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A Simple Stereoselective Route to α-Trifluoromethyl Analogues of Piperidine Alkaloids

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The highly diastereoselective synthesis of five trifluoro-substituted analogues of mono-, di-, and trisubstituted piperidine alkaloids was accomplished in two to four steps from 2-trifluoromethyl keto-protected 4-piperidones, prepared by an intramolecular Mannich-type reaction methodology. A simple stereoselective elaboration of new 2-(trifluoromethyl)-4-piperidinols and 4-amino-2-(trifluoromethyl)piperidines is also described.

Introduction

Endowed with diverse and notable bioactivities, piperidine alkaloids, together with their nonnatural analogues, are the objects of continuous and intensive synthetic efforts.[1] From a different viewpoint, it is generally acknowledged that incorporation of one or more fluorine atom(s) into an active molecule may profoundly modify its physicochemical and biological properties.[2] Indeed, because of the unique specificities of the fluorine atom, substitution of an hydrogen by a fluorine or introduction of a trifluoromethyl group in place of a methyl may significantly improve the pharmacodynamic and pharmacokinetic profiles of a drug through simultaneous alteration of its electronic, lipophilic, and steric characteristics, as well as its metabolic stability.[2,3] As a consequence, selectively (poly)fluorinated analogues of biologically active compounds are regarded as tools of relevant interest for pharmaceutical research,[3,4] in part explaining the considerable progress of fluoroorganic chemistry.[5] If some domains of organofluorine chemistry are well documented, however, others still need to be developed. This applies, for instance, to the selective preparation of α-trifluoromethyl-substituted saturated N-heterocycles, including piperidines, an area weakly explored to date.[6–10] Actually, and even though trifluoromethylated analogues of aliphatic N-heterocyclic alkaloids constitute attractive targets for reasons evoked above,[9] stereoselective elaboration of this kind of compound has rarely been described.

Part of our research activity is devoted to the asymmetric synthesis of saturated N-heterocycles. In this context, we have studied a simple and efficient Mannich-type cyclization permitting rapid and highly stereoselective access to polysubstituted piperidine systems,[11] which we were able to validate through the enantioselective synthesis of various alkaloids.[12,13] In order to extend the field of applications of this approach to more challenging synthetic questions, we decided to evaluate its potential in the field of organofluorine chemistry. Effectively, we reasoned that intramolecular Mannich reactions of 1,3-aminoketals, offering a double opportunity for the selective incorporation of a trifluoromethyl group as summarized in Scheme 1, seemed particularly suitable for the elaboration of piperidines trifluoromethylated in the key α position.

Accordingly, we have recently been able to demonstrate[14] that α-trifluoromethylated piperidines **1** are accessible, diastereoselectively, either from aminoketals **2**, through the use of a stable fluoral equivalent as fluorine source (route A), or from a preformed α-(trifluoromethyl)amine **3** (route B). If the first pathway, presumably involving the *N*,*O*-hemiacetal **4** and then the (trifluoromethyl)iminium ion **5** as intermediates,[15] may appear quite limited, since it requires the systematic preparation of amines **2**, the alternative route B has a more general character, potentially permitting the preparation of a range of targets **1** from the single precursor **3**. These promising preliminary results prompted us to consider direct applications of this strategy, and we naturally focused our attention on piperidine-based natural products. The synthesis of fluorinated analogues of representative mono-, di- and trisubstituted piperidine alkaloids was thus entered into.

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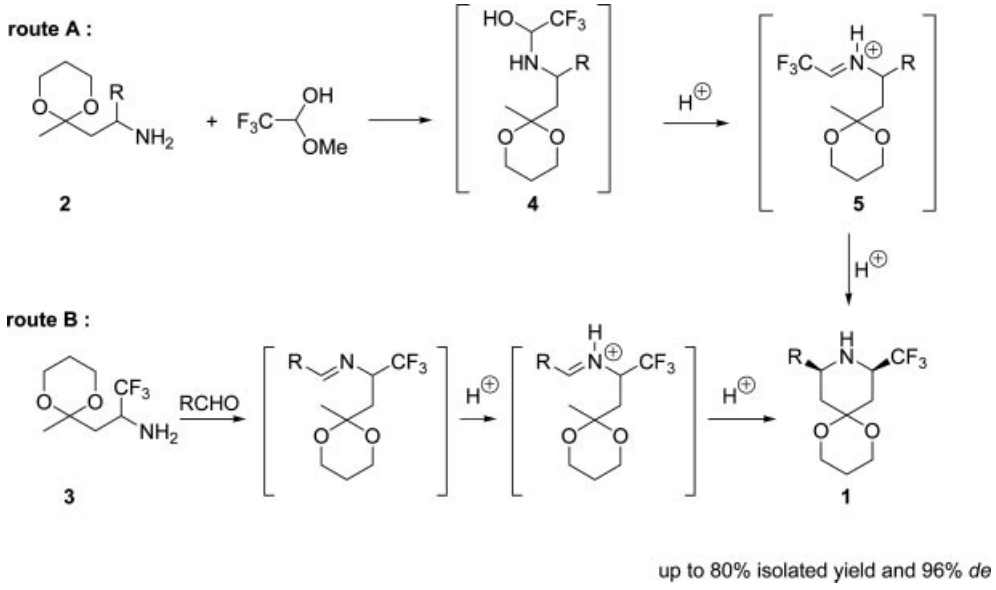


Scheme 1. Diastereoselective synthesis of α-(trifluoromethyl)piperidines through intramolecular Mannich-type reactions.

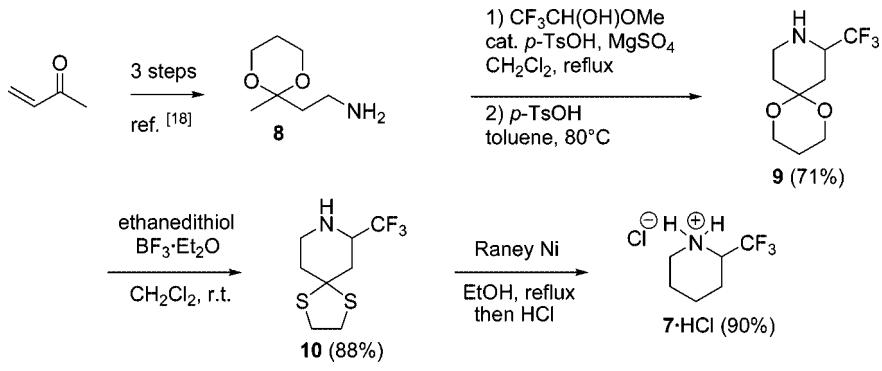
Results and Discussion

As far as we know, the simplest monosubstituted piperidine alkaloid, pipecoline (**6**), is also the only one for which the preparation of a trifluoro analogue **7** has been reported.[16]

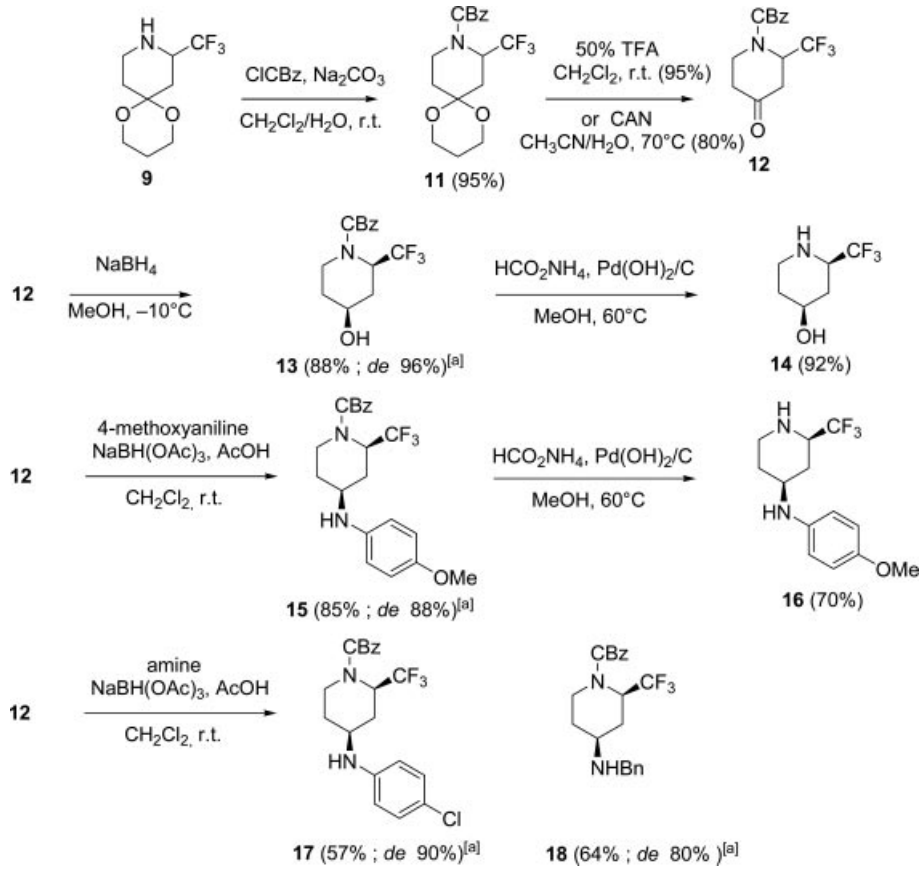
The first synthesis of **7** (free base) was achieved by Raasch,[17] through conversion of the pipecolic acid carboxyl group into a trifluoromethyl group by treatment with sulfur tetrafluoride in hydrogen fluoride. Recently, Billard, Langlois et al.[10b] prepared the same compound (HCl salt) through an efficient ring-closure metathesis as the key heterocycle formation step. In our case, we thought that trifluoropipecoline **7** should be easily accessible by route A (Scheme 1) and therefore decided to embark upon its synthesis. Treatment of the aminoketal **8**[18] with trifluoroacetaldehyde under our standard acidic cyclization conditions[11] thus cleanly afforded the expected (trifluoromethyl)piperidine **9** in 71% yield (Scheme 2).

