.2 (C-Ar) ; 127.4 (C-Ar) ; 126.3 (q, J_{C-F} = 283 Hz, CF_3) ; 67.2 (C-6) ; 62.2 (C-5) ; 53.5 (q, J_{C-F} = 29 Hz, C-4) ; 43.0 (C-3) ; 30.6 (C-1).

EI-MS (70eV) m/z : 259 (M+, 1) ; <u>244</u> (100) ; 200 (25) ; 186 (30) ; 159 (40) ; 120 (50) ; 105 (90) ; 77 (40) ; 43 (50).

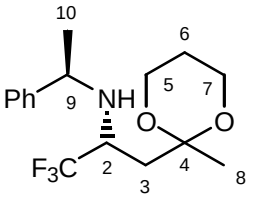
HR-ESI-MS calculated for $C_{13}H_{17}NOF_3$ $(M+H)^+$: 260.1262, found 260.1258.

(2*S*)-(-)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)-*N*-[(*R*)-1-phenylethyl]propan-2-amine 134.



and

(2*R*)-(+)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)-*N*-[(*R*)-1-phenylethyl]propan-2-amine 135.



In a flask fitted with a Dean-Stark apparatus, was added to a solution of ketone **131** (12 g, 46.3 mmol) in toluene (200 mL), propane-1-3-diol (8.3 mL, 109 mmol) and *p*-TsOH (3.5 g, 18.4 mmol). The resulting mixture was heated at reflux for 5h, then cooled to room temperature and was treated with 50 mL of a satured $NaHCO_3$ solution. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The 2 diastereoisomers were separated by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/19) to afford 5.03 g (34%, pale yellow liquid) of (*2R*)-(-)-**134**, and 4.60 g (31%, pale yellow liquid) of its diastereomer (2*S*)-(+)-**135**.

Data for (*2S*)-(-)-134 :

R_f : 0.55 (ethyl acetate/cyclohexane = 1/3).

$[\alpha]_D^{25}$ = -1.5 (c 1.06, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3357 (NH) ; 2967 ; 2874 ; 1245 ; 1151 ; 1107 (C-O) ; 701.

^{1}H NMR ($CDCl_3$) δ : 7.40-7.20 (m, 5H, H-Ar) ; 4.05 (m, 3H, H-9 and H-5) ; 3.89 (m, 2H, H-7) ; 3.56 (Qd,1H, J = 8 and 1.5 Hz, H-2) ; 2.05 (dd, 1H, J = 15 and 1.5 Hz, H-3) ; 1.95 (m, 2H, H-6 and NH) ; 1.82 (dd, 1H, J = 15 and 8 Hz, H-3) ; 1.52 (s, 3H, H-8) ; 1.46 (m, 1H, H-6) ; 1.40 (d, 3H, J = 6.5 Hz, H-10).

^{13}C NMR ($CDCl_3$) δ : 145.7 (C*ipso*) ; 128.2 (C-Ar) ; 126.8 (2C-Ar) ; 127.3 (q, J_{C-F} = 280 Hz, CF_3) ; 98.2 (C-4) ; 59.8 (C-5 and C-7) ; 56.6 (C-9) ; 53.7 (q, J_{C-F} = 28 Hz, C-2) ; 40.7 (C-3) ; 25.3 (C-6) ; 23.1 (C-8) ; 19.7 (C-10).

EI-MS (70eV) m/z : 317 (M^+, 2) ; 302 (60) ; 258 (45) ; 244 (65) ; 200 (30) ; 186 (35) ; 120 (35) ; 105 (100) ; 101 (80) ; 77 (20) ; 43 (40).

HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_2$ $(M+H)^+$: 318.1681, found 318.1669.

Data for (*2R*)-(+)-135 :

R_f : 0.51 (ethyl acetate/cyclohexane = 1/3).

$[\alpha]_D^{25}$ = + 27.5 (c 1.06, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3350 (NH) ; 2973 ; 2873 ; 1247 ; 1150 ; 1107 (C-O) ; 701.

^{1}H NMR ($CDCl_3$) δ : 7.30 (m, 5H, H-Ar) ; 3.99 (q, 1H, J = 6.5 Hz, H-9) ; 3.87 (m, 2H, H-7) ; 3.71 (m, 2H, H-5) ; 3.28 (m, 1H, H-2) ; 2.40 (br s, 1H, NH) ; 1.83 (m, 2H, H-3) ; 1.62 (m, 1H, H-6) ; 1.39 (d, 3H, J = 6.5 Hz, H-10) ; 1.29 (m, 1H, H-6) ; 1.20 (s, 3H, H-8).

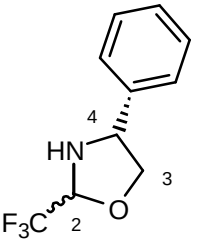
^{13}C NMR ($CDCl_3$) δ : 144.3 (C*ipso*) ; 128.3 (C-Ar) ; 127.2 (C-Ar) ; 127.1 (C-Ar) ; 127.1 (q, J_{C-F} = 282 Hz, CF_3) ; 98.3 (C-4) ; 59.6 (C-5 and C-7) ; 56.6 (C-9) ; 53.0 (q, J_{C-F} = 27 Hz, C-2); 40.0 (C-3) ; 24.8 (C-6) ; 24.1 (C-8) ; 18.8 (C-10).

^{19}F NMR ($CDCl_3$) δ : -77.6.

EI-MS (70eV) m/z : 317 (M^+, 1) ; 302 (60) ; 258 (45) ; 244 (65) ; 200 (30) ; 186 (35) ; 120 (70) ; 105 (100) ; 101 (80) ; 77 (20) ; 43 (40).

HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_2$ $(M+H)^+$: 318.1681, found 318.1669.

(4*R*)-4-Phenyl-2-(trifluoromethyl)-1,3-oxazolidine 136.



To a stirred solution of trifluoroacetaldehyde methylhemiacetal (10.68 g, 82.1 mmol) in toluene (130 mL) was added, (*R*)-(-)-phenylglycinol (11.26 g, 82 mmol) and *p*-TsOH (1.56 g, 8.2 mmol). The resulting mixture was heated at reflux under Dean-Stark conditions for 4 hours then cooled to room temperature. The toluene was eliminated under reduced pressure. After rapid elution (filtration like) on a silica gel column (ethyl acetate/cyclohexane = 1/5), the oxazolidine **136** (17.4 g, colorless liquid, yield : 97%) was obtained as an 1/2 unseparable mixture of diastereoisomers.

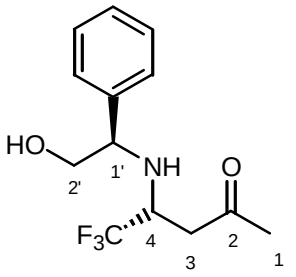
R_f : 0.70 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3365 (NH) ; 2895 ; 1458 ; 1291 ; 1153 ; 1122 (C-O).

^{1}H NMR ($CDCl_3$) δ : 7.35 (m, 5H, H-Ar) ; 5.16 (q, J = 5.5 Hz, 0.66H, H-2, 1st dia) ; 5.10 (q, J = 5 Hz, 0.33H, H-2, 2nd dia) ; 4.61 (dd, J = 9 and 7 Hz, 0.33H, H-3, 2nd dia) ; 4.52 (t, J = 7.5 Hz, 0.66H, H-3, 1st dia) ; 4.41 (t, J = 7.5 Hz, 0.66H, H-3, 1st dia) ; 4.34 (m, 0.33H, H-3, 2nd dia) ; 3.76 (m, 1H, H-4) ; 2.64 (br s, 1H, NH).

EI-MS (70eV) m/z : 216 (M^+, 1) ; <u>186</u> (100) ; 148 (75) ; 120 (60) ; 103 (45) ; 91 (45) ; 77 (25) ; 51 (20).

(4*R*)-(-)-5,5,5-Trifluoro-4-[(1*R*)-2-hydroxy-1-phenylethylamino]pentan-2-one 141.



To a stirred solution of oxazolidine **136** (1.00 g, 4.6 mmol) in dichloromethane (30 mL) was added isopropenyloxytrimethylsilane (1.15 mL, 10 mmol) and the reaction mixture was cooled to -15°C before addition of borontrifluoride diethyl etherate (1.41 mL, 10 mmol). The resulting mixture was stirred at -15°C for 1h before addition of 10 mL of saturated $NaHCO_3$. After separation, the aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate, filtered then concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave ketone **141** (1.07 g, yield : 85%) as a colorless liquid.

R_f : 0.15 (ethyl acetate/cyclohexane = 1/3).

$[\alpha]_D^{25}$ = -24.1 (c 0.90, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3421 (OH) ; 3346 (NH) ; 2934 ; 1719 (C=O) ; 1362 ; 1266 ; 1165 ; 1130.

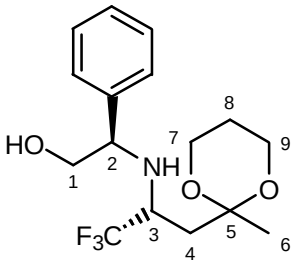
^{1}H NMR ($CDCl_3$) δ : 7.32 (m, 5H, H-Ar) ; 4.03 (dd, 1H, J = 8 and 4 Hz, H-1') ; 3.81 (m, 1H, H-4) ; 3.75 (dd, 1H, J = 11 and 4 Hz, H-2') ; 3.58 (dd, 1H, J = 11.5 and 8 Hz, H-2') ; 2.94 (br s, 1H, OH) ; 2.80 (dd, 1H, J = 17.5 and 4 Hz, H-3) ; 2.70 (dd, 1H, J = 17.5 and 8.5 Hz, H-3) ; 2.18 (s, 3H, H-1) ; 1.90 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) δ : 205.7 5 (C-2) ; 140.3 (C*ipso*) ; 128.6 (C-Ar) ; 128.2 (C-Ar) ; 127.4 (C-Ar) ; 126.3 (q, J_{C-F} = 283 Hz, CF_3) ; 67.2 (C-2') ; 62.2 (C-1') ; 53.5 (q, J_{C-F} = 29 Hz, C-4) ; 43.0 (C-3) ; 30.6 (C1).

EI-MS (70eV) m/z : <u>244</u> ($(M-CH_2OH)^+$; 100) ; 186 (20) ; 159 (25) ; 104 (10) ; 77 (20) ; 43 (15).

HR-ESI-MS calculated for $C_{13}H_{16}F_3NNaO_2$ $(M+Na)^+$: 298.10131, found 298.1018.

(2*R*)-2-Phenyl-2-[(2*R*)-1,1,1-trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-ylamino]ethanol 142.



In a flask fitted with a Dean-Stark apparatus, was added to a solution of **141** (915 mg, 3.3 mmol) in benzene (40 mL), propane-1,3-diol (640 µL, 8.25 mmol) and *p*-TsOH (316 mg, 1.6 mmol). The resulting mixture was heated at reflux for 2h then allowed to cool to room temperature and was treated with a satured $NaHCO_3$ solution (10 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave compound **142** (775 mg, yield : 75%), accompanied with a minor unseparable and unidentified impurity.

R_f : 0.32 (ethyl acetate/cyclohexane = 1/2).

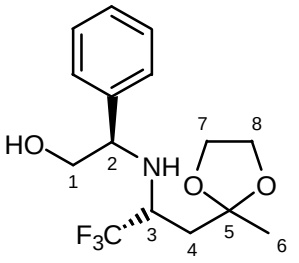
^{1}H NMR ($CDCl_3$) δ : 7.34 (m, 5H, H-Ar) ; 4.10-3.46 (m, 8H, H-1, H-2, H-3, H-7 and H-9) ; 3.40 (br s, 1H, OH) ; 2.03 (dd, 1H, J = 15 and 2 Hz, H-4) ; 1.99 (m, 1H, H-8) ; 1.87 (dd, 1H, J = 15 and 8 Hz, H-4) ; 1.87 (br s, 1H, NH) ; 1.80 (s, 3H, H-6) ; 1.46 (m, 1H, H-8).

^{13}C NMR ($CDCl_3$) δ : 141.2 (C*ipso*) ; 128.6 (C-Ar) ; 128.2 (C-Ar) ; 127.3 (C-Ar) ; 126.8 (q, J_{C-F} = 280 Hz, CF_3) ; 98.5 (C-5) ; 66.7 (C-1) ; 63.2 (C-2) ; 60.0 (C-7 and C-9) ; 54.3 (q, J_{C-F} = 28 Hz, C-3) ; 41.7 (C-4) ; 25.1 (C-8) ; 19.5 (C-6).

EI-MS (70eV) m/z : 318 ($(M-Me)^+$, 5) ; 302 (100) ; 244 (90) ; 186 (50) ; 159 (25) ; 106 (25) ; 43 (40).

HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_3$ $(M+H)^+$: 334.1630, found 334.1615.

(2*R*)-(-)-2-Phenyl-2-[(2*R*)-1,1,1-trifluoro-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-ylamino]ethanol 143.



In a flask fitted with a Dean-Stark apparatus, was added, to a solution of **141** (2.0 g, 7.3 mmol) in benzene (30 mL), 1,2-ethanediol (1.15mL, 18.25 mmol) and *p*-TsOH (700 mg, 3.6 mmol). The resulting mixture was heated at reflux for 6h then allowed to cool to room temperature and was treated with 30 mL of a satured $NaHCO_3$ solution. The two layers were separated and the aqueous phase was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave compound **143** (1.59 g, yield : 68%) as a pale yellow oil.

R_f : 0.29 (ethyl acetate/cyclohexane = 1/2).

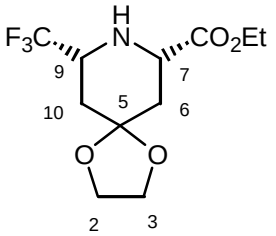
$[\alpha]_D^{25}$ = -19.2 (c 1.19, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3422 (OH) ; 2984 ; 2888 ; 1380 ; 1260 ; 1133 ; 1117 ; 1040 (C-O) ; 703.

^{1}H NMR ($CDCl_3$) δ : 7.33 (m, 5H, H-Ar) ; 4.00 (m, 5H, H-2 , H-7 and H-8) ; 3.74 (m, 1H, ,H-1) ; 3.55 (m, 1H, H-1) ; 3.36 (Q, 1H, J = 8 Hz, H-3) ; 3.09 (br s, 1H, OH) ; 2.17 (d, 1H, J = 15 Hz, H-4) ; 1.87 (dd, 1H, J = 15 and 8 Hz, H-4) ; 1.58 (br s, 1H, NH) ; 1.44 (s, 3H, H-6).

EI-MS (70eV) m/z : <u>288</u> ($(M-CH_2OH)^+$, 100) ; 244 (20) ; 186 (25) ; 159 (15) ; 87 (40) ; 43 (35).

(±)-(7*S, 9*R**) Ethyl [9-(trifluoromethyl)-8-aza-1,4-dioxaspiro[4.5]decane-7-yl]carboxylate 147a.**



To a stirred solution of amine (±)-**105** (500 mg, 2.52 mmol) in toluene (20 mL) was added a 50% ethyl glyoxylate solution (266 µL, 2.60 mmol) and 500 mg of $MgSO_4$. The mixture was stirred at room temperature for 30 min and imine thus formed was filtered, followed by evaporation of solvent under reduced pressure. A solution of dry *para*-toluenesulfonic acid (863 mg, 1.8 mmol, previously dried under Dean-Stark conditions in 60 mL of toluene) was transferred into the stirred solution of imine at 70°C and stirred at same temperature for 1hour. The reaction mixture was cooled to room temperature and treated with a saturated $NaHCO_3$ solution (10 mL). The two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/9) afforded piperidine **147a** (305 mg, yield : 43%) as a yellow oil.

R_f : 0.35 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3346 (NH) ; 2982 ; 1736 (C=O) ; 1260 (C-O) ; 1179 ; 1133 (C-O).

^{1}H NMR ($CDCl_3$) δ : 4.19 (m, 2H, CH_2 ester) ; 3.99 (m, 4H, H-2 and H-3) ; 3.60 (dd, 1H, J = 12.5 and 3 Hz, H-7) ; 3.42 (m, 1H, H-9) ; 2.12 (br s, 1H, NH) ; 2.07 (dt, 1H, J = 12.5 and 2.5 Hz, H-6eq) ; 1.86 (dt, 1H, J = 12.5 and 2.5 Hz, H-10eq) ; 1.63 (t, 1H, J= 12.5, H-6ax) ; 1.62 (t, 1H, J= 12.5, H-10ax) ; 1.27 (t, 3H, J = 7 Hz, Me).

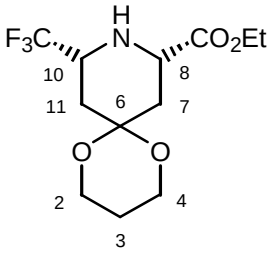
^{13}C NMR ($CDCl_3$) δ : 171.4 (C=O) ; 125.1 (q, J_{C-F} = 277 Hz, CF_3) ; 106.4 (C-5) ; 64.7 (C-2) ; 64.6 (C-3) ; 61.4 (CH_2 ester) ; 55.8 (C-7) ; 55.6 (q, J_{C-F} = 29 Hz, C-9) ; 37.7 (C-6) ; 34.3 (C-10) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.3.

EI-MS (70eV) m/z : 283 (M^+, 1) ; 210 (70) ; 167 (100) ; 124 (25) ; 87 (70) ; 43 (25).

HR-ESI-MS calculated for $C_{11}H_{17}F_3NO_4$ $(M+H)^+$: 284.1110, found 284.1106.

(8*S*, 10*R*)-(+)-Ethyl [10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]carboxylate 148a.



To a stirred solution of amine (+)-**19** (1 g, 4.7 mmol) in toluene (20 mL) was added a 50% ethyl glyoxylate solution (1.1 mL, 10.6 mmol) and 500 mg of $MgSO_4$. The mixture was stirred at room temperature for 30min and imine thus formed was filtered followed by elimination of solvent under reduced pressure. A solution of dry *para*-toluenesulphonic acid (863 mg, 1.8 mmol, previously dried under Dean-Stark conditions in 100 mL of toluene) was transferred into the stirred solution of imine at 70°C and stirred at same temperature for 1h. The reaction mixture was cooled to room temperature and treated with a saturated $NaHCO_3$ solution (10 mL). The two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/7) afforded piperidine **148a** (767 mg, yield : 55%) as a yellow oil.

$\mathbf{R_f}$: 0.50 (ethyl acetate/cyclohexane = 1/3).
$\mathbf{[\alpha]_D^{25}}$ = + 16. 5 (c 1.02, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3347 (NH) ; 2980 ; 1740 (C=O) ; 1265 (C-O) ; 1179 ; 1129 (C-O) ; 1084 (C-O) ; 1040 (C-O).

^{1}H NMR ($CDCl_3$) δ : 4.21 (m, 2H, CH_2 ester) ; 4.02-3.84 (m, 4H, H-2 and H-4) ; 3.57 (dd, 1H, J = 12.5 and 3 Hz, H-8) ; 3.39 (m, 1H, H-10) ; 2.68 (dt, 1H, J = 13.5 and 2.5 Hz, H-7eq) ; 2.39 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 2.22 (br s, 1H, NH) ; 1.76 (m, 2H, H-3) ; 1.45 (t, 2H, J= 13 Hz, H-7ax and H-11ax) ; 1.28 (t, 3H, J= 7.5 Hz, Me).

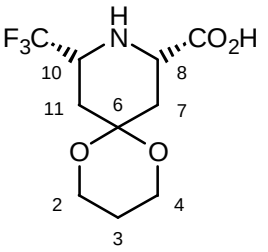
^{13}C NMR ($CDCl_3$) δ : 171.7 (COO) ; 125.4 (q, J_{C-F} = 277 Hz, CF_3) ; 95.9 (C-6) ; 61.3 (CH_2 ester) ; 59.4 (C-2 and C-4) ; 54.5 (C-8) ; 54.4 (q, J_{C-F} = 29 Hz, C-10) ; 35.2 (C-7) ; 33.2 (C-11); 25.2 (C-3) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.1.

EI-MS (70eV) m/z : 297 (M^+, 1) ; 224 (80) ; <u>181</u> (100) ; 166 (20) ; 124 (25) ; 101 (20) ; 43 (15).

HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_4$ $(M+H)^+$: 298.1266, found 298.1262.

(8*S*, 10*R*)-(+)-[10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]carboxylic acid 149.



Following the saponification general procedure, ester **148a** (150 mg, 0.5 mmol) in methanol (7 mL) was treated with a 0.3M NaOH solution (2.2 ml, 0.6 mmol) to give aminoacid **149** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure aminoacid **149** (127 mg, yield : 93%) as a white solid.

M.p : 118°C.

R_f : 0.18 (ethyl acetate).

$[\alpha]_D^{25}$ = +9.84 (c 0.62, MeOH).

IR (KBr) σ (cm^{-1}) : 3500-2500 (COOH+NH) ; 1589 ; 1269 (C-O) ; 1183 ; 1126 (C-O) ; 1084 (C-O) ; 1035.

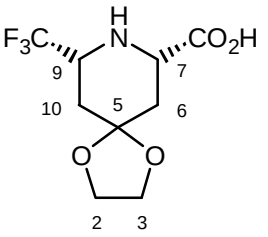
^{1}H NMR (D_2O) δ : 3.94 (m, 4H, H-2 and H-4) ; 3.50 (m, 1H, H-10) ; 3.31 (dd, 1H, J = 13 and 3 Hz, H-8) ; 2.69 (dt, 1H, J = 13.5 and 3 Hz, H-7eq) ; 2.43 (dt, 1H, J = 13.5 and 2.5 Hz, H-11eq) ; 1.70 (m, 2H, H-3) ; 1.48 (t, 1H, J= 13 Hz, H-7ax) ; 1.36 (t, 1H, J= 13.5, H-11ax).

^{13}C NMR (D_2O) δ : 177.3 (COO) ; 124.8 (q, J_{C-F} = 277 Hz, CF_3) ; 96.8 (C-6) ; 59.7 (C-2 and C-4) ; 56.4 (C-8) ; 53.5 (q, J_{C-F} = 30 Hz, C-10) ; 35.3 (C-7) ; 34.7 (C-11) ; 24.5 (C-3).

^{19}F NMR (CD_3OD) δ : -79.5.

HR-ESI-MS calculated for $C_{10}H_{15}F_3NO_4$ $(M+H)^+$: 270.0953, found 270.0944

(7*S*, 9*R*)-(+)-[9-(Trifluoromethyl)-1,4-dioxa-8-azaspiro[4.5]decan-7-yl]carboxylic acid 150.



Following the saponification general procedure, compound **147a** (80 mg, 0.28 mmol) in methanol (6 mL) was treated with a 0.3M NaOH solution (1.13 ml, 0.34 mmol) to give aminoacid **150** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure aminoacid **150** (61 mg, yield : 85%) as a white solid.

M.p: 128-130°C.

$\mathbf{R_f}$: 0.12 (ethyl acetate).

$\mathbf{[\alpha]_D^{25}}$ = +13.9 (c 0.91, MeOH).

IR (KBr) σ (cm^{-1}) : 3450-2780 (COOH+NH) ; 1728 (C=O) ; 1407 ; 1268 (C-O) ; 1170 ; 1078 (C-O) ; 1018 (C-O) ; 953 ; 744.