Piperidine **9** was then treated with an excess of ethanedithiol in the presence of excess boron trifluoride etherate in dichloromethane at room temperature to give the dithioketal derivative **10** (88% yield). Finally, hydrogenolysis of **10** (W2 Raney nickel[19]) in ethanol at reflux furnished the volatile trifluoropipecoline **7**, which was isolated (90%) as its hydrochloride salt, presenting physical and spectroscopic data consistent with those already reported.[10b] As the involved intramolecular Mannich-type process affords heterocycles possessing masked keto functions, it provides the opportunity to apply further selective transformations of these. We then decided to regenerate the carbonyl group in order to examine its stereoreactivity under some reductive and amino-reductive conditions (Scheme 3).

As attempts to deprotect the keto function in free amine **9** directly under standard acidic conditions did not gave satisfactory results, this compound was at first transformed into the parent benzyl carbamate derivative **11**. Regenera-



Scheme 2.

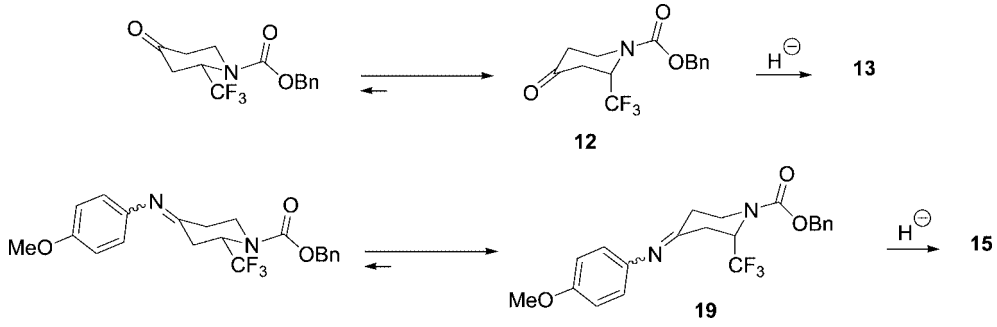


Scheme 3. a) *de* determined from GC/MS analysis of the crude reaction mixture; yield refers to the pure isolated diastereomer.

tion of the carbonyl group of **11** was then quantitatively achieved after a three-day exposure period to 50% aqueous trifluoroacetic acid in dichloromethane at room temperature. We also noticed that the same transformation could be accomplished (80% yield) within a few minutes by Markò's procedure,[20] with ceric ammonium nitrate at 70 °C in water/acetonitrile.

To anticipate the stereochemical behavior of the *N*-protected-4-piperidone **12** under reductive conditions, it has to be considered that its conformational equilibrium, unlike that of the free cyclic amine, should be displaced in favor of a pseudoaxial position of the trifluoromethyl group in order to minimize A(1,3) strain[1a] (Scheme 4). Accordingly, a predominantly equatorial hydride attack was expected. This could be verified by treatment of **12** with sodium borohydride in methanol at –10 °C, which gave the axial 4-piperidinol **13** almost exclusively (88% yield, *de* = 96%[21]). The relative *cis* configuration of **13** was unambiguously confirmed after catalytic hydrogenolysis into **14**, the ^{1}H NMR spectroscopic data for which clearly indicated a 2,4-diequatorial disubstitution pattern in a chair conformation.

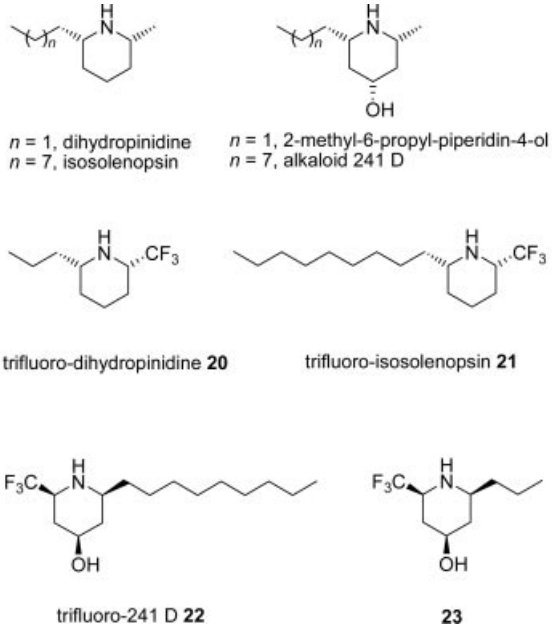
Similarly, treatment of piperidone **12** with *p*-methoxyaniline at room temperature in dichloromethane in the presence of sodium acetoxyborohydride and acetic acid[22] gave the desired *cis*-4-aza-2-(trifluoromethyl)piperidine **15** in 85% yield and with an interesting 94:6 diastereomeric ratio.[21] Such discrimination confirmed the involvement of imine conformer **19** as the probable intermediate (Scheme 4). The *cis* relationship of the heterocycle substituents in **15** was clearly established through ^{1}H NMR analysis



Scheme 4.

of diamine **16**, easily obtained by selective removal of the piperidine *N*-protective group. Employment of other amines (4-chloroaniline, benzylamine) for the reductive amination of **12** permitted the corresponding 4-aminopiperidines **17** and **18** to be isolated with comparable stereoselectivities (Scheme 3). In the process, we were able to demonstrate that the readily available piperidone **12** constitutes a valuable source of new functionalized α-trifluoromethylated piperidine scaffolds, compounds of interest for pharmaceutical research.[1a] It is noteworthy that a generalizable stereoselective reductive amination of **12** should give access to a broad library of original 2-(trifluoromethyl)-4-azapiperidines and this question is currently under investigation in our laboratory.

Next was the evaluation of our intramolecular Mannich reaction strategy towards the elaboration of α-trifluoromethyl analogues of polysubstituted piperidine alkaloids. Route B, (Scheme 1), permitting the substitution of the 6-position of the heterocycle, seemed particularly appropriate for this purpose and so was investigated. Compounds **20**–**22** – trifluoro analogues of the representative di- and trisubstituted piperidine alkaloids dihydropinidine, isosolenopsin, and alkaloid 241 D – were selected as targets, as was **23**, an analogue of the less well known[23] naturally occurring *cis*,*cis*-2-methyl-6-propylpiperidin-4-ol.



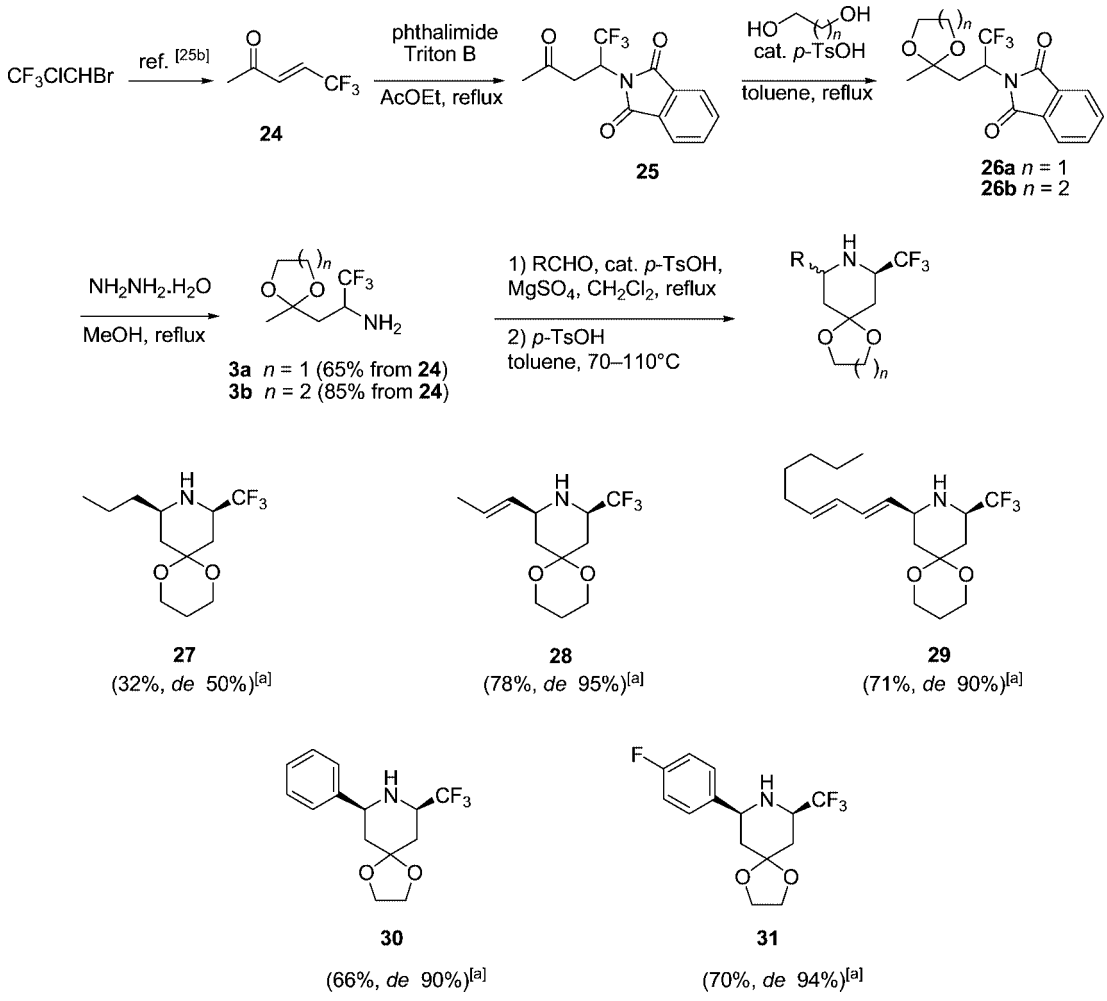
The *N*-hetero-Michael acceptor[24] 5,5,5-trifluoropent-3-en-2-one (**24**),[25] conveniently obtained as described by Dmowski et al.,[25b] was considered a suitable precursor for the preparation of the α-(trifluoromethyl)amine **3**, the key synthon of route B (Scheme 5). The enone **24** was treated with phthalimide in ethyl acetate at reflux, in the presence of Triton B, to afford the phthalimido derivative **25**, which was transformed into the parent ketals **26** with ethylene glycol or propane-1,3-diol under Dean–Stark conditions. Protection of the keto function of **25** as a 1,3-dioxane **26b**, as well as the 1,3-dioxolane **26a**, is justified by the fact that dioxanes are much more easily cleaved than the parent dioxolanes,[26] and this may constitute a nonnegligible advantage for the further transformations. Finally, hydrazinolysis of the phthalimide moiety furnished the trifluoro-substituted 1,3-aminoketals **3** in 65–85% overall yield from **24** (Scheme 5).