^{1}H NMR (D_2O) δ : 4.09 (m, 5H, H-2, H-3 and H-9) ; 3.77 (dd, 1H, J = 13.5 and 3.5 Hz, H-7) ; 2.27 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.21 (dt, 1H, J = 13.5 and 3 Hz, H-10eq) ; 1.92 (t, 1H, J= 13 Hz, H-6ax) ; 1.85 (t, 1H, J= 13.5 Hz, H-10ax).

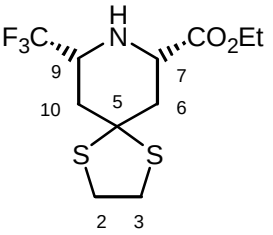
^{13}C NMR (D_2O) δ : 172.5 (COO) ; 123.1 (q, J_{C-F} = 278 Hz, CF_3) ; 104.7 (C-5) ; 65.0 (C-2) ; 64.8 (C-3) ; 58.1 (C-7) ; 54.6 (q, J_{C-F} = 32 Hz, C-9) ; 35.2 (C-6) ; 30.8 (C-10).

^{19}F NMR (CD_3OD) δ : -77.8.

HR-ESI-MS calculated for $C_9H_{13}F_3NO_4$ $(M+H)^+$: 256.0797, found 256.0786.

(7*S*, 9*R*)-(+)-Ethyl [9-(trifluoromethyl)-1,4-dithia-8-azaspiro[4.5]decan-7-yl]carboxylate

152.



Following the general procedure for dithioketalization, protected piperidone **148a** (535 mg, 1.8 mmol) in dichloromethane (20 mL), ethanedithiol (1.2 mL, 12.7 mmol) and $BF_3.Et_2O$ (1.7 mL, 12 mmol) gave, after purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/9) dithiolane **152** (549 mg, yield : 96%) as a yellow oil.

R_f : 0.62 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = + 10. 0 (c 1.0, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3326 (NH) ; 2979 ; 1736 (C=O) ; 1260 (C-O) ; 1174 ; 1133 (C-O) ; 1028.

^{1}H NMR ($CDCl_3$) δ : 4.20 (m, 2H, CH_2 ester) ; 3.58 (br d, 1H, J = 12 Hz, H-7) ; 3.40 (m, 1H, H-9) ; 3.36 (s, 4H, H-2 and H-3) ; 2.46 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-10eq) ; 2.21 (br s 1H, NH) ; 2.00 (t, 1H, J = 12 Hz, H-6ax) ; 1.99 (t, 1H J = 12 Hz, H-10ax) ; 1.28 (t, 3H, J = 7 Hz, Me).

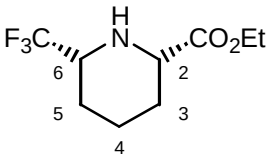
^{13}C NMR ($CDCl_3$) δ : 171.0 (COO) ; 124.5 (q, J_{C-F} = 278 Hz, CF_3) ; 64.6 (C-5) ; 61.5 (CH_2 ester) ; 57.3 (C-7) ; 57.1 (q, J_{C-F} = 29 Hz, C-9) ; 44.0 (C-2) ; 40.6 (C-3) ; 39.4 (C-6) ; 38.3 (C-10) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -79.9.

EI-MS (70eV) m/z : 315 (M^+, 20) ; 286 (20) ; <u>242</u> (100) ; 222 (65) ; 199 (80) ; 182 (55) ; 124 (70) ; 119 (80).

HR-ESI-MS calculated for $C_{11}H_{17}F_3NO_2S_2(M+H)^+$: 316.0639, found 316.0653.

(2*S*, 6*R*)-(-)-Ethyl 6-(trifluoromethyl)piperidine-2-carboxylate 153.



Following the general procedure of Raney nickel hydrogenolysis, dithioketal **152** (127 mg, 0.40 mmol) in absolute ethanol (8 mL) treated with W2 Raney nickel (*ca* 500 mg), gave pure compound **153** (83 mg, yield : 90%) as a colorless oil.

R_f : 0.60 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = -5.5 (c 1.0, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3347 (NH) ; 2945 ; 1738 (C=O) ; 1216 (C-O) ; 1181 (C-O) ; 1157 ; 1120 ; 1091 ; 1032.

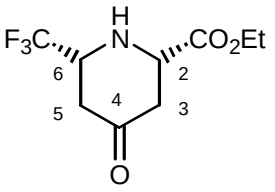
^{1}H NMR ($CDCl_3$) δ : 4.19 (m, 2H, CH_2 ester) ; 3.34 (m, 1H, H-2) ; 3.17 (m, 1H, H-6) ; 2.17 (br s, 1H, NH) ; 2.04 (m, 2H) ; 1.84 (m, 2H) ; 1.42 (m, 2H) ; 1.27 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 172.0 (COO) ; 125.5 (q, J_{C-F} = 278 Hz, CF_3) ; 61.1 (CH_2 ester) ; 58.2 (C-2) ; 58.1 (q, J_{C-F} = 29 Hz, C-6) ; 28.2 (C-3) ; 24.3 (C-5) ; 23.0 (C-4) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.3.

EI-MS (70eV) m/z : 225 (M^+, 1) ; 152 (100) ; 132 (10) ; 124 (10) ; 82 (10) ; 55 (25).

(2*S*, 6*R*)-(-)-Ethyl 4-oxo-6-(trifluoromethyl)piperidine-2-carboxylate 154.



To a stirred solution of ketal **148a** (500 mg, 1.68 mmol) in CH_3CN (5 mL) was added, at 70°C, in one portion, a solution of CAN (2.2 g , 4 mmol) in H_2O (10 mL). The resulting mixture was stirred at 70°C for 5h then was allowed to cool to room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and then neutralized by addition of saturated K_2CO_3 before extraction with diethyl ether (4 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/5) to afford piperidone **154 (**333 mg, yield : 78%) as a white solid.

M.p : 68-70°C.

$[\alpha]_D^{25}$ = -14.0 (c 0.91, $CHCl_3$).

R_f : 0.40 (ethyl acetate/cyclohexane = 1/3).

IR (KBr) σ (cm^{-1}) : 3340 (NH) ; 2982 ; 1743 (C=O ester) ; 1706 (C=O ketone) ; 1284 (C-O) ; 1176 ; 1133 (C-O) ; 1055 ; 1026.

^{1}H NMR ($CDCl_3$) δ : 4.25 (m, 2H, CH_2 ester) ; 3.66 (dd, 1H, J = 12.5 and 2.5 Hz, H-2) ; 3.52 (m , 1H, H-6) ; 2.78 (ddd, 1H, J = 15, 3.5 and 2 Hz, H-3 *pseudo*-eq) ; 2.61 (ddd, 1H, J = 14.5, 3.5 and 2 Hz, H-5 *pseudo*-eq) ; 2.48 (m, 3H, H-3 *pseudo*-ax, H-5 *pseudo*- ax and NH) ; 1.30 (t, 3H, J = 7 Hz , Me).

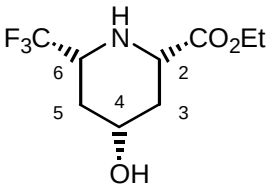
^{13}C NMR ($CDCl_3$) δ : 203.2 (C=O) ; 170.1 (COO) ; 124.4 (q, J_{C-F} = 278 Hz, CF_3) 62.0 (CH_2 ester) ; 56.6 (C-2) ; 56.6 (q, J_{C-F} = 29 Hz, C-6) ; 43.8 (C-3) ; 40.5 (C-5) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.7.

EI-MS (70eV) m/z : 239 (M^+, 1) ; 166 (70) ; 124 (100).

HR-ESI-MS calculated for $C_9H_{13}F_3NO_3$ $(M+H)^+$: 240.0848, found 240.0853.

(2*S*, 4*S*, 6*R*)-(-)-Ethyl 4-hydroxy-6-(trifluoromethyl)piperidine-2-carboxylate 155.



To a cooled (-30°C) stirred solution of piperidone **154** (140 mg, 0.58 mmol) in ethanol (10 mL) was added sodium borohydride (27 mg, 0.71 mmol). The resulting mixture was stirred for 1h before addition of saturated aqueous NH_4Cl (5 mL). After warming to room temperature, the ethanol was removed *in vacuo*. The residue was then extracted with dichloromethane (4 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvents, followed by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/5) afforded piperidinol **155** (120 mg, yield : 85%) as a white solid.

M.p : 102°C.

$[\alpha]_D^{25}$ = -0.1 (c 0.94, $CHCl_3$).

R_f : 0.30 (ethyl acetate/cyclohexane = 1/3).

IR (KBr) σ (cm^{-1}) : 3340 (NH + OH) ; 2972 ; 1727 (C=O) ; 1268 (C-O) ; 1243 ; 1179 (C-O) ; 1048 (C-O) ; 831 ; 701.

^{1}H NMR ($CDCl_3$) δ : 4.22 (m, 2H, CH_2 ester) ; 3.79 (m, 1H, H-4) ; 3.39 (dd, 1H, J = 12.5 and 2.5 Hz , H-2) ; 3.22 (m, 1H, H-6) ; 2.38 (dQ, 1H, J = 12.5 and 2 Hz, H-3eq) ; 2.18 (dQ, 1H, J = 12 and 2 Hz, H-5eq) ; 1.60 (br s, 2H, NH and OH) ; 1.41 (q, 1H, J = 12 Hz, H-3ax) ; 1.39 (q, 1H, J = 12 Hz, H-5ax) ; 1.29 (t, 3H, J = 7 Hz, Me).

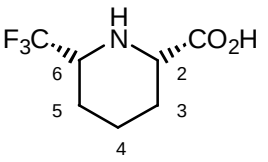
^{13}C NMR ($CDCl_3$) δ : 171.2 (COO) ; 125.0 (q, J_{C-F} = 277 Hz, CF_3) ; 67.8 (CH_2 ester) ; 61.5 (C-4) ; 56.2 (C-2) ; 55.7 (q, J_{C-F} = 30 Hz, H-6) ; 37.5 (C-3) ; 33.7 (C-5) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.2.

EI-MS (70eV) m/z : 241 (M^+, 1) ; 168 (100) ; 150 (70) ; 124 (50).

HR-ESI-MS calculated for $C_9H_{15}F_3NO_3$ $(M+H)^+$: 242.1004, found 242.0991.

(2*S*, 6*R*)-(-)-6-(Trifluoromethyl)piperidine-2-carboxylic acid 156.



Following the general procedure of saponification, compound **153** (56 mg, 0.45 mmol) in methanol (4 mL) was treated with a 0.3M NaOH solution (1.8 mL, 0.54 mmol) to give aminoacid **156** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure aminoacid **156** (47 mg, yield : 96%) as a white solid.

M.p: 118°C.

$[\alpha]_D^{25}$ = -11.2 (c 1.0, MeOH).

IR (KBr) σ (cm^{-1}) : 3500-2500 (COOH+NH) ; 1587 ; 1383 ; 1263 ; 1184 ; 1117 ; 1091.

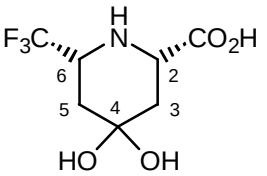
^{1}H NMR (D_2O) δ : 3.50 (m, 1H, H-6) ; 3.27 (dd, 1H, J = 12 and 3 Hz, H-2) ; 2.01 (m, 1H, H-3eq) ; 1.90 (m, 2H, H-5eq and H-4) ; 1.55-1.25 (m, 3H, H-3ax, H-5ax and H-4).

^{13}C NMR (D_2O) δ : 177.2 (COO) ; 124.6 (q, J_{C-F} = 270 Hz, CF_3) ; 68.3 (C-2) ; 56.7 (q, J_{C-F} = 30 Hz, C-6) ; 27.4 (C-3) ; 22.5 (C-5) ; 22.0 (C-4).

^{19}F NMR (CD_3OD) δ : -80.0.

HR-ESI-MS calculated for $C_7H_{11}F_3NO_2$ $(M+H)^+$: 197.0742, found 197.0724.

(2*S*, 6*R*)-(-)-4,4-Dihydroxy-6-(trifluoromethyl)piperidine-2-carboxylic acid 158.



Following the saponification general procedure, compound **154** (70 mg, 0.29 mmol) in methanol (5 mL) was treated with a 0.3M NaOH solution (1.17 ml, 0.38 mmol) to give aminoacid **158** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure amino acid **158** (56 mg, yield : 90%) as a white solid.

M.p: 95°C.

$[\alpha]_D^{25}$ = -2.1 (c 1.0, MeOH).

IR (KBr) σ (cm^{-1}) : 3426 (OH+NH) ; 1736 , (COOH) ; 1635 ; 1264 ; 1203 ; 1145 ; 1083 ; 946.

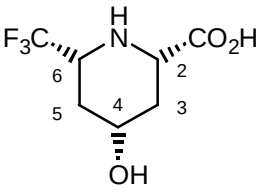
^{1}H NMR (D_2O) δ : 4.34 (m, 1H, H-6) ; 4.23 (dd, 1H, J = 13 and 3.5 Hz, H-2) ; 2.53 (dt, 1H, J = 14 and 3.5 Hz, H-3eq) ; 2.37 (dt, 1H, J = 14 and 3 Hz, H-5eq) ; 2.08 (t, 2H, J= 13.5 Hz, H-3ax and H-5ax).

^{13}C NMR (D_2O) δ : 169.5 (COO) ; 122.6 (q, J_{C-F} = 279 Hz, CF_3) ; 90.3 (C-4) ; 56.1 (C-2) ; 54.3 (q, J_{C-F} = 33 Hz, C-6) ; 36.8 (C-3) ; 33.2 (C-5).

^{19}F NMR (CD_3OD) δ : -75.1.

HR-ESI-MS calculated for $C_7H_9F_3NO_3$ $[(M-H_2O) + H]^+$: 212.0535, found 212.0545.

(2*S*, 4*S*, 6*R*)-(-)-4-Hydroxy-6-(trifluoromethyl)piperidine-2-carboxylic acid 159.



Following the saponification general procedure, compound **155** (102 mg, 0.42 mmol) in methanol (6 mL) was treated with a 0.3M NaOH solution (1.68 mL, 0.5 mmol) to give aminoacid **159** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure aminoacid **159** (81 mg, yield : 90%) as a white solid.

M.p : 145°C.

$[\alpha]_D^{25}$ = -9.3 (c 0.95, MeOH).

IR (KBr) σ (cm^{-1}) : 3500-2500 (OH+NH) ; 1679 ; 1580 ; 1423 ; 1388 ; 1272 ; 1190 ; 1154 ; 1105 ; 1063.

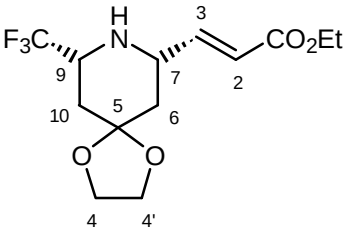
^{1}H NMR (D_2O) δ : 3.92 (tt, 1H, J = 11.5 and 4.5 Hz, H-4) ; 3.62 (m, 1H, H-6) ; 3.40 (dd, 1H, J = 12.5 and 3 Hz, H-2) ; 2.37 (dQ, 1H, J = 12 and 3 Hz, H-3eq) ; 2.26 (dQ, 1H, J = 12.5 and 2.5 Hz, H-5eq) ; 1.44 (q, 1H, J = 12 Hz, H-3ax) ; 1.38 (td, 1H, J = 12.5 and 11 Hz, H-5ax).

^{13}C NMR (D_2O) δ : 176.6 (COO) ; 124.4 (q, J_{C-F} = 277 Hz, CF_3) ; 66.3 (C-4) ; 58.3 (C-2) ; 55.0 (q, J_{C-F} = 30 Hz, C-6) ; 36.2 (C-3) ; 31.3 (C-5).

^{19}F NMR (CD_3OD) δ : -77.7.

HR-ESI-MS calculated for $C_7H_{11}F_3NO_3$ $(M+H)^+$: 214.0691, found 214.0700.

(±)-(2*E*)- Ethyl 3-[(7*S, 9*R**)-9-(trifluoromethyl)-1,4-dioxa-8-azaspiro[4.5]decan-7-yl]prop-2-enoate 160.**



To a stirred solution of amine **105** (500 mg, 2.5 mmol) in toluene (20 mL) was added ethyl *trans*-4-oxo-2-butenoate (355µL, 2.75 mmol) and 500 mg of $MgSO_4$. The mixture was stirred at room temperature for 30min and imine thus formed was filtered, followed by elimination of solvent under reduced pressure. A solution of dry *para*-toluenesulphonic acid (864 mg, 4.5 mmol, previously dried under Dean-Stark conditions in 70 mL of toluene) was transferred into the stirred solution of imine at 70°C and stirred at same temperature for 1h. The reaction mixture was cooled to room temperature and treated with a saturated $NaHCO_3$ solution (10 mL). The two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/9) afforded piperidine **160** (382 mg, yield : 51%) as a yellow oil.

R_f : 0.40 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3317 (NH) ; 2982 ; 2892 ; 1716 (C=O) ; 1659 (C=C) ; 1275 (C-O) ; 1173 (C-O) ; 1136 (C-O).

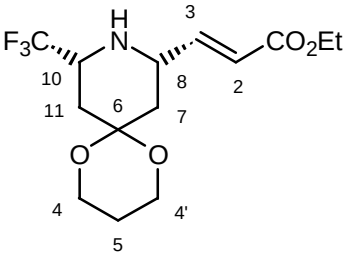
^{1}H NMR ($CDCl_3$) δ : 6.89 (dd, 1H, J = 16 and 6 Hz, H-3) ; 6.01 (m, 1H, H-2) ; 4.19 (m, 2H, CH_2 ester) ; 3.99 (m, 4H,H-4 and H-4') ; 3.61 (m, 1H, H-7) ; 3.47 (m, 1H, H-9) ; 1.88 (dt, 1H, J = 12.5 and 2.5 Hz, H-6eq) ; 1.79 (dt, 1H, J = 13 and 2.5 Hz, H-10eq) ; 1.64 (t, 1H, J = 12.5 Hz, H-6ax) ; 1.49 (t, 1H, J = 12.5 Hz, H-10ax) ; 1.28 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 166.2 (COO) ; 150.3 (C-3) ; 125.3 (q, J_{C-F} = 277 Hz, CF_3) ; 121.4 (C-2); 106.4 (C-5) ; 64.6 (C-4 and C-4') ; 60.6 (CH_2 ester) ; 55.8 (q, J_{C-F} = 30 Hz, C-9) ; 54.4 (C-7) ; 40.3 (C-6) ; 34.0 (C-10) ; 14.1 (Me).

EI-MS (70eV) m/z : 309 (M^+, 10) ; 280 (90) ; 264 (40) ; 236 (35) ; <u>167</u> (100) ; 150 (20) ; 87 (70) ; 43 (20).

HR-ESI-MS calculated for $C_{13}H_{19}F_3NO_4$ $(M+H)^+$: 310.1266, found 310.1277.

(2*E*)-(+)-Ethyl 3-[(8*S*, 10*R*)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]prop-2-enoate 161.



To a stirred solution of amine (*R*)-(+) **19** (1 g, 4.7 mmol) in toluene (25 mL) was added ethyl *trans*-4-oxo-2-butenoate 96% (625 µL, 4.9 mmol) and 500 mg of $MgSO_4$. The mixture was stirred at room temperature for 30 minutes. Intermediate imine solution thus formed was filtered in order to remove the magnesium sulfate. A solution of dry *para*-toluenesulphonic acid (864 mg, 4.5 mmol, previously dried for 3h under Dean-Stark conditions in 70 mL of toluene) was transferred into the stirred solution of imine at 70°C and stirred at same temperature for 1h. The reaction mixture was cooled to room temperature and treated with a saturated $NaHCO_3$ solution (15 mL). The two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica-gel column chromatography (ethyl acetate/cyclohexane = 1/7) afforded piperidine **161** (1.03 g, yield : 68%) as a yellow oil.

R_f : 0.55 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = + 18.5 (c 1.02, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3315 (NH) ; 1715 (C=O) ; 1659 (C=C) ; 1273 (C-O) ; 1173 (C-O) ; 1131 (C-O).

^{1}H NMR ($CDCl_3$) δ : 6.81 (dd, 1H, J = 16 and 6 Hz, H-3) ; 5.95 (dd, 1H, J = 16 and 0.5 Hz, H-2) ; 4.10 (q, 2H, J = 7 Hz, CH_2 ester) ; 3.85 (t, 2H, J = 5.5 Hz, H-4) ; 3.80 (t, 2H, J = 5.5 Hz, H-4') ; 3.49 (m, 1H, H-8) ; 3.35 (m, 1H, H-10) ; 2.38 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.26 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 1.67 (m, 3H, H-5 and NH) ; 1.38 (t, 1H, J = 13 Hz, H-7ax) ; 1.23 (t, 1H, J = 13 Hz, H-11ax) ; 1.22 (t, 3H, J = 7 Hz, Me).

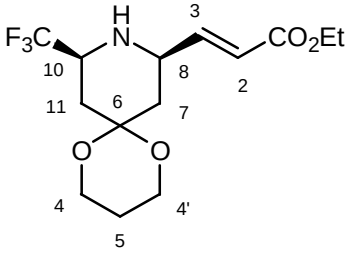
^{13}C NMR ($CDCl_3$) δ : 166.2 (COO) ; 148.1 (C-3) ; 125.5 (q, J_{C-F} = 277 Hz, CF_3) ; 121.3 (C-2) 95.8 (C-6) ; 60.5 (CH_2 ester) ; 59.4 (C-4) ; 59.3 (C-4') ; 54.7 (q J_{C-F} = 30 Hz, C-10) ; 52.9 (C-8) ; 38.1 (C-7) ; 31.8 (C-11) ; 25.3 (C-5) ; 14.2 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 323 (M^+, 10) ; <u>294</u> (100) ; 264 (40) ; 236 (40) ; 181 (60) ; 150 (20) ; 101 (60) ; 43 (40).

HR-ESI-MS calculated for $C_{14}H_{21}F_3NO_4$ $(M+H)^+$: 324.1423, found 324.1437.

(2*E*)-(-)-Ethyl 3-[(8*R*, 10*S*)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]prop-2-enoate 161.

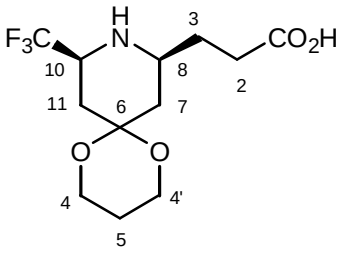


Following the same procedure as previous,but starting from amine (*S*)-(-)-**19** (1 g, 4.7 mmol) and ethyl *trans*-4-oxo-2-butenoate (680 µL, 5.3 mmol), afforded piperidine (-) **161** (1 g, yield : 66%) as yellow oil.

$[\alpha]_D^{25}$ = - 18.5 (c 1.10, $CHCl_3$).

Note : other analytical data are identical to those given for the compound (+)-**161** (*vide supra*).