Amine **3b** was next engaged in the key cyclization step, at first with *n*-butanal. While piperidine **27** 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 ring formation. Consequently, non-enolizable aldehydes were considered, and treatment of amines **3** with crotonaldehyde, *trans*,*trans*-2,4-decadienal, and even with benzaldehyde and 4-fluorobenzaldehyde under our standard reaction conditions[11] yielded (66–78%) the corresponding *cis*-2,6-disubstituted piperidines **28**–**31** (Scheme 5). Consistently with results previously observed for a parent nonfluorinated series,[11c] the expected *cis* 2,6-diastereomer was formed highly predominantly (*de* up to 95%, GC/MS of the crude product). The relative configurations of **28**–**31** were unambiguously deduced from their ^{1}H NMR spectroscopic data, particularly 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.

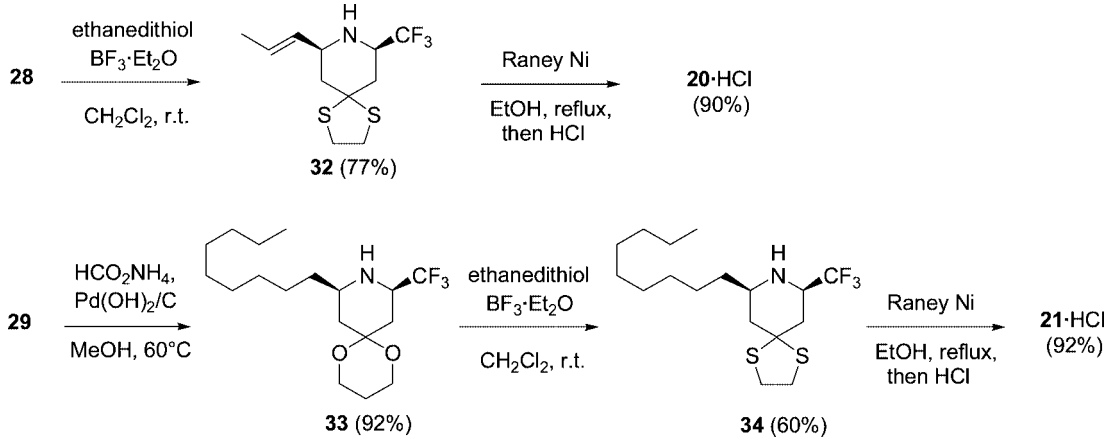
The synthesis of trifluorodihydropinidine **20** (which may also be regarded as the α′-trifluoromethylated analogue of the well known alkaloid coniine) and trifluoroisosolenopsin **21** could then be easily achieved in two or three steps from **28** and **29**, respectively, by simple deoxygenation and hydrogenation methods as summarized in Scheme 6. Both products were isolated and characterized as their hydrochloride salts.

Although not necessary, the reduction of crude **29** into **33** 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 used for the elaboration of **29** revealed (GC/MS) contamination with isomers (a few %), perturbing any accurate valuation of its diastereomeric excess, a problem that could be solved after saturation of the nonadienyl side chain.

We next turned our attention to the preparation of the trifluoro analogues of the *cis*,*cis*-2,4,6-trisubstituted piperidine alkaloids alkaloid 241 D (**22**) and **23**. Once again (vide supra), direct attempts to regenerate the keto function of the free piperidine **28** under acidic conditions (HCl, TFA) failed to give the corresponding 4-piperidone in a reasonable time, necessitating 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 **28** as an amide, even though those functional groups are reputed to be resistant to hydrolysis, and selected the trifluoroacetamide, one of the more easily cleaved amides.[27] Treatment of **28** with trifluoroacetic anhydride at 0 °C in dichloromethane, in the presence of triethylamine and *N*,*N*-dimethylaminopyridine gave trifluorocetamide **35** in 93% yield (Scheme 7).

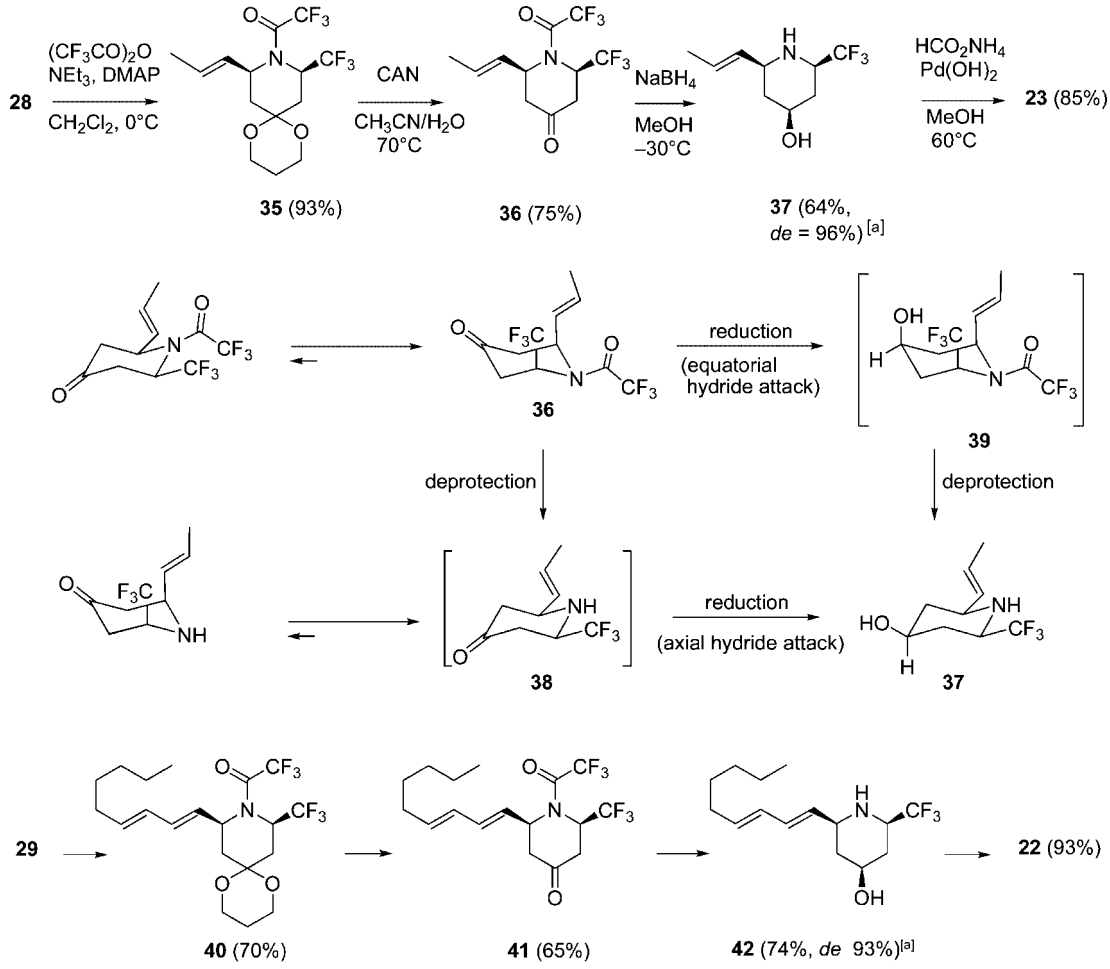


Scheme 5. (a) *de* determined from GC/MS analysis of the crude reaction mixture; yield refers to the pure isolated diastereomer.



Scheme 6.

Keto-deprotection of **35** was then cleanly and rapidly carried out by treatment with ceric ammonium nitrate[19] at 70 °C in acetonitrile/water to give the 4-piperidone **36** (75% yield). The last problems to solve were the stereoselective reduction of the keto function of **36**, together with the *N*-deprotection. Interestingly, whilst sodium borohydride may be used for the keto reduction, this reagent is also prone to cleave some trifluoroacetamides,[27] making these transformations simultaneously possible. Meanwhile, as an *all-cis* stereochemistry is required for the target, the inevitable question of the effect of the reaction sequence (reduction/deprotection v/s deprotection/reduction) on the reduction stereoselectivity arose. As shown in Scheme 7, and for reasons identical to those seen above, we thought that the



Scheme 7. [a] *de* determined from GC/MS analysis of the crude reaction mixture; yield refers to the pure isolated diastereomer.

conformational equilibrium of **36** should be strongly displaced in favor of 2,6-diaxal disubstitution. If deprotection were to occur first, the diequatorial conformer **38**, liberated from A(1,3) strain, would be expected as the stable intermediate. In this case, and as already observed with similar non-fluorinated systems,[12b,22] an axial hydride attack should predominate, mostly giving the *cis*,*cis*-piperidinol **37**. The inversion of the sequence should entail an equatorial hydride attack on ketone **36**, due to significant steric hindrance, but still leading after deprotection of the intermediate **39** to the same *all-cis* reaction product **37**. We thus reasoned that, whatever the pathway involved, there was no concern since they are stereoconvergent and should both selectively give the desired epimer. This proved to be justified, since treatment of piperidone **36** with an excess of sodium borohydride in methanol at –30 °C gave the predicted *cis*,*cis*-2,4,6-trisubstituted piperidine **37** as almost the sole epimer (*de* = 96%, GC/MS of the crude product), and this was easily hydrogenated to afford the trifluoro analogue of the trisubstituted piperidine alkaloid **23**. Finally, the same synthetic scheme was applied to piperidine **29** to afford, in four steps (40% overall yield) and in a highly stereoselective manner, the 4-piperidinol **22**, the trifluoro analogue of alkaloid 241 D (Scheme 7).

Conclusions

From the results detailed here we assume that intramolecular Mannich reactions of 1,3-aminoketals, and notably those involving α-(trifluoromethyl)amines **3**, constitute a valuable stereoselective source of a broad range of new α-(trifluoromethyl)piperidines, compounds of undeniable biological interest. The validity of this method was illustrated through the simple and highly diastereoselective synthesis of five trifluoro analogues of mono-, di-, and trisubstituted piperidine alkaloids. The crucial question of the extension of this strategy to the field of enantioselective synthesis is of course in our minds. For this purpose, several concise routes to homochiral amines **3** are currently being developed in our laboratory and will be reported in due course.

Experimental Section

General Remarks: Solvents were distilled prior to use. Other reagents were used as received. Product organic solutions were dried with sodium sulfate prior to removal of the solvents under reduced pressure on a rotary evaporator. Thin layer chromatography was performed on precoated aluminium-backed silica TLC plates and spots were visualized under UV light (254 nm) before treatment

with ethanolic phosphomolybdic acid solution (heating). Column chromatography was carried out on silica gel (70–230 mesh). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively. Chemical shifts are reported in ppm relative to $SiMe_4$. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), Q (quintet), m (multiplet), br (broad), and coupling constant (*J*) values are given in Hertz. Infrared spectra were recorded on a FTIR spectrophotometer. Electron Impact Mass Spectra (EI-MS) were obtained at 70 eV. High Resolution Electro-Spray Ionization Mass Spectra (HR-ESI-MS) were obtained from the Centre Régional de Mesures Physiques de l'Université Blaise Pascal (Clermont II), France. GC/MS analysis conditions used for determination of diastereomeric excess were as follows; column: UB 1701 (14% cyanopropylphenyl-methylpolysiloxane); injector temperature: 250 °C; oven temperature: 50 °C for 2 min then heating 50 °C min^{-1} until 290 °C. Amine **8** was prepared according to ref.[18], with propane-1,3-diol in place of ethane-1,2-diol. Enone **24** was prepared by the procedure described in ref.[25b] and was used either purified by distillation or without purification.

General Procedures

Intramolecular Mannich-Type Cyclization with Amines 3: $MgSO_4$ (ca. 1 g) was added to a stirred solution of amine **3a** or **3b** (1 mmol) in dichloromethane (10 mL), followed by the aldehyde (1.1 mmol) and then a catalytic amount of *p*TsOH. The resulting mixture was heated at gentle reflux until complete disappearance (TLC monitoring) of the amine (1–4 h) and was then allowed to cool 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) for 3–12 h. After the system had cooled 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, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography with ethyl acetate/cyclohexane as eluent.

Dithioketalization: Ethane-1,2-dithiol (5 mmol) and then $BF_3{\cdot}Et_2O$ (5 mmol) were added dropwise at room temperature to a stirred solution of keto-protected piperidone (1 mmol) in dichloromethane (10 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the starting material and was then allowed to cool to room temperature and treated with an excess of aqueous NaOH (2 M). The layers were separated, and the aqueous phase was extracted (3 × 30 mL) with dichloromethane. The combined organic extracts were washed with brine, dried, and filtered. After evaporation of the solvent, the residue was purified by column chromatography with ethyl acetate/cyclohexane as eluent.

Reduction with W2 Raney Nickel: Freshly prepared W2 Raney nickel[19] (ca. 1.0 g) was added to a stirred solution of dithioketal (100 mg) in absolute ethanol (5 mL). The resulting suspension was heated at reflux for 30 min and then allowed to cool to room temperature. The solution was filtered through Celite® and 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 12: Sodium triacetoxyborohydride (300 mg, 1.4 mmol) and then AcOH (60 μL, 1 mmol) were added to a stirred solution of piperidone **12** (301 mg, 1 mmol) and amine (1 mmol) in CH_2Cl_2 (4 mL). The resulting solution was stirred at room temperature until completion of the reaction (TLC or GC analysis). The reaction was quenched by addition of NaOH (1 N) and the product was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried, filtered, and concentrated before purification of the product by column chromatography (ethyl acetate/cyclohexane).

(±)-8-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecane (9): Trifluoroacetaldehyde methyl hemiacetal (3.36 g, 27.9 mmol) in CH_2Cl_2 (3 mL), $MgSO_4$ (ca. 1 g), and a catalytic amount of *p*-toluenesulfonic acid were added to a stirred solution of amine **8** (2.5 g, 17.2 mmol) in dichloromethane (25 mL). The resulting mixture was heated at gentle reflux for 4 hours, allowed to cool to room temperature, and then transferred into a solution of *p*TsOH (4.5 g, 23.7 mmol; previously dried under Dean–Stark conditions) in toluene (250 mL). The resulting mixture was heated at 80 °C for 1.5 hours, and was then allowed to cool to room temperature and diluted with ethyl acetate (100 mL) before addition of saturated $NaHCO_3$ (35 mL). After separation, the aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were dried, filtered, and concentrated under reduced pressure to afford clean piperidine **9** as a pale brown oil (2.75 g, 71%), which solidified upon standing in freezer and could be engaged in the next step without purification. Silica gel column chromatography (ethyl acetate/cyclohexane, 1:1) gave pure piperidine **9** (1.90 g, 49%) as a pale yellow solid. M.p. 44–45 °C. ^{1}H NMR ($CDCl_3$): δ = 3.94 (t, *J* = 5 Hz, 2 H), 3.88 (t, *J* = 5 Hz, 2 H), 3.37 (m, 1 H), 3.12 (m, 1 H), 2.85 (t, *J* = 12 Hz, 1 H), 2.44 (d, *J* = 12 Hz, 1 H), 2.30 (br. s, 1 H), 2.28 (d, *J* = 12 Hz, 1 H), 1.75 (m, 2 H), 1.50 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.5 (q, J_{C-F} = 265 Hz), 95.7, 59.1, 55.0 (q, J_{C-F} = 29 Hz), 41.7, 32.5, 25.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3300, 1283, 1173, 1095 cm^{-1}. EI-MS (70 eV): *m*/*z* = 225 $[M]^+$ (10), 224 (12), 166 (90), *156* (100), 124 (60), 113 (55), 101 (80), 100 (80), 98 (90), 56 (70), 43 (60) cm^{-1}. HR-ESI-MS calculated for $C_9H_{15}F_3NO_2$ $[M+H]^+$: 226.1055; found 226.1060.

(±)-7-(Trifluoromethyl)-1,4-dithia-8-azaspiro[5.4]decane (10): Treatment of piperidine **9** (225 mg, 1 mmol) as described in the dithioketalization General Procedure furnished dithioketal **10** (214 mg, 88%) as a colorless oil after silica gel column chromatography (ethyl acetate/cyclohexane, 1:6). ^{1}H NMR ($CDCl_3$): δ = 3.36 (m, 5 H), 3.20 (dt, *J* = 12 and 3 Hz, 1 H), 2.87 (m, 1 H), 2.24 (dt, *J* = 12 and 1.5 Hz, 1 H), 2.09 (m, 2 H), 2.00 (dd, *J* = 11.5 and 11 Hz, 1 H), 1.67 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.3 (q, J_{C-F} = 279 Hz), 65.0, 57.4 (q, J_{C-F} = 29 Hz), 45.2, 41.5, 41.45, 39.0, 38.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3308, 1277, 1162, 1133, 1097 cm^{-1}. EI-MS (70 eV): *m*/*z* = 243 $[M]^+$ (15), 182 (20), *150* (100), 124 (10), 110 (12). HR-ESI-MS calculated for $C_8H_{13}F_3NS_2$ $[M+H]^+$: 244.0442; found 244. 0450.

HCl Salt of (±)-2-(Trifluoromethyl)piperidine (Trifluoropipecoline, 7): Treatment of dithioketal **10** (100 mg, 0.41 mmol) as described in the reduction with Raney nickel General Procedure afforded the hydrochloride salt of trifluoropipecoline **7** (70 mg, 90%). M.p. 218 °C (dec.), lit.[10b] 220 °C (dec.). EI-MS (70 eV) (free base): *m*/*z* = 153 $[M]^+$ (8), 152 (7), 84 (100), 56 (20). Other spectroscopic data were identical with those already reported.[10b]

(±)-*N*-(Benzyloxycarbonyl)-8-(trifluoromethyl)-1,5-dioxa-9-azaspiro-[5.5]undecane (11): Aqueous sodium carbonate solution (0.44 M, 20 mL) and then, at 0 °C, benzyl chloroformate (1.27 mL, 8.8 mmol) were added to a stirred solution of piperidine derivative **9** (1 g, 4.4 mmol) in dichloromethane (20 mL). The resulting mixture was stirred overnight at room temperature before addition of dichloromethane (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic extracts were dried and filtered, and the solvent was eliminated under reduced pressure. Purification by column chromatography (ethyl acetate/cyclohexane, 1:5) gave carbamate **11** (1.51 g, 95%) as a white solid. M.p. 97–

98 °C. ^{1}H NMR ($CDCl_3$): δ = 7.36 (m, 5 H), 5.19 (d, J = 12 Hz, 1 H), 5.16 (d, J = 12 Hz, 1 H), 4.83 (br. s, 1 H), 4.15 (m, 1 H), 3.88 (m, 4 H), 3.25 (dt, J = 12 and 3 Hz, 1 H), 2.48 (dd, J = 12 and 3 Hz, 1 H), 2.00 (m, 2 H), 1.80 (m, 2 H), 1.66 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.5, 136.1, 128.5, 128.1, 127.8, 125.4 (q, J_{C-F} = 285 Hz), 95.2, 67.8, 59.5, 51.6 (q, J_{C-F} = 32 Hz), 38.2, 25.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1698, 1429, 1362, 1142, 1109 cm^{-1}. EI-MS (70 eV): 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.