(±)-3-[(8*S, 10*S**)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]propanoic acid 162.**



Following the general procedure of saponification, ester **163** (56 mg, 0.45 mmol) in methanol (5 mL) was treated with a 0.3M NaOH solution (1.4 mL, 0.54 mmol) to give aminoacid **162** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50 w X 8-100) afforded pure aminoacid **162** (47 mg, yield : 92%) as a white solid.

M.p : 149°C.

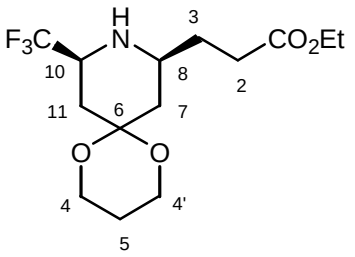
R_f : 0.10 (ethyl acetate).

IR (KBr) σ (cm^{-1}) : 3434 (OH) ; 3240 (NH) ; 2962 ; 1704 (C=O) ; 1276 (C-O) ; 1117 (C-O) ; 1026 ; 929.

^{1}H NMR (D_2O) δ : 4.08-3.92 (m, 5H, H-10, H-4 and H-4') ; 3.26 (m, 1H, H-8) ; 2.77 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.59 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 2.49-2.32 (m, 2H, H-2); 1.97 (m, 1H, H-5) ; 1.85-1.75 (m, 3H, H-5 and H-3) ; 1.75 (t, 1H, J = 14 Hz, H-7 ax) ; 1.52 (dd, J = 13 and 12.5 Hz, H-11ax).

^{13}C NMR (D_2O) δ : 180.1 (COO) ; 123.6 (q, J_{C-F} = 277 Hz, CF_3) ; 95.4 (C-6) ; 60.0 (C-4) ; 59.9 (C-4') ; 54.3 (q, J_{C-F} = 31 Hz, C-10) ; 54.1 (C-8) ; 35.5 (C-2) ; 32.5 (C-5) ; 29.6 (C-7) ; 28.6 (C-11) ; 24.4 (C-3).

(±)-Ethyl 3[(8*S, 10*S**)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]propanoate 163.**



To a stirred solution of compound (±)-**161** (500 mg, 1.5 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ 20% (200 mg). The mixture was stirred at room temperature under hydrogen atmosphere for 1h then filtered through Celite®.The filtrate was concentrated under reduced pressure then purified by column chromatography on silica-gel (ethyl actetate/cyclohexane = 1/3), to afford saturated piperidine **163** (477 mg, yield : 95%) as a colorless liquid.

$\mathbf{R_f}$: 0.40 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3321 (NH) ; 2976 ; 1731 (C=O) ; 1266 (C-O) ; 1171 (C-O) ; 1133 (C-O) ; 1088 ; 1016.

^{1}H NMR ($CDCl_3$) δ : 3.89 (q, 2H, J = 7 Hz, CH_2 ester) ; 3.70 (t, 2H, J = 5.5 Hz, H-4) ; 3.63 (t, 2H, J = 5.5 Hz, H-4') ; 3.12 (m, 1H, H-10) ; 2.60 (m, 1H, H-8) ; 2.22 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.17 (t, 2H, J = 7 Hz, H-2) ; 2.02 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 1.51 (m, 4H, H-5 and H-3) ; 1.38 (t, 1H, J = 12.5 Hz, H-7ax) ; 1.38 (br s, 1H, NH) ; 1.25 (t, 3H, J = 7 Hz, Me) ; 1.15 (t, 1H, J = 12 Hz, H-11ax).

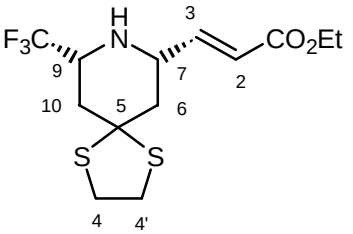
^{13}C NMR ($CDCl_3$) δ : 173.4 (COO) ; 125.5 (q, J_{C-F} = 277 Hz, CF_3) ; 96.3 (C-6) ; 60.5 (CH_2 ester) ; 59.3 (C-4) ; 59.2 (C-4') ; 55.0 (q, J_{C-F} = 29 Hz, C-10) ; 51.5 (C-8) ; 39.0 (C-2) ; 32.1 (C-5) ; 31.1 (C-7) ; 30.6 (C-11) ; 25.3 (C-3) ; 14.1 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.4.

EI-MS (70eV) m/z : 325 (M^+, 5) ; 280 (20) ; 266 (50) ; 224 (50) ; 181 (100) ; 166 (20) ; 124 (20) ; 101 (30) ; 43 (25).

HR-ESI-MS calculated for $C_{14}H_{23}F_3NO_4$ $(M+H)^+$: 326.1579, found 326.1569.

(2*E*)-Ethyl 3-[(7S, 9*R*)-9-(trifluoromethyl)-1,4-dithia-8-azaspiro[4.5]dec-7-yl]prop-2-enoate 164.



Following the general procedure for dithioketalization, protected piperidone **(+)-161** (200 mg, 0.62 mmol) in dichloromethane (10 mL), ethanedithiol (260 µL, 2.7 mmol) and $BF_3.Et_2O$ (382 µL, 2.7 mmol) gave, after purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/5), dithiolane **164** (194 mg, yield : 91%) as a yellow oil.

R_f : 0.50 (ethyl acetate/cyclohexane = 1/3).

IR (neat) σ (cm^{-1}) : 3310 (NH) ; 2923 ; 1713 (C=O) ; 1658 (C=C) ; 1397 ; 1270 ; 1172 ; 1040; 978.

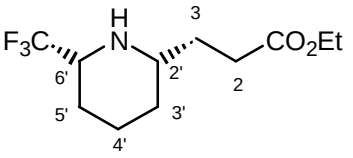
^{1}H NMR ($CDCl_3$) δ : 6.88 (dd, 1H, J = 16 and 6 Hz, H-3) ; 6.03 (d, 1H, J = 16 Hz, H-2) ; 4.19 (q, 2H, J = 7 Hz, CH_2 ester) ; 3.58 (m, 1H, H-7) ; 3.47 (m, 1H, H-9) ; 3.34 (s, 4H, H-4 and H-4') ; 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.17 (dt, 1H, J = 13 and 2.5 Hz, H-10eq) ; 2.0 (dd, 1H, J = 13 and 11.5 Hz, H-6ax) ; 1.84 (dd, 1H, J = 13 and 11.5 Hz, H-10ax) ; 1.82 (br s , 1H, NH) ; 1.30 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 166.0 (COO) ; 147.8 (C-3) ; 128.0 (q, J_{C-F} = 278 Hz, CF_3) ; 121.5 (C-2); 64.4 (C-5) ; 60.5 (CH_2 ester) ; 57.1 (q, J_{C-F} = 29 Hz, C-9) ; 56.0 (C-7) ; 46.6 (C-4) ; 40.5 (C-4') ; 39.4 (C-6) ; 38.2 (C-10) ; 14.2 (Me).

EI-MS (70eV) m/z : 341 (M^+, 20) ; 312 (20) ; 280 (30) ; 248 (100) ; 199 (25) ; 163 (20) ; 112 (15).

HR-ESI-MS calculated for $C_{13}H_{19}F_3NO_2S_2$ $(M+H)^+$: 342.0809, found 342.0792.

(+)-Ethyl 3-[(2*S*, 6*R*)-6-(trifluoromethyl)piperidin-2-yl]propanoate 165.



Following the general procedure of Raney nickel hydrogenolysis, dithioketal **164** (140 mg, 0.41 mmol) in absolute ethanol (7 mL) treated with W2 Raney nickel (*ca* 500 mg), gave pure compound **165 (**83 mg, yield : 80%) as a colorless liquid.

R_f : 0.45 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = + 12.1 (c 0.96, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3323 (NH) ; 2940 ; 1732 (COO) ; 1277 (C-O) ; 1175 ; 1116 (C-O).

^{1}H NMR ($CDCl_3$) δ : 4.12 (q, 2H, J = 7 Hz, Hz, CH_2 ester) ; 3.12 (m, 1H, H-6') ; 2.56 (m, 1H, H-2') ; 2.37 (t, 2H, J = 7.5 Hz, H-2) ; 1.90-1.64 (m, 5H) ; 1.46 (br s, 1H, NH) ; 1.28 (m, 2H) ; 1.22 (t, 3H, J = 7 Hz, Me) ; 1.07 (m, 1H, H-4').

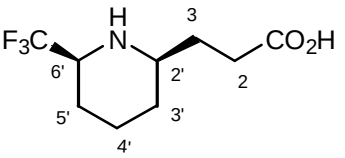
^{13}C NMR ($CDCl_3$) δ : 173.5 (C=O) ; 125.7 (q, J_{C-F} = 277 Hz , CF_3) ; 60.4 (CH_2 ester) ; 58.4 (q, J_{C-F} = 29 Hz , C-6') ; 55.5 (C-2') ; 31.8 (C-2) ; 31.2 (C-3) ; 30.5 (C-3') ; 24.7 (C-5') ; 23.2 (C-4') ; 14.1 (Me).

^{19}F NMR (CD_3OD) δ : -80.0.

EI-MS (70eV) m/z : 253 (M^+, 1) ; 208 (30) ; 152 (100) ; 96 (10) ; 55 (10).

HR-ESI-MS calculated for $C_{11}H_{19}F_3NO_2$ $(M+H)^+$: 254.1368, found 254.1359.

(-)-3-[(2*S*, 6*R*)-6-(Trifluoromethyl)piperidin-2-yl]propanoic acid 166.



Following the general procedure of saponification, ester (+)-**165** (75 mg, 0.29 mmol) in methanol (5 mL) was treated with a 0.3M NaOH solution (1.2 mL, 0.35 mmol) to give aminoacid **166** in its sodium salt form. Passage through an ion-exchange resin (Dowex® 50WX8-100) afforded pure aminoacid-(-)-**166** (64 mg, yield : 97%), as a white solid.

M.p : 160°C.

$[\alpha]_D^{25}$ = -14.6 (c 0.65, MeOH).

R_f : 0.10 (ethyl acetate/ cyclohexane = 1/1).

IR (KBr) σ (cm^{-1}) : 2500-3500 (CO<u>OH</u>) ; 1735 (C=O) ; 1404 ; 1263 ; 1200 (C-O) ; 1120.

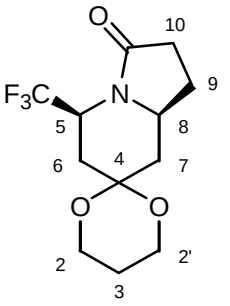
^{1}H NMR (D_2O) δ : 3.98 (m, 1H, H-6') ; 3.27 (m, 1H, H-2') ; 2.46 (m, 2H, H-2) ; 2.02 (m, 4H, H-3, H-3'eq, H-4' and H-5'eq) ; 1.79 (m, 1H, H-3) ; 1.62 (qd, 1H, J = 13 and 3.5 Hz, H-5'ax) ; 1.51 (qt, 1H, J = 13 and 3.5 Hz, H-4'ax) ; 1.35 (qd, 1H, J = 12.5 and 3.5 Hz, H-3'ax).

^{13}C NMR (D_2O) δ : 176.8 (COO) ; 122.9 (q, J_{C-F} = 278 Hz, CF_3) ; 58.1 (C-2') ; 57.2 (q, J_{C-F} = 32 Hz, C-6') ; 29.4 (C-2) ; 27.5 (C-3) ; 26.6 (C-5') ; 21.3 (C-3') ; 20.3 (C-4').

^{19}F NMR (CD_3OD) δ : -75.5.

HR-ESI-MS calculated for $C_9H_{15}F_3NO_2$ $(M+H)^+$: 296.2201, found 296.2195.

(±)-(5'*S, 8a'*S**)-5'-(Trifluoromethyl)tetrahydro-1'*H*-spiro[1,3-dioxane-2,7'-indolizin]-3'(3'*H*)-one 174.**



To a stirred solution of 2-chloro-1-methylpyridinium iodide (19.7 mg, 0.84 mmol) and triethylamine (21 µL, 0.21 mmol) in anhydrous CH_2Cl_2 (15 mL) was added compound **162** (20 mg, 0.06 mmol).The resulting mixture was stirred for 2h at room temperature before evaporation of solvent under reduced pressure. The residue was purified by column chromatography (ethyl acetate/cyclohexane = 1/3) to afford compound **174 (**13 mg, yield : 67%) as a white solid.

M.p : 112°C.

R_f : 0.40 (ethyl acetate/cyclohexane = 1/3).

IR (KBr) σ (cm^{-1}) : 2971 ; 1714 (C=O) ; 1407 ; 1277 ; 1242 ; 1135 (C-O) ; 1012.

^{1}H NMR ($CDCl_3$) δ : 4.08 (m, 1H ,H-5) ; 3.91 (m, 4H, H-2 and H-2') ; 3.65 (m, 1H, H-8) ; 2.48-2.14 (m, 6H) ; 1.80-1.63 (m, 3H) ; 1.59 (t, 1H, J = 13.5 Hz).

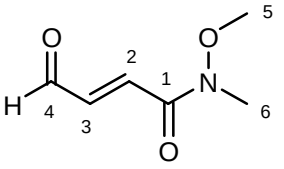
^{13}C NMR ($CDCl_3$) δ : 173.5 (C=O) ; 125.5 (q, J_{C-F} = 280 Hz, CF_3) ; 96.6 (C-4) ; 59.7 (C-2) ; 59.6 (C-2') ; 54.7 (C-8) ; 52.1 (q, J_{C-F} = 33 Hz, C-5) ; 39.3 (C-10) ; 32.2 (C-3) ; 30.1 (C-6) ; 25.1 (C-7 and C-9).

^{19}F NMR ($CDCl_3$) δ : -72.1.

EI-MS (70eV) m/z : 279 (M^+, 10) ; 259 (15) ; 220 (100) ; 210 (25) ; 181 (40) ; 152 (50) ; 123 (40) ; 110 (60) ; 83 (30) ; 55 (30) ; 42 (25).

HR-ESI-MS calculated for $C_{12}H_{17}F_3NO_3$ $(M+H)^+$: 280.1161, found 280.1169.

(2*E*)-*N*-methoxy-*N*-methyl-4-oxobut-2-enamide 178.



To a stirred solution of (2*E*)-*N*-methoxy-*N*-methyl-4-hydroxybut-2-enamide[77] **179** (318 mg, 2.19 mmol) in toluene (40 mL) was added MnO_2 (428 mg, 5 mmol). The mixture was heated at 60°C for 4h, cooled to room temperature then filtrated through Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by chomatography on silica gel (acetone/dichloromethane = 1/3). Aldehyde **178** (298 mg, yield : 94%) was thus obtained as a yellow oil.

R_f : 0.55 (ethyl acetate/cyclohexane = 1/1).

IR (neat) σ (cm^{-1}) ; 2941 ; 2830 (CHO) ; 2735 (CHO) ; 1693 (C=O) ; 1652 (C=C) ; 1423 ; 1380 ; 1180 ; 1118 (C-O) ; 997.

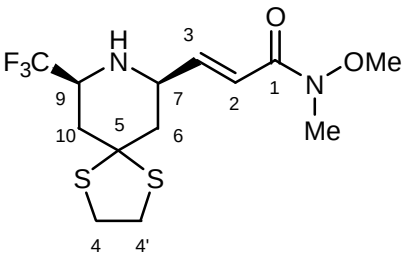
^{1}H NMR ($CDCl_3$) δ : 9.80 (d, 1H, J = 7 Hz, H-4) ; 7.38 (d, 1H, J = 16 Hz, H-2) ; 7.05 (dd, 1H, J = 16 and 7 Hz, H-3) ; 3.80 (s, 3H, H-5) ; 3.31 (s, 3H, H-6).

^{13}C NMR ($CDCl_3$) δ : 193.6 (C-4) ; 164.3 (C-1) ; 139.5 (C-3) ; 137.7 (C-2) ; 62.2 (C-5) ; 32.4 (C-6).

^{19}F NMR ($CDCl_3$) δ : -75.0.

EI-MS (70eV) m/z : 143 (M^+, 5) ; 114 (70) ; 83 (70) ; 61 (10) ; 55 (100).

(±)-(2*E*)-*N*-Methoxy-*N*-methyl-3-[(7*R, 9*S**)-9-(trifluoromethyl)-1,4-dithia-8-azaspiro[4.5]dec-7-yl]prop-2-enamide 184.**



To a stirred solution of triethylamine (112 µL, 1.5 mmol) and 2-chloro-1-methyl pyridinium iodide (112 mg, 0.44 mmol) in dichloromethane (3 mL) was added, in one portion, a solution of *N,O*-dimethylhydroxylamine hydrochloride salt (70 mg, 0.71mmol), triethylamine (112 µL, 1.5 mmol) and crude hydrochloride salt of aminoacid **183** (125 mg, 0.35 mmol, prepared by quantitative saponification of ester **164**) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 2h. Evaporation of the solvent, followed by column chromatography (ethyl acetate/cyclohexane 1/1) afforded compound **184** (100 mg, yield : 79%) as a yellow oil.

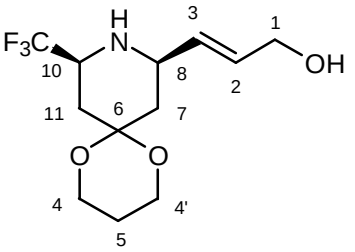
R_f : 0.75 (ethyl acetate).

IR (neat) σ (cm^{-1}) : 3301 (NH) ; 2929 ; 1732 (C=O) ; 1633 (C=C) ; 1424 ; 1375 ; 1274 ; 1244 (C-O) ; 1172 ; 1134 (C-O) ; 1046.

^{1}H NMR ($CDCl_3$) δ : 6.90 (dd, 1H, J = 15.5 and 6 Hz, H-3) ; 6.58 (d, 1H, J = 16 Hz, H-2) ; 3.71 (s, 3H, OMe) ; 3.62 (m, 1H, H-7) ; 3.56 (m, 1H, H-9) ; 3.35 (m, 4H, H-4 and H-4') ; 3.24 (s, 3H, NMe) ; 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.17 (dt, 1H, J = 13 and 2.5 Hz, H-10eq) ; 2.01 (br s , 1H, NH) ; 2.00 (dd, 1H, J = 13 and 12.5 Hz, H-6ax) ; 1.91 (t, 1H, J = 13 and 12.5 Hz, H-10ax).

EI-MS (70eV) m/z :356 (M^+, 25) ; 325 (55) ; 242 (25) ; 199 (50) ; 84 (100) ; 42 (55).

(2*E*)-(-)-3-[(8*R*, 10*S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]prop-2-en-1-ol 186.



To a cooled (-10°C) stirred solution of piperidine (-)-**161** (323 mg, 1 mmol) in toluene (10 mL) was added dropwise a 20% solution of diisobutyl aluminium hydride in toluene (1.7 mL, 12 mmol). The resulting mixture was stirred at -10°C for 20min before addition of methanol (1 mL). After heating to room temperature, the resulting mixture was poured into a mixture of ethyl acetate / saturated sodium chloride (6/1, 70 ml) before extraction with dichloromethane (4 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvents, followed by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) afforded alcohol (-)-**186** (253 mg, yield : 90%) as a colorless liquid.

R_f : 0.20 (ethyl acetate/cyclohexane = 1/1).

$[\alpha]_D^{25}$ = -11.58 (c 1.07, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3407 (OH) ; 3302 (NH) ; 2962 ; 1266 ; 1134 (C-O) ; 1020 (C-O) ; 974 ; 862.

^{1}H NMR ($CDCl_3$) δ : 5.86 (dtd, 1H, J = 15.5, 5.5 and 1 Hz, H-2) ; 5.71 (ddt, 1H, J = 15.5, 7 and 1.5 Hz, H-3) ; 4.14 (dd, 2H, J = 5.5 and 1.5 Hz, H-1) ; 3.91 (t, 2H, J = 5.5 Hz, H-4) ; 3.80 (t, 2H, J = 5.5 Hz, H-4') ; 3.42 (m, 2H, H-8 and H-10) ; 2.43 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.28 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 1.74 (Q, 2H, J = 5.5 Hz, H-5) ; 1.57 (br s, 2H, OH and NH) ; 1.38 (t, 1H, J = 12.5 Hz, H-7ax) ; 1.23 (dd, 1H, J = 13 and 12 Hz, H-11ax).

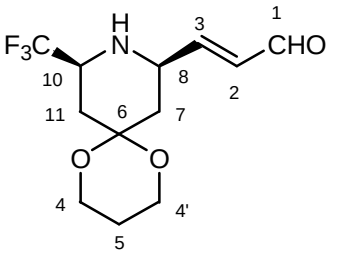
^{13}C NMR ($CDCl_3$) δ : 132.5 (C-2) ; 130.7 (C-3) ; 125.5 (q, J_{C-F} = 277 Hz, CF_3) ; 96.1 (C-6) ; 62.7 (C-1) ; 59.3 (C-4) ; 59.2 (C-4') ; 54.6 (q J_{C-F} = 29 Hz, C-10) ; 53.7 (C-8) ; 38.6 (C-5) ; 32.0 (C-7) ; 25.3 (C-11).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 281 (M^+, 5) ; 263 (40) ; 250 (30) ; 222 (100) ; 181 (95) ; 150 (40) ; 101 (80) ; 69 (50) ; 43 (60).

HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_3$ $(M+H)^+$: 282.1317, found 282.1325.

(2*E*)-(-)3-[(8*R*, 10*S*) -10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]prop-2-enal 187.



To a stirred solution of alcohol (-)-**186** (400 mg, 1.4 mmol) in toluene (15 mL) was added MnO_2 (371 mg, 4.27 mmol). The mixture was heated at gentle reflux for 3h, cooled to room temperature, then filtrated through Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by chomatography on silica gel (ethyl acetate/cyclohexane = 1/5). Aldehyde (-)-**185** (210 mg, yield : 53%) was thus obtained as a colorless oil.

R_f : 0.25 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = -30.1 (c 1.08, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3306 (NH) ; 2953 ; 1694 (C=O) ; 1275 ; 1171 (C-O) ; 1124 (C-O) ; 1088 (C-O) ; 974.

^{1}H NMR ($CDCl_3$) δ : 9.55 (dd, 1H , J = 7.5 and 1.5, H-1) ; 6.75 (dd, 1H, J = 16 and 6 Hz, H-3) ; 5.95 (m, 1H, H-2) ; 3.93 (m, 4H, H-4 and H-4') ; 3.72 (m, 1H, H-8) ; 3.45 (m, 1H, H-10) ; 2.52 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.32 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 1.76 (m, 2H, H-5) ; 1.65 (br s, 1H, NH) ; 1.45 (t, 1H, J = 13 Hz, H-7ax) ; 1.35 (t, 1H, J = 13 Hz, H-11ax).

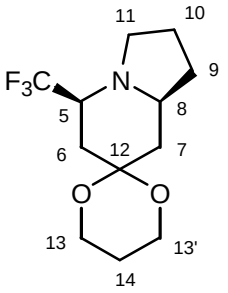
^{13}C NMR ($CDCl_3$) δ : 193.4 (C-1) ; 156.6 (C-3) ; 131.7 (C-2) ; 125.4 (q, J_{C-F} = 278 Hz, CF_3) ; 95.7 (C-6) ; 59.4 (C-4 and C-4') ; 54.6 (q, J_{C-F} = 30 Hz, C-10) ; 53.1 (C-8) ; 38.3 (C-5) ; 31.4 (C-11) ; 25.2 (C-7).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 279 (M , 100) ; 220 (35) ; 192 (60) ; 150 (40) ; 101 (90) ; 43 (55).