(±)-*N*-(Benzyloxycarbonyl)-2-(trifluoromethyl)piperidin-4-one (12): Aqueous trifluoroacetic acid solution (50%, 6 mL) was added to a stirred solution of piperidine **11** (1 g, 2.8 mmol) in dichloromethane (10 mL). The resulting mixture was vigorously stirred for 3 days and was then neutralized by addition of NaOH (4 N). The deprotected product was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were dried, filtered, and then concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/cyclohexane, 1:5) furnished piperidone **12** (796 mg, 95%) as a white solid. M.p. 67–68 °C. ^{1}H NMR ($CDCl_3$, low-resolution spectrum due to the coexistence of carbamate rotamers): δ = 7.36 (m, 5 H), 5.40–5.05 (m, 3 H), 4.60–4.35 (m, 1 H), 3.45 (m, 1 H), 2.69 (m, 2 H), 2.50, (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 203.5, 155.4, 135.4, 128.6, 128.5, 128.1, 125.0 (q, J_{C-F} = 267 Hz), 68.2, 53.3 (q, J_{C-F} = 32 Hz), 40.1, 39.3, 37.7 ppm. IR (neat) $\tilde{\nu}_{max}$ = 1713, 1423, 1271, 1169, 1135 cm^{-1}. EI-MS (70 eV): 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.

(±)-(2*R,4*S**)-*N*-(Benzyloxycarbonyl)-2-(trifluoromethyl)piperidin-4-ol (13):** Sodium borohydride (76 mg, 2 mmol) was added at –10 °C to a stirred solution of piperidone **12** (301 mg, 1 mmol) in methanol (8 mL). The resulting mixture was stirred for 1 hour before addition of saturated NH_4Cl (3 mL) and subsequent heating to room temperature. The methanol was eliminated under reduced pressure and the piperidinol was extracted with dichloromethane (4 × 20 mL). The combined organic extracts were washed with brine, dried, and filtered. Evaporation of the solvent followed by column chromatography (ethyl acetate/cyclohexane, 1:3) gave piperidinol **13** (267 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$, low-resolution spectrum due to the coexistence of carbamate rotamers): δ = 7.35 (m, 5 H), 5.19 (d, J = 12 Hz, 1 H), 5.15 (d, J = 12 Hz, 1 H), 4.82 (m, 1 H), 4.11 (m, 2 H), 3.40 (m, 1 H), 2.06 (m, 2 H), 1.77 (m, 2 H), 1.6 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.5, 135.9, 128.5, 128.2, 127.9, 125.5 (q, J_{C-F} = 285 Hz), 68.0, 62.0, 50.4 (q, J_{C-F} = 31 Hz), 35.7, 31.2, 29.1 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3457, 1710, 1424, 1283, 1141, 1051 cm^{-1}. EI-MS (70 eV): 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 (14):** $Pd(OH)_2$/C (20%, 50 mg) and ammonium formate (208 mg, 3.3 mmol) were added to a stirred solution of compound **13** (200 mg, 0.66 mmol) in methanol (10 mL). The mixture was heated at 60 °C for 2 h. After the system had cooled to room temperature, the solution was filtered through celite®, and the filtrate was concentrated under reduced pressure to give a residue that was diluted with saturated aqueous $NaHCO_3$ (5 mL) before extraction with dichloromethane (5 × 20 mL). The combined organic extracts were dried and filtered. Evaporation of the solvent followed by column chromatography (ethyl acetate/cyclohexane, 1:1 to pure ethyl acetate) gave piperidinol **14** (102 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 3.70 (m, 1 H), 3.22 (dd, J = 12.5 and 1.5 Hz, 1 H), 3.14 (m, 1 H), 2.65 (dt, J = 12 and 1.5 Hz, 1 H), 2.17 (m, 1 H), 1.98 (m, 1 H), 1.70 (br. s, 2 H), 1.42 (qd, J = 12 and 3 Hz, 1 H), 1.38 (q, J = 12 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 124.8 (q, J_{C-F} = 279 Hz), 67.6, 56.9 (q, J_{C-F} = 29 Hz), 43.8, 34.7, 34.1 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3279, 1273, 1182, 1070 cm^{-1}. EI-MS (70 eV): m/z = 169 [M]$^+$ (5), 150 (15), 124 (20), 110 (30), *100* (100), 82 (50), 56 (50). HR-ESI-MS calculated for $C_6H_{11}F_3NO$ [M + H]$^+$: 170.093; found 170.091.

(±)-(2*R,4*S**)-*N*-Benzyloxycarbonyl-4-[*N*-(4-methoxyphenyl)-amino]-2-(trifluoromethyl)piperidine (15):** Treatment of piperidone **12** (1 g, 3.3 mmol) and 4-methoxyaniline as described in the reductive amination General Procedure afforded 4-aminopiperidine **15** (1.17 g, 85%) as a brown oil after column chromatography (ethyl acetate/cyclohexane, 1:3). ^{1}H NMR ($CDCl_3$, low-resolution spectrum due to the coexistence of carbamate rotamers): δ = 7.37 (m, 5 H), 6.80 (dd, J = 9 and 1.5 Hz, 2 H), 6.57 (dd, J = 9 and 1.5 Hz, 2 H), 5.21 (d, J = 14 Hz, 2 H), 5.17 (d, J = 14 Hz, 2 H), 4.70 (m, 1 H), 4.14 (m, 1 H), 3.75 (s, 3 H), 3.54 (m, 1 H), 3.40 (br. s, 1 H), 3.27 (m, 1 H), 2.25 (m, 1 H), 2.14 (m, 1 H), 1.86 (m, 1 H), 1.58 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.7, 152.5, 135.9, 128.5, 128.2, 127.9, 125.5 (q, J_{C-F} = 281 Hz), 115.0, 114.9, 67.9, 55.6, 51.6 (q, J_{C-F} = 31 Hz), 45.2, 37.2, 29.1, 26.1 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3379, 1706, 1513, 1422, 1270, 1234, 1150, 1036 cm^{-1}. EI-MS (70 eV): 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-[*N*-(4-Methoxyphenyl)amino]-2-(trifluoromethyl)-piperidine (16):** $Pd(OH)_2$/C (20%, 100 mg) and ammonium formate (386 mg, 6.1 mmol) were added to a stirred solution of compound **15** (500 mg, 1.2 mmol) in methanol (20 mL). The mixture was heated at 60 °C for 2 h. After the system had cooled 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) before extraction with dichloromethane (5 × 40 mL). The combined organic extracts were dried and filtered. Evaporation of the solvent followed by column chromatography (ethyl acetate/cyclohexane, 1:1 to ethyl acetate) gave 4-aminopiperidine **16** (235 mg, 70%) as a red oil. ^{1}H NMR ($CDCl_3$): δ = 6.79 (m, 2 H), 6.59 (m, 2 H), 3.75 (s, 3 H), 3.25 (m, 3 H), 2.76 (td, J = 13 and 2.5 Hz, 1 H), 2.40 (br. s, 2 H), 2.30 (m, 1 H), 2.09 (m, 1 H), 1.29 (qd, J = 12.5 and 4 Hz, 1 H), 1.21 (q, J = 11.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 152.4, 140.6, 125.3 (q, J_{C-F} = 280 Hz), 115.2, 114.9, 57.5 (q, J_{C-F} = 29 Hz), 55.6, 50.8, 44.8, 33.1, 32.2 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3333, 2953, 1518, 1228, 1138, 1036, 821 cm^{-1}. EI-MS (70 eV): 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.

(±)-(2*R,4*S**)-*N*-Benzyloxycarbonyl-4-[*N*-(4-chlorophenyl)amino]-2-(trifluoromethyl)piperidine (17):** Treatment of piperidone **12** (301 mg, 1 mmol) and 4-chloroaniline as described in the General Procedure for reductive amination afforded 4-aminopiperidine **17** (235 mg, 60%) as a brown oil after column chromatography (ethyl acetate/cyclohexane, 1:5). ^{1}H NMR ($CDCl_3$, low-resolution spectrum due to the coexistence of carbamate rotamers): δ = 7.38 (m, 5 H), 7.12 (m, 2 H), 6.50 (m, 2 H), 5.21 (d, J = 12.5 Hz, 1 H), 5.18 (d, J = 12.5 Hz, 1 H), 4.82 (m, 1 H), 4.15 (m, 1 H), 3.60 (m, 1 H), 3.26 (m, 1 H), 2.23 (m, 1 H), 2.11 (m, 1 H), 1.91 (m, 1 H), 1.62 (m, 1 H) ppm. IR (neat) $\tilde{\nu}_{max}$ = 3383, 1704, 1599, 1499, 1422, 1276, 1150, 1118, 817, 698 cm^{-1}. EI-MS (70 eV): 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.

(±)-(2*R,4*S**)-*N*-Benzyloxycarbonyl-4-(*N*-benzylamino)-2-(trifluoromethyl)piperidine (18):** Treatment of piperidone **12** (301 mg,

1 mmol) and benzylamine as described in General Procedure for the reductive amination afforded 4-aminopiperidine **18** (251 mg, 64%) as a pale yellow oil after column chromatography (ethyl acetate/cyclohexane, 1:3). ^{1}H NMR ($CDCl_3$): δ = 7.32 (m, 10 H), 5.18 (d, J = 12 Hz, 1 H), 5.14 (d, J = 12 Hz, 1 H), 4.61 (m, 1 H), 4.06 (m, 1 H), 3.82 (d, J = 12 Hz, 1 H), 3.75 (d, J = 12 Hz, 1 H), 3.27 (m, 1 H), 2.83 (m, 1 H), 2.08 (m, 2 H), 1.81 (m, 1 H), 1.47 (m, 1 H), 1.33 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.8, 139.9, 136.0, 128.5, 128.4, 128.1, 127.9, 127.8, 127.0, 125.5 (q, J_{C-F} = 284 Hz), 115.2, 114.9, 52.0 (q, J_{C-F} = 31 Hz), 67.9, 51.1, 48.6, 37.3, 29.3, 26.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3314, 1713, 1422, 1274, 1151, 698 cm^{-1}. EI-MS (70 eV): m/z = 392 [M]$^+$ (1), 301 (20), 257 (15), 106 (15), *91* (100).