HR-ESI-MS calculated for $C_{12}H_{17}F_3NO_3$ $(M+H)^+$: 280.1166, found 280.1163.

(5'*S*, 8a'*S*)-(-)-5'-(Trifluoromethyl)hexahydro-1'*H*-spiro[1,3-dioxane-2,7'-indolizine] 188.



To a stirred solution of aldehyde (-)-**187** (72 mg, 0.25 mmol) in absolute ethanol (5 mL) was added $Pd(OH)_2$/C 20% (100 mg). The mixture was stirred at room temperature under an hydrogen atmosphere for 1h then filtered through Celite®. The filtrate was concentrated under reduced pressure. Purification on silica gel-column (ethyl acetate/cyclohexane = 1/5) afforded indolizidine-(-)-**188** (60 mg, yield : 93%) as a colorless oil.

R_f : 0.50 (ethyl acetate/cyclohexane = 1/3).
$[\alpha]_D^{25}$ = -31.6 (c 1.0, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 2966 ; 2869 ; 1341 ; 1272 ; 1175 (C-O) ; 1126 (C-O) ; 1017 (C-O) ; 927.

^{1}H NMR ($CDCl_3$) δ : 3.93 (m, 2H, H-13) ; 3.88 (t, 2H, J = 5.5, Hz, H-13') ; 3.23 (m, 1H, H-8); 2.83 (m, 1H, H-5) ; 2.44 (br d, 2H, J = 13 Hz, H-6eq and H-7eq) ; 2.33 (m, 1H, H-11) ; 2.25 (q, 1H, J = 9 Hz, H-11) ; 1.91-1.65 (m, 5H, H-14, H-10 and H-9) ; 1.61 (t, 1H, J = 12.5 Hz, H-6ax) ; 1.45 (m, 1H, H-9) ; 1.31 (t, 1H, J = 12.5 Hz, H-7ax).

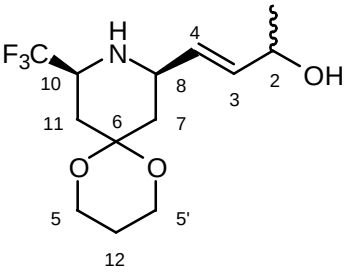
^{13}C NMR ($CDCl_3$) δ : 125.6 (q, J_{C-F} = 279 Hz, CF_3) ; 98.8 (C-12) ; 60.6 (C-8) ; 60.0 (q, J_{C-F} = 29 Hz, C-5) ; 59.6 (C-13) ; 59.2 (C-13') ; 51.1 (C-11) ; 37.0 (C-14) ; 32.8 (C-7) ; 29.0 (C-6) ; 25.4 (C-10) ; 21.5 (C-9).

^{19}F NMR ($CDCl_3$) δ : -75.3.

EI-MS (70eV) m/z : 265 (M^+, 10) ; 206 (80) ; 196 (50) ; 164 (20) ; 96 (100) ; 41 (15).

HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_2$ $(M+H)^+$: 266.1378, found 266.1378.

(3*E*)-4-[(8*R*, 10*S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]but-3-en-2-ol 189.



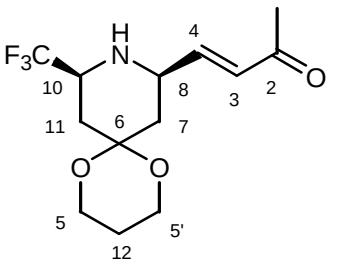
To a cooled (-78°C) stirred solution of aldehyde (-)-**187**(100 mg, 0.36 mmol) in anhydrous THF (5 mL), under argon, was added a 3M solution of methyl magnesium bromide in diethylether (360 µL, 1.1 mmol). The resulting mixture was stirred at -78°C for 15min then at 0°C for 1h. After warming to room temperature, the reaction mixture was diluted with diethyl ether (5 mL) and a saturated solution of NH_4Cl (3 mL) was added before extraction with diethyl ether (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (ethyl acetate/cyclohexane 1/1) afforded alcohol **189** (unseparable 1/1 epimeric mixture, 75 mg, yield : 71%) as a pale yellow oil.

R_f : 0.15 (ethyl acetate/cyclohexane = 1/2).

^{1}H NMR ($CDCl_3$) δ : 5.75 (dd, 1H, J = 15.5 and 6 Hz, H-3) ; 5.65 (dd, 1H, J = 15.5 and 6.5 Hz, H-4) ; 4.30 (Q, 1H, J = 6 Hz, H-2) ; 3.93 (t , 2H, J = 5.5 Hz, H-5) ; 3.89 (t, 2H, J = 5.5 Hz, H-5') ; 3.39 (m, 2H, H-8 and H-10) ; 2.42 (m, 1H, H-7eq) ; 2.29 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 1st dia) ; 2.26 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 2nd dia) ; 1.74 (Q, 2H, J = 5 Hz, H-12) ; 1.58 (br s, 2H, NH and OH) ; 1.44 (t, 1H, J = 13 Hz, H-7ax) ; 1.29 (t, 1H, J = 13 Hz, H-11ax) ; 1.27 (d, 3H, J = 6.5 Hz, Me).

EI-MS (70eV) m/z : 295 (M^+, 1) ; 277 (50) ; 250 (25) ; <u>236</u> (100) ; 198 (30) ; 181 (80) ; 150 (25) ; 101 (50) ; 43 (60).

(3*E*)-(-)-4-[(8*R*, 10*S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]but-3-en-2-one 190.



To a stirred solution of alcohol **189** (100 mg, 0.34 mmol) in toluene (5 mL) was added MnO_2 (88 mg, 1.02 mmol). The resulting suspension was heated at gentle reflux for 5h, then was cooled to room temperature and filtered through Celite®. The filtrate was concentrated under reduced pressure. Following, a silica gel-column chromatography (ethyl acetate/cyclohexane = 1/3) afforded pure ketone **190** (50 mg, yield : 50%) as yellow oil.

R_f : 0.44 (ethyl acetate/cyclohexane = 1/1).
$[\alpha]_D^{25}$ = -28.6 (c 1.4, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3309 (NH) ; 2971 ; 1680 (C=O) ; 1632 (C=C) ; 1265 ; 1173 (C-O) ; 1130 (C-O) ; 1021 ; 979.

^{1}H NMR ($CDCl_3$) δ : 6.70 (dd, 1H, J = 16 and 6 Hz, H-4) ; 6.50 (dd, 1H, J = 16 and 1.5 Hz, H-3) ; 3.95 (t, 2H, J = 5.5 Hz, H-5) ; 3.90 (t , 2H, J = 5.5 Hz, H-5') ; 3.60 (m, 1H, H-8) ; 3.45 (m, 1H, H-10) ; 2.47 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.32 (dt, 1H, J = 13 and 2.5 Hz, H-11eq) ; 2.28 (s, 3H, Me) ; 1.75 (m, 2H, H-12) ; 1.65 (br s, NH) ; 1.45 (t, 1H, J = 12 Hz, H-7ax) ; 1.32 (t, 1H, J = 12 Hz, H-11ax).

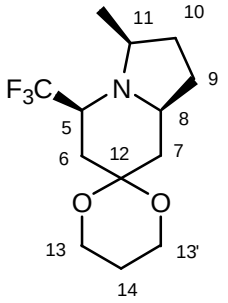
^{13}C NMR ($CDCl_3$) δ : 198.3 (C-2) ; 146.8 (C-4) ; 130.3 (C-3) ; 125.4 (q, J_{C-F} = 277 Hz, CF_3) ; 95.8 (C-6) ; 59.4 (C-5) ; 59.3 (C-5') ; 54.1 (q J_{C-F} = 29 Hz, C-10) ; 53.2 (C-8) ; 38.3 (C-12) ; 31.7 (C-11) ; 27.2 (Me) ; 25.2 (C-7).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 293 (M^+, 90) ; 250 (65) ; 234 (50) ; 192 (100) ; 181 (60) ; 150 (50) ; 101 (65) ; 82 (50) ; 43 (90).

HR-ESI-MS calculated for $C_{13}H_{19}F_3NO_3$ $(M+H)^+$: 294.1317, found 294.1318.

(-)-(3'*S*, 5'S, 8a'*S*)-3'-Methyl-5'-(trifluoromethyl)hexahydro-1'*H*-spiro[1,3-dioxane-2,7'-indolizine] 191.



To a stirred solution of enone (-)-**190** (62 mg, 0.21 mmol) in absolute ethanol (5 mL) was added $Pd(OH)_2$/C 20% (100 mg). The mixture was stirred under an hydrogen atmosphere for 1h then filtered through Celite®.The filtrate was concentrated under reduced pressure. Following, a purification on silica gel column (ethyl acetate/cyclohexane = 1/2) afforded indolizidine (-)-**191** (40 mg, yield : 68%) as a yellow oil.

$\mathbf{R_f}$: 0.60 (ethyl acetate/cyclohexane = 1/3).
$\mathbf{[\alpha]_D^{25}}$ = -25.6 (c 0.92, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 2960 ; 1593 ; 1340 ; 1272 ; 1114 (C-O) ; 1086 (C-O) ; 1039 ; 997.

^{1}H NMR ($CDCl_3$) δ : 3.92 (m, 2H, H-13) ; 3.88 (t, 2H, J = 5.5 Hz , H-13') ; 2.95 (m, 2H ,H-5 and H-11) ; 2.58 (m, 1H, H-8) ; 2.45 (dt, 1H, J = 13 and 2.5 Hz, H-6eq) ; 2.40 (dt, 1H, J = 13 and 2.5 Hz, H-7eq) ; 2.06-1.96 (m, 1H, H-9) ; 1.79-1.68 (m, 2H, H-14) ; 1.66-1.58 (m, 2H, H-9 and H-7ax) ; 1.55-1.40 (m, 2H, H-10) ; 1.35 (t, 1H, J = 12.5 Hz, H-6ax) ; 1.11 (d, 3H, J = 6 Hz, Me).

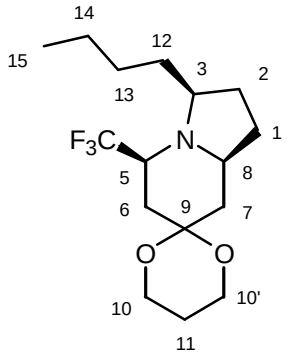
^{13}C NMR ($CDCl_3$) δ : 125.5 (q, J_{C-F} = 279 Hz, CF_3) ; 96.7 (C-12) ; 60.0 (C-8) ; 60.2 (q, J_{C-F} = 27 Hz, C-5) ; 59.6 (C-13) ; 59.1 (C-13') ; 55.8 (C-11) ; 37.4 (C-14) ; 34.4 (C-6) ; 33.2 (C-7) ; 28.9 (C-9) ; 25.4 (C-10) ; 24.3 (Me).

^{19}F NMR ($CDCl_3$) δ : -73.6.

EI-MS (70eV) m/z :279 (M^+, 5) ; <u>264</u> (100) ; 206 (20) ; 188 (85) ; 164 (15) ; 110 (60) ; 41 (20).

HR-ESI-MS calculated for $C_{13}H_{21}F_3NO_2$ $(M+H)^+$: 280.1524, found 280.1524.

(3'*S*, 5'*S*, 8a'*S*)-(+)-3'-Butyl-5'-(trifluoromethyl)hexahydro-1'*H*-spiro[1,3-dioxane-2,7'-indolizine] 192.