5,5,5-Trifluoro-4-*N*-phthalimidopentan-2-one (25): Phthalimide (8.53 g, 58 mmol) and a solution of Triton B® in methanol (40%, 1 mL) were added to a stirred solution of enone **24** (8.0 g, 58 mmol) in ethyl acetate (230 mL). The resulting solution was heated at reflux for 5 h, and was then allowed to cool to room temperature and treated with NaOH solution (1 M, 50 mL). The two layers were separated, and the aqueous phase was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried, filtered, and concentrated to afford **25** (15.94 g, 96%) very cleanly as a pale yellow solid that could be engaged directly in the following step. Recrystallization (EtOH) afforded pure phthalimido compound **25** (10.74 g, 65%) as a white solid. M.p. 100–101 °C. ^{1}H NMR ($CDCl_3$): δ = 7.85 (m, 2 H), 7.74 (m, 2 H), 5.27 (m, 1 H), 4.03 (dd, J = 19.0 and 11.0 Hz, 1 H), 3.08 (dd, J = 19.0 and 4.0 Hz, 1 H), 2.18 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 202.8, 167.1, 134.5, 134.2, 127.0 (q, J_{C-F} = 282 Hz), 123.7, 123.5, 47.8 (q, J_{C-F} = 33 Hz), 37.6, 29.8 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 2966, 1775, 1722, 1386, 1284, 1174, 1105, 729 cm^{-1}. EI-MS (70 eV): 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-Methyl-2-(3,3,3-trifluoro-2-*N*-phthalimidopropyl)-1,3-dioxolane (26a): Ethane-1,2-diol (4.1 mL, 73 mmol) and *p*TsOH (200 mg) were added to a solution of **25** (10.4 g, 36.5 mmol) in toluene (140 mL) in a flask fitted with a Dean–Stark apparatus. The resulting mixture was heated at reflux until complete disappearance (TLC monitoring) of the compound **25**. The mixture was then allowed to cool to room temperature and concentrated in vacuo. The residue, diluted with ethyl acetate (100 mL), was then treated with a saturated $NaHCO_3$ solution. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (2×100 mL). The combined organic extracts were dried, filtered, and concentrated. Simple washing of the solid residue with cold cyclohexane afforded pure phthalimido compound **26a** (9.60 g, 80%) as a white solid. M.p. 94–95 °C. ^{1}H NMR ($CDCl_3$): δ = 7.87–7.85 (m, 2 H), 7.75–7.73 (m, 2 H), 5.08–4.99 (m, 1 H), 3.92–3.85 (m, 2 H), 3.79–3.73 (m, 1 H), 3.67–3.62 (m, 1 H), 3.20 (dd, J = 15 and 11.5 Hz, 1 H), 2.14 (dd, J = 15 and 1.5 Hz, 1 H), 1.28 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.1, 134.5, 134.1, 124.4 (q, J_{C-F} = 232 Hz), 123.5, 123.4, 108.1, 64.6, 64.3, 48.2 (q, J_{C-F} = 33 Hz), 31.4, 23.8 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 2980, 2894, 1774, 1727, 1382, 1289, 1186, 1119, 1079, 1067, 1036, 909, 890, 735, 720 cm^{-1}. EI-MS (70 eV): 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-Methyl-2-(3,3,3-trifluoropropyl-2-*N*-phthalimido)-1,3-dioxane (26b): By starting from **25** (9.24 g, 32.4 mmol), propane-1,3-diol (4.7 mL, 64.8 mmol), and *p*TsOH (200 mg) as described in the above procedure, compound **26b** (10.78 g, 97%) was obtained as a white solid. M.p. 124 °C. ^{1}H NMR ($CDCl_3$): δ = 7.89–7.85 (m, 2 H), 7.76–7.71 (m, 2 H), 5.40–4.30 (m, 1 H), 3.91 (dt, J = 12 and 3 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.76 (dt, J = 12 and 3 Hz, 1 H), 3.30–3.25 (m, 1 H), 3.08 (dd, J = 15.0 and 11.0 Hz, 1 H), 2.01 (dd, J = 15.0 and 1.5 Hz, 1 H), 1.83–1.71 (m, 1 H), 1.42 (s, 3 H), 1.22–1.16 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.5, 134.2, 134.0, 132.2, 131.3, 124.7 (q, J_{C-F} = 282 Hz), 123.5, 123.4, 97.6, 60.0, 59.9, 47.7 (q, J_{C-F} = 33 Hz), 34.6, 24.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2959, 2888, 1778, 1725, 1383, 1290, 1247, 1186, 1118, 1086, 1068, 889, 729 cm^{-1}. EI-MS (70 eV): m/z = 328 [M – Me]$^+$ (85), 181 (95), 123 (45), *101* (100), 43 (60). HR-ESI-MS calculated for $C_{16}H_{16}F_3NNaO_4$ [M + Na]$^+$: 366.0929; found 366.0947.

(±)-2-(2-Amino-3,3,3-trifluoropropyl)-2-methyl-1,3-dioxolane (3a): Hydrazine monohydrate (4.6 mL, 95 mmol) was added to a solution of **26a** (6.24 g, 19 mmol) in methanol (100 mL). The resulting mixture was heated at reflux until complete disappearance (TLC monitoring) of the compound **26a**. The mixture was then allowed to cool to room temperature and cautiously concentrated under reduced pressure. The residue, diluted with dichloromethane (100 mL), was then treated with KOH solution (2 M, 76 mL, 152 mmol; vigorous stirring for 30 min.). The two layers were separated, and the aqueous phase was extracted with dichloromethane (3×100 mL). The combined organic extracts were dried and filtered, and the solvents were evaporated. Amine **3a** (3.21 g, 85%) 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 **3a** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.02–3.94 (m, 4 H), 3.54–3.46 (m, 1 H), 2.05 (br. d, J = 14.5 Hz, 1 H), 1.63 (dd, J = 14.5 and 10 Hz, 1 H), 1.65 (br. s, 2 H), 1.38 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 126.3 (q, J_{C-F} = 280 Hz), 108.7, 64.6, 64.2, 50.3 (q, J_{C-F} = 29 Hz), 38.1, 24.0 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3405, 3340, 2988, 2892, 1618, 1381, 1307, 1249, 1219, 1148, 1112, 1045, 949, 813 cm^{-1}. EI-MS (70 eV): 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.

(±)-2-(2-Amino-3,3,3-trifluoropropyl)-2-methyl-1,3-dioxane (3b): By starting from **26b** (5.3 g, 15.5 mmol) in methanol (200 mL) and hydrazine monohydrate (3.7 mL, 77 mmol) as described in the procedure above, amine **3b** (2.99 g, 91%) was obtained as a pale yellow liquid, which could be used without purification. Silica gel column chromatography (ethyl acetate/cyclohexane, 1:3) afforded pure amine **3b** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 4.04–3.96 (m, 2 H), 3.91–3.80 (m, 2 H), 3.80–3.71 (m, 1 H), 2.11 (br. s, 2 H), 1.98 (dd, J = 14.5 and 1.5 Hz, 1 H), 1.97–1.87 (m, 1 H), 1.79 (dd, J = 14.5 and 10.0 Hz, 1 H), 1.49 (s, 3 H), 1.49–1.12 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 126.5 (q, J_{C-F} = 280 Hz), 98.2, 59.7, 59.6, 49.6 (q, J_{C-F} = 29 Hz), 40.3, 25.2, 19.5 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3402, 3338, 2973, 2877, 1617, 1376, 1246, 1152, 1108, 1081, 966, 804 cm^{-1}. EI-MS (70 eV): m/z = 213 [M]$^+$ (1), 198 (40), *101* (100), 73 (40), 43 (90). HR-ESI-MS calculated for $C_8H_{15}F_3NO_2$ [M + H]$^+$: 214.1055; found 214.1050.

(±)-(8*R,10*R**)-10-Propyl-8-(trifluoromethyl)-1,5-dioxa-9-azaspiro-[5.5]undecane (27):** Amine **3b** (400 mg, 1.9 mmol), butanal (186 μL, 2.1 mmol), and *p*TsOH (711 mg, 3.7 mmol), treated as described in the General Procedure for the intramolecular Mannich-type reaction (reaction temperature = 72 °C), gave *cis*-piperidine **27** (161 mg, 32%, yellow oil) after chromatography (ethyl acetate/cyclohexane, 1:6). The *trans* isomer could not be separated from undesired side products (see "Results and Discussion"). ^{1}H NMR ($CDCl_3$): δ = 3.94 (t, J = 5.5 Hz, 2 H), 3.88 (t, J = 5.5 Hz, 2 H), 3.42–3.33 (m, 1 H), 2.86–2.77 (m, 1 H), 2.47 (br. d, J = 13 Hz, 1 H), 2.26 (br. d, J = 13 Hz, 1 H), 1.81–1.67 (m, 3 H), 1.52–1.31 (m, 5 H), 1.28–1.11

(m, 1 H), 0.92 (t, 3 H, J = 6.5 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.6 (q, J_{C-F} = 279 Hz), 96.4, 59.3, 59.2, 55.0 (q, J_{C-F} = 29 Hz), 51.9, 39.2, 38.4, 32.0, 25.3, 18.9, 14.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3316, 2961, 2933, 2873, 1337, 1268, 1180, 1142, 1092, 1023, 934, 793 cm^{-1}. EI-MS (70 eV): m/z = 267 $[M]^+$ (1), 224 (60), 208 (25), *181* (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)-1,5-dioxa-9-azaspiro[5.5]undecane (28):** Amine **3b** (2.0 g, 9.4 mmol), crotonaldehyde (842 μL, 10.4 mmol), and *p*TsOH (3.58 g, 18.8 mmol), treated as described in the General Procedure for the intramolecular Mannich-type reaction (reaction temperature = 76 °C), gave piperidine **28** (1.94 g, 78%) as a pale yellow oil after chromatography (ethyl acetate/cyclohexane, 1:9). ^{1}H NMR ($CDCl_3$): δ = 5.67 (dq, J = 15 and 6.5 Hz, 1 H), 5.45 (dd, J = 15 and 7 Hz, 1 H), 3.94 (br. t, J = 5.5 Hz, 2 H), 3.89 (t, J = 5.5 Hz, 2 H), 3.45–3.38 (m, 1 H), 3.35–3.30 (m, 1 H), 2.40 (dt, J = 13 and 3 Hz, 1 H), 2.26 (dd, J = 13.5 and 3 Hz, 1 H), 1.78–1.70 (m, 2 H), 1.68 (d, J = 6.5 Hz, 3 H), 1.45 (t, J = 12.5 Hz, 1 H), 1.3 (t, J = 13 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 132.6, 127.0, 125.6 (q, J_{C-F} = 279 Hz), 96.2, 59.3, 59.2, 54.6 (q, J_{C-F} = 29 Hz), 54.3, 38.7, 32.0, 25.3, 17.7 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3310, 2969, 2868, 1336, 1279, 1267, 1176, 1137, 1020, 971 cm^{-1}. EI-MS (70 eV): m/z = 265 $[M]^+$ (5), *206* (100), 181 (30), 101 (25). HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_2$ $[M+H]^+$: 266.1368; found 266.1362.

(±)-(8R*,10S*)-10-((*E*,*E*)-Nona-1,3-dienyl)-8-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecane (29): Amine **3b** (2.88 g, 13.5 mmol), *trans*,*trans*-2,4-decadienal (2.60 mL, 14.9 mmol), and *p*TsOH (5.15 g, 27.1 mmol), treated as described in the General Procedure for the intramolecular Mannich-type reaction (reaction temperature = 70 °C), gave piperidine **29** (3.33 g, 71%) as a yellow oil after column chromatography (ethyl acetate/cyclohexane, 1:19). ^{1}H NMR ($CDCl_3$): δ = 6.18 (dd, J = 15 and 10.5 Hz, 1 H), 5.99 (dd, J = 15 and 10.5 Hz, 1 H), 5.72–5.65 (m, 1 H), 5.53 (dd, J = 15 and 7.5 Hz, 1 H), 3.90 (m, 4 H), 3.47–3.35 (m, 2 H), 2.38 (dt, J = 13.0 and 3 Hz, 1 H), 2.29 (dt, J = 13 and 3 Hz, 1 H), 2.06 (q, J = 7 Hz, 2 H), 1.81–1.66 (m, 2 H), 1.48–1.21 (m, 8 H), 0.88 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.7, 131.7, 131.5, 129.3, 125.6 (q, J_{C-F} = 279 Hz), 96.1, 59.3, 59.2, 54.7 (q, J_{C-F} = 29 Hz), 54.3, 38.6, 32.5, 33.1, 31.3, 28.8, 25.4, 22.5, 13.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3321, 2958, 2930, 2861, 1728, 1459, 1429, 1400, 1379, 1337, 1280, 1175, 1135, 1018, 990 cm^{-1}. EI-MS (70 eV): m/z = 347 $[M]^+$ (20), 290 (20), 276 (20), *181* (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)-1,4-dioxa-8-azaspiro-[5.4]decane (30):** Amine **3a** (200 mg, 1 mmol), benzaldehyde (112 μL, 1.1 mmol), and *p*TsOH (382 mg, 2 mmol), treated as described in the General Procedure for the intramolecular Mannich-type reaction (reaction temperature = 110 °C), gave piperidine **30** (191 mg, 66%) as a pale yellow oil after chromatography (ethyl acetate/cyclohexane, 1:6). ^{1}H NMR ($CDCl_3$): δ = 7.43–7.27 (m, 5 H), 4.05–3.98 (m, 4 H), 3.95 (dd, J = 12 and 3 Hz, 1 H), 3.56 (m, 1 H), 1.93 (dt, J = 12.5 and 3 Hz, 1 H), 1.85 (dt, J = 13 and 3 Hz, 1 H), 1.77 (t, J = 12 Hz, 1 H), 1.75 (t, J = 12 Hz, 1 H), 1.60 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.9, 128.6, 127.7, 126.8, 125.6 (q, J_{C-F} = 278 Hz),107.0, 64.6, 64.5, 58.1, 56.4 (q, J_{C-F} = 29.0 Hz), 43.3, 34.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3313, 3032, 2977, 2887, 1455, 1401, 1337, 1280, 1247, 1174, 1124, 1077, 1058, 1015, 948, 761, 701 cm^{-1}. EI-MS (70 eV): m/z = 287 $[M]^+$ (10), *242* (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)-1,4-dioxa-8-azaspiro[5.4]decane (31):** Amine **3a** (200 mg, 1 mmol), 4-fluorobenzaldehyde (117 μL, 1.1 mmol), and *p*TsOH (382 mg, 2 mmol), treated as described in the General Procedure for the intramolecular Mannich-type reaction (reaction temperature = 70 °C), gave piperidine **31** (215 mg, 70%) as a white solid after column chromatography (ethyl acetate/cyclohexane, 1:6). M.p. 85–89 °C. ^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 2 H), 7.02 (m, 2 H), 6.04–3.93 (m, 5 H), 3.55 (m, 1 H), 1.92 (br. s, 1 H), 1.92 (dt, J = 12.5 and 3 Hz, 1 H), 1.82 (dt, J = 13 and 3 Hz, 1 H), 1.76 (t, J = 12.5 Hz, 1 H), 1.73 (t, J = 13 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 163.4 (d, J_{C-F} = 245.5 Hz), 138.6, 128.4, 128.3, 125.5 (q, J_{C-F} = 279 Hz), 115.5, 115.2, 106.8, 64.6, 64.5, 57.4, 56.3 (q, J_{C-F} = 30 Hz), 43.4, 33.8 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3305, 1605, 1509, 1276, 1180, 1135, 1013, 840 cm^{-1}. EI-MS (70 eV): 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.

(±)-(7*R,9*S**)-9-(Prop-1-enyl)-7-(trifluoromethyl)-1,4-dithia-8-azaspiro[5.4]decane (32):** Protected piperidone **28** (200 mg, 0.75 mmol) in dichloromethane (10 mL), ethanedithiol (320 μL, 3.8 mmol), and $BF_3{\cdot}Et_2O$ (481 μL, 3.8 mmol), treated as described in the General Procedure for dithioaketalization, gave dithiolane **32** (164 mg, 77%) as a pale yellow oil after purification by column chromatography (ethyl acetate/cyclohexane, 1:19). ^{1}H NMR ($CDCl_3$): δ = 5.70 (dq, J = 15 and 6.5 Hz, 1 H), 5.44 (dd, J = 15 and 7.0 Hz, 1 H), 3.51–3.41 (m, 1 H), 3.36–3.29 (m, 5 H), 2.22 (ddd, J = 13, 4.5 and 2.5 Hz, 1 H), 2.10 (ddd, J = 13.5, 5 and 2.5 Hz, 1 H), 1.98 (m, 1 H), 1.85 (m, 1 H), 1.68 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 132.2, 127.4, 125.3 (q, J_{C-F} = 279 Hz), 64.8, 57.7, 57.3 (q, J_{C-F} = 29 Hz), 47.4, 40.7, 39.3, 38.0, 17.7 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3308, 2957, 2926, 2837, 1275, 1173, 1139, 1125, 1060, 968, 815, 786 cm^{-1}. HR-ESI-MS calculated for $C_{11}H_{17}F_3NS_2$ $[M+H]^+$: 284.0755; found 284.0750.

(±)-(2*R,6*R**)-6-Propyl-2-(trifluoromethyl)piperidine Hydrochloride (Trifluorodihydropinidine Hydrochloride) (20·HCl):** Dithioketal **32** (70 mg, 0.24 mmol) in solution in absolute ethanol (7 mL) and treated with W2 Raney nickel (ca. 700 mg), as described in the General Procedure for hydrogenolysis, gave pure compound **20·HCl** (51 mg, 90%) as a white solid. M.p. 201 °C (dec.). ^{1}H NMR (CD_3OD): δ = 5.15–5.06 (m, 1 H), 4.39–4.31 (m, 1 H), 3.29–3.16 (m, 2 H), 3.13–3.06 (m, 1 H), 2.83–2.37 (m, 7 H), 1.98 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (CD_3OD): δ = 124.6 (q, J_{C-F} = 280 Hz), 60.3, 58.6 (q, J_{C-F} = 32 Hz), 36.0, 28.4, 23.1, 22.0, 19.6, 14.0 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 2935, 1271, 1192, 1119 cm^{-1}. EI-MS (70 eV, 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.

(±)-(8*R,10*R**)-10-Nonyl-8-(trifluoromethyl)-1,5-dioxa-9-azaspiro-[5.5]undecane (33):** $Pd(OH)_2$/C (20%, 50 mg) and ammonium formate (182 mg, 2.9 mmol) were added to a stirred solution of compound **29** (200 mg, 0.6 mmol) in methanol (10 mL). The mixture was heated at reflux for 2 h. After the system had cooled to room temperature, the solution was filtered through celite®, and the filtrate was concentrated under reduced pressure to give a residue that was diluted with saturated aqueous $NaHCO_3$ (5 mL) before extraction with dichloromethane (3 × 20 mL). The combined organic extracts were dried, filtered, and evaporated, to afford saturated piperidine **33** (186 mg, 92%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.93 (t, J = 5.5 Hz, 2 H), 3.87 (t, J = 5.5 Hz, 2 H), 3.39–3.30 (m, 1 H), 2.79–2.72 (m, 1 H), 2.45 (dt, J = 13 and 2.5 Hz, 1 H), 2.24, (dt, J = 13 and 2.5 Hz, 1 H), 2.12–1.93 (m, 1 H), 1.79–1.66 (m, 2 H), 1.40 (t, J = 12.5 Hz, 1 H), 1.34–1.18 (m, 16 H), 1.12

(t, J = 13 Hz, 1 H), 0.89–0.87 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.7 (q, J_{C-F} = 279 Hz), 96.4, 66.8, 59.2, 59.1, 54.9 (q, J_{C-F} = 29 Hz), 52.0, 39.2, 36.4, 32.0, 31.8, 29.6, 29.4, 29.2, 25.7, 25.3, 22.6, 14.0 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3338, 2956, 2927, 2856, 1671, 1467, 1338, 1279, 1172, 1137, 1091, 1018. 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)-1,4-dithia-8-azaspiro-[5.4]decane (34):** By starting from ketal **33** (378 mg, 1.1 mmol) in dichloromethane (12 mL), ethanedithiol (450 μL, 5.4 mmol), and $BF_3{\cdot}Et_2O$ (700 μL, 5.4 mmol), as described in the General Procedure for dithioketalization, dithiolane **34** (238 mg, 60%) was obtained as a yellow oil after purification by column chromatography (ethyl acetate/cyclohexane, 1:19). ^{1}H NMR ($CDCl_3$): δ = 3.48–3.31 (m, 1 H), 3.33 (br. s, 4 H), 2.79–2.73 (m, 1 H), 2.25 (dt, J = 13 and 2.5 Hz, 1 H), 2.13 (dt, J = 13 and 2.5 Hz, 1 H), 1.96 (t, J = 12 Hz, 1 H), 1.72 (t, J = 12 Hz, 1 H), 1.48–1.23 (m, 17 H), 0.90 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.4 (q, J_{C-F} = 279 Hz), 65.2, 57.5 (q, J_{C-F} = 29 Hz), 55.7, 47.4, 41.5, 39.2, 38.0, 36.5, 31.8, 29.6, 29.5, 29.3, 25.6, 22.6, 14.1 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3339, 2926, 2854, 1466, 1397, 1277, 1172, 1142 cm^{-1}. EI-MS (70 eV): m/z = 369 $[M]^+$ (2), 308 (30), 276 (70), *242* (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.