To a stirred solution of ketone (-)-**194** (100 mg, 0.29 mmol) in absolute ethanol (5 mL) was added 20% $Pd(OH)_2/C$ (80 mg). The mixture was stirred under hydrogen atmosphere at room temperature for 1h then filtered through Celite®.The filtrate was concentrated under reduced pressure. The crude product was purified on silica-gel column (ethyl acetate/cyclohexane = 1/2) to afford indolizidine-(+)-**192** (75 mg, yield : 79%) as a yellow oil.

R_f : 0.78 (ethyl acetate/cyclohexane = 1/2).
$[\alpha]_D^{25}$ = +1.8 (c 1.0, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 2960 ; 1468 ; 1340 ; 1272 ; 1165 ; 1116 (C-O) ; 1090 (C-O) ; 1000 ; 928.

^{1}H NMR ($CDCl_3$) δ : 3.89 (m, 4H, H-10 and H-10') ; 3.95 (m, 1H, H-5) ; 2.81 (m, 1H, H-8) ; 2.47 (m, 1H, H-3) ; 2.42 (m, 2H, H-6eq and H-7eq) ; 1.85-1.10 (m, 14H, H-1, H-2, H-6ax, H-7ax, H-11, H-12, H-13 and H-14) ; 0.87 (t, 3H, J = 7 Hz, Me).

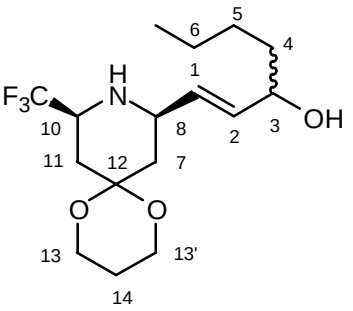
^{13}C NMR ($CDCl_3$) δ : 125.5 (q, J_{C-F} = 279 Hz, CF_3) ; 96.7 (C-9) ; 62.4 (C-8) ; 60.7 (C-3) ; 60.1 (q J_{C-F} = 27 Hz, C-5) ; 59.6 (C-10) ; 59.1 (C-10') ; 37.6 (C-11) ; 37.3 (C-6) ; 34.5 (C-7) ; 30.6 (C-1) ; 29.1 (C-2) ; 29.0 (C-12) ; 25.4 (C-13) ; 22.7 (C-14) ; 14.1 (C-15).

^{19}F NMR ($CDCl_3$) δ : -73.8.

EI-MS (70eV) m/z : 321 $(M–C_4H_9)^+$; 264 (100) ; 206 (20) ; 188 (90) ; 41 (20).

HR-ESI-MS calculated for $C_{16}H_{27}F_3NO_2$ $(M+H)^+$: 322.1994, found 322.1984.

(1*E*)-1-[(8*R*, 10*S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]hept-1-en-3-ol 193.



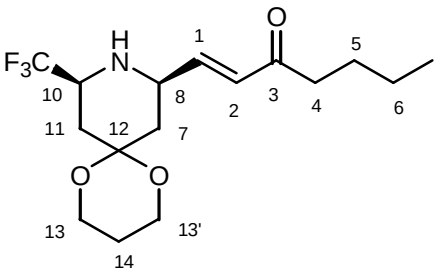
To a cooled (-78°C) stirred solution of aldehyde (-)-**187** (100 mg, 0.36 mmol) in anhydrous THF (5 mL) and under argon, was added a 2M solution of *n*-butylmagnesium chloride in THF (360 µL, 1.1 mmol). The resulting mixture was stirred at -78°C for 15min under argon and then at 0°C for 1h. After warming to room temperature, the reaction mixture was diluted with diethyl ether (5 mL) and a saturated solution of NH_4Cl (3 mL) was added before extraction with diethyl ether (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) afforded alcohol **193** (unseparaple 1/1 epimeric mixture, 82 mg, yield : 68%) as a pale yellow oil.

R_f : 0.14 (ethyl acetate/cyclohexane = 1/2).

^{1}H NMR ($CDCl_3$) δ : 5.68 (m, 2H, H-1 and H-2) ; 4.08 (m, 1H, H-3) ; 3.93 (t, 2H, J = 5.5 Hz, H-13) ; 3.89 (t, 2H, J = 6 Hz, H-13') ; 3.39 (m, 2H, H-8 and H-10) ; 2.45 (dt, 0.5H, J = 13 and 2.5 Hz, H-7eq, 1st dia) ; 2.43 (dt, 0.5H, J = 13 and 2.5 Hz, H-7eq, 2nd dia) ; 2.28 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 1st dia) ; 2.23 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 2nd dia) ; 1.74 (m, 2H, H-14) ; 1.62 (br s, 2H, NH and OH) ; 1.56-1.22 (m, 8H, H-4, H-5, H-6, H-7ax and H-11ax) ; 0.90 (t, 3H, J = 7 Hz, Me).

EI-MS (70eV) m/z : 337 (M^+, 21) ; 319 (30) ; <u>278</u> (100) ; 250 (40) ; 198 (40) ; 181 (95) ; 150 (25) ; 123 (30) ; 101 (50) ; 41 (50).

(1*E*)-(-)-1-[(8*R*, 10*S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]hept-1-en-3-one 194.



To a stirred solution of alcohol **193** (290 mg, 0.86 mmol) in toluene (10 mL) was added MnO_2 (224 mg, 2.58 mmol). The mixture was heated at gentle reflux for 5h then cooled to room temperature before filtration through Celite®. The filtrate was concentrated under reduced pressure. Following, a column chomatography on silica gel (ethyl acetate/cyclohexane = 1/3) gave ketone (-)-**194** (156 mg, yield: 54%) as a yellow oil.

R_f : 0.74 (ethyl acetate/cyclohexane = 1/1).
$[\alpha]_D^{25}$ = -23.5 (c 1.0, $CHCl_3$).

IR (neat) σ (cm^{-1}) : 3310 (NH) ; 2959 ; 1697 (C=O) ; 1633 (C=C) ; 1266 ; 1174 (C-O) ; 1130 (C-O) ; 1034 ; 979.

^{1}H NMR ($CDCl_3$) δ : 6.73 (dd, 1H, J = 16 and 6 Hz, H-1) ; 6.26 (dd, 1H, J = 16 and 1.5 Hz, H-2) ; 3.95 (t, 2H, J = 5.5 Hz H-13) ; 3.90 (t, 2H, J = 5.5 Hz, H-13') ; 3.58 (m, 1H, H-8) ; 3.44 (m, 1H, H-10) ; 2.55 (t, 2H, J = 7 Hz, H-4) ; 2.46 (dt, 1H, J = 13 and 3 Hz, H-7eq) ; 2.32 (dt, 1H, J = 13 and 3 Hz, H-11eq) ; 1.75 (Q, 2H, J = 5.5 Hz, H-14) ; 1.62 (br s, 1H, NH) ; 1.58 (Q, 2H, J = 7 Hz, H-5) ; 1.42 (t, 1H, J = 12 Hz, H-7ax) ; 1.38-1.25 (m, 3H, H-6 and H-11ax) ; 0.90 (t, 3H, J = 7 Hz, Me).

^{13}C NMR ($CDCl_3$) δ : 200.5 (C-3) ; 145.7 (C-1) ; 129.2 (C-2) ; 125.4 (q, J_{C-F} = 277 Hz, CF_3) ; 95.8 (C-12) ; 59.7 (C-13) ; 59.4 (C-13') ; 54.6 (q, J_{C-F} = 29 Hz, C-10) ; 53.2 (C-8) ; 40.2 (C-4); 38.3 (C-14) ; 31.8 (C-7) ; 26.1 (C-11) ; 25.2 (C-5) ; 22.3 (C-6) ; 13.8 (Me).

^{19}F NMR ($CDCl_3$) δ : -80.5.

EI-MS (70eV) m/z : 335 (M^+, 85) ; 276 (35) ; <u>250</u> (100) ; 192 (70) ; 181 (95) ; 150 (35) ; 123 (65) ; 101 (70) ; 41 (35).

HR-ESI-MS calculated for $C_{16}H_{25}F_3NO_3$ $(M+H)^+$: 336.1787, found 336.1769.

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Abstract

In this manuscript is proposed a novel method to elaborate saturated N-heterocycles possessing a trifluoromethyl (Tfm) group at α-position. These fluoro-organic compounds are attractive targets, due to their high potential interest for pharmaceutical and as well for agro-chemical industry.

By using a methodology developped at Laboratory, based on an intramolecular Mannich type reaction of β-aminoketals, we could prepare a wide range of original Tfm-piperidine based structures.

First of all we applied this methodology for the diastereoselective synthesis of Tfm-piperidines. β-aminoketals synthons were easily obtained by the conjugated addition of phthalimide on required enones, followed by keto-protection and then hydrazinolysis. These key intermediates were submitted to Mannich intramolecular reactions with various aldehydes, giving a stereoselective access to triluoro-analogues of naturally occuring piperidine as well as some new 4-aza- and 4-hydroxy- Tfm-piperidines scaffolds.

An enantioselective version of this strategy was then successfully carried out, starting from enantio-enriched β-aminoketals prepared from a fluorinated oxazolidine (FOX) by a Mukaiyama-Mannich type reaction. Employment of these new enantio-enriched amines under identical cyclization conditions with different aldehydes furnished a variety of enantiopure Tfm-piperidines. This strategy was then validated by the first asymmetric synthesis of trifluoromethyl analogues of pipecolic acids, Tfm-piperidine based analogues of γ-aminobutyric acid (GABA) and polycyclic structures, as indolizidines, bearing a trifluoromethyl group.

Keywords: Tfm-piperidines, intamolecular Mannich reaction, Tfm-pipecolic acids, Tfm-analogues of GABA, Tfm-indolizidines.

Résumé

Dans ce manuscrit est proposé une méthode originale pour élaborer des N-hétérocycles saturés possédant un groupe trifluoromethyl (Tfm) en position α. Ces composés fluoro-organiques sont des cibles attrayantes, dues à leur intérêt potentiel élevé pour l'industrie pharmaceutique ainsi que pour l'agrochimie. En employant une méthode développée au laboratoire, basée sur une réaction de type Mannich intramoléculaire des β-aminocétals sur des dérivés carbonylés, nous avons préparé un éventail de structures pipéridiniques originales.

Tout d'abord nous avons appliqué cette méthodologie pour la synthèse diastéréoselective des Tfm-pipéridines. Les β-aminocétals nécessaires à cette étude ont été facilement obtenus par l'addition conjuguée du phtalimide sur les énones correspondantes, suivi d'une céto-protection et d'une hydrazinolyse. Ces intermédiaires ont été soumis aux réactions de Mannich intramoléculaires avec divers aldéhydes, donnant ainsi un accès stéréoseléctif aux analogues trifluorés de la pipéridine naturelle. Des réactions chimiques sur ces composés ont également permis la synthèse de nouveaux substrats tels que les 4-aza et 4-hydroxy Tfm-pipéridines.

Une version énantioselective de cette stratégie alors a été réalisée avec succès au départ de β-aminocétals enantiomériquement enrichi, préparés à partir d'une oxazolidine fluorée (FOX) par une réaction de type Mukaiyama-Mannich. L'emploi de ces nouvelles amines énantio-enrichies dans des conditions identiques de cyclisation avec différents aldéhydes a fourni une série de Tfm-pipéridines énantiopure. Cette stratégie a été alors validée par la première synthèse asymétrique des analogues trifluoromethylés des acides pipécolique, des analogues l'acide γ-aminobutyrique (GABA) et des structures polycycliques, comme les indolizidines, contenant un groupe trifluoromethyle.

Mots Clés: Tfm-piperidines, réaction de Mannich intamoleculaire, acides Tfm-pipecolique, Tfm-analogues du GABA, Tfm-indolizidines.