(±)-(2*R,6*R**)-7-Nonyl-2-(trifluoromethyl)piperidine·HCl (Trifluoroisosolenopsin) (21·HCl):** By starting from thioketal **34** (200 mg, 0.5 mmol) in absolute ethanol (20 mL), and W2 Raney nickel (ca. 2.0 g), as described in the General Procedure, trifluoroisosolenopsine HCl salt **21·HCl** (157 mg, 92%) was obtained without purification as a white solid. M.p. 165–166 °C (dec.); ^{1}H NMR (CD_3OD): δ = 5.19–5.10 (m, 1 H), 4.27–4.20 (m, 1 H), 3.18–3.07 (m, 2 H), 3.04–2.98 (m, 1 H), 2.87–2.78 (m, 1 H), 2.74–2.54 (m, 3 H), 2.49–2.22 (m, 16 H), 1.87 (t, 3 H, J = 7 Hz) ppm. ^{13}C NMR (CD_3OD): δ = 124.6 (q, J_{C-F} = 280 Hz), 60.5, 58.6 (q, J_{C-F} = 32 Hz), 34.0, 33.0, 30.6, 30, 30.4, 28.4, 26.3, 23.7, 23.2, 23.1, 22.6, 14.5 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3420, 2023, 1468, 1270, 1190, 1135 cm^{-1}. EI-MS (70 eV, 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.

(±)-(8*R,10*S**)-10-(Prop-1-enyl)-8-(trifluoromethyl)-9-(trifluoromethylcarbonyl)-1,5-dioxa-9-azaspiro[5.5]undecane (35):** Triethylamine (4.2 mL, 30.1 mmol) and DMAP (139 mg, 1.1 mmol) were added to a stirred solution of compound **28** (1.0 g, 3.8 mmol) in dichloromethane (30 mL), and trifluoroacetic anhydride (2.1 mL, 15.2 mmol) was added at 0 °C to the resulting solution. The resulting mixture was stirred at room temperature for 30 min, and then concentrated in vacuo. The residue was separated by column chromatography (ethyl acetate/cyclohexane, 1:3) to afford compound **36** (1.27 g, 93%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers): δ = 5.90–5.36 (m, 2 H), 5.15–5.04 (m, 1 H), 4.82–4.55 (m, 1 H), 4.02–3.81 (m, 4 H), 2.71–2.42 (m, 2 H), 2.19–1.53 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.0, 129.9, 128.7, 124.5 (q, J_{C-F} = 282 Hz), 116.3 (q, J_{C-F} = 287 Hz), 94.9, 60.0, 59.8, 52.9, 51.0 (q, J_{C-F} = 34 Hz), 36.1, 27.5, 24.9, 17.5 ppm. IR (neat) $\tilde{\nu}_{max}$ = 2974, 2872, 1705, 1433, 1360, 1287, 1254, 1212, 1182, 1150, 1119, 1016, 964, 958 cm^{-1}. HR-ESI-MS calculated for $C_{14}H_{17}F_6NNaO_3$ $[M+Na]^+$: 384.1010; found 384.1017.

(±)-(2*R,6*S**)-6-(Prop-1-enyl)-2-(trifluoromethyl)-1-(trifluoromethylcarbonyl)piperidin-4-one (36):** A solution of CAN (3.08 g, 5.6 mmol) in H_2O (10 mL) was added, at 70 °C, in one portion, to a stirred solution of ketal **36** (815 mg, 2.2 mmol) in CH_3CN (5 mL). The resulting mixture was stirred for 30 min. The reaction mixture was then allowed to cool to room temperature and poured into H_2O (75 mL) before extraction with dichloromethane (3 × 75 mL). The combined organic extracts were dried and filtered, and the solvents were evaporated. The residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:3) to afford compound **36** (513 mg, 75%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers): δ = 8.80–5.07 (m, 4 H), 2.96–2.71 (m, 4 H), 1.72 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 158.0, 131.0, 128.2, 124.0 (q, J_{C-F} = 284 Hz), 116.1 (q, J_{C-F} = 287 Hz), 54.3 (m), 42.5, 36.4, 17.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3042, 2977, 2926, 2862, 1732, 1708, 1433, 1384, 1346, 1297, 1275, 1210, 1182, 1148, 1128, 1006, 972, 941, 760, 694 cm^{-1}. 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-(Prop-1-enyl)-2-(trifluoromethyl)piperidin-4-ol (37):** Sodium borohydride (74 mg, 1.97 mmol) was added to a cooled (–30 °C), stirred solution of piperidone **37** (298 mg, 0.98 mmol) in methanol (20 mL). The resulting mixture was stirred for 1 h before addition of saturated aqueous NH_4Cl (8 mL). After the mixture had been heated to room temperature, the methanol was removed in vacuo and the residue was then extracted with dichloromethane (5 × 20 mL). The combined organic extracts were dried and filtered. Evaporation of the solvent, followed by column chromatography (ethyl acetate/cyclohexane, 1:3) afforded piperidinol **37** (132 mg, 64%) as a white solid. M.p. 77–80 °C. ^{1}H NMR ($CDCl_3$): δ = 5.66 (dq, J = 15 and 6.5 Hz, 1 H), 5.77 (ddq, J = 15, 7 and 1.5 Hz, 1 H), 3.75 (m, 1 H), 3.23 (m, 1 H), 3.14 (m, 1 H), 2.14 (m, 1 H), 1.99 (m, 1 H), 1.69 (d, J = 6.5 Hz, 3 H), 1.58, (br. s, 2 H), 1.37 (q, J = 11.5 Hz, 1 H), 1.24 (q, J = 11.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 132.3, 127.1, 125.2 (q, J_{C-F} = 279 Hz), 67.7, 56.5, 56.4 (q, J_{C-F} = 29 Hz), 41.0, 38.4, 17.6 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3296, 1677, 1268, 1185, 1153, 1089, 1046, 879 cm^{-1}. EI-MS (70 eV): m/z = 209 $[M]^+$ (25), *194* (100), 176 (50), 164 (40), 150 (60), 96 (570), 68 (80), 41 (50). HR-ESI-MS calculated for $C_9H_{15}F_3NO$ $[M+H]^+$: 210.1106; found 210.1112.

(±)-(2*R,4*S**,6*R**)-6-Propyl-2-(trifluoromethyl)piperidin-4-ol (23):** By starting from compound **37** (82 mg, 0.39 mmol) in anhydrous methanol (10 mL), ammonium formate (123 mg, 1.95 mmol), and $Pd(OH)_2$/C (20%, 30 mg), as described in the procedure employed for the synthesis of compound **33**, piperidinol **23** (70 mg, 85%) was obtained as a white solid without need for purification. M.p. 47–49 °C. ^{1}H NMR ($CDCl_3$): δ = 3.70 (tt, J = 11 and 4.5 Hz, 1 H), 3.18 (qdd, J = 10, 7 and 2.5 Hz, 1 H), 2.60 (m, 1 H), 2.14 (dQ, J = 12 and 2 Hz, 1 H), 2.00 (dQ, J = 12 and 2 Hz, 1 H), 1.66 (br. s, 2 H), 1.50–1.31 (m, 5 H), 1.06 (q, J = 11.5 Hz, 1 H), 0.92 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.3 (q, J_{C-F} = 278 Hz), 68.0, 56.7 (q, J_{C-F} = 29 Hz), 54.1, 41.1, 38.6, 34.1, 18.9, 14.0 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3264, 2956, 1267, 1150, 1111, 1086 1046, 884 cm^{-1}. EI-MS (70 eV): m/z = 211 $[M]^+$ (1), *168* (100), 150 (50), 124 (40), 98 (10): HR-ESI-MS calculated for $C_9H_{17}F_3NO$ $[M+H]^+$: 212.1262; found 212.1279.

(±)-(8*R,10*S**)-10-(Nona-1,3-dienyl)-8-(trifluoromethyl)-9-(trifluoromethylcarbonyl)-1,5-dioxa-9-azaspiro[5.5]undecane (40):** By starting from ketal **29** (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), as described in the procedure employed for the synthesis of compound **35**, compound **40** (447 mg, 70%) was obtained after purification by column chromatography (ethyl acetate/cyclohexane, 1:19) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, very complex spectrum due to the coexistence of amide rotamers): δ = 6.38–4.51 (m, 6 H), 3.99–3.83 (m, 4 H), 2.72–2.45 (m, 2 H), 2.20–1.57 (m, 6 H), 1.42–1.24

(m, 6 H), 0.88 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.0, 136.3, 133.6, 131.8, 127.7, 123.5 (q, J_{C-F} = 286 Hz), 115.3 (q, J_{C-F} = 286 Hz), 93.9, 59.1, 58.9, 52.0, 50.5 (q, J_{C-F} = 34.0 Hz), 35.4, 31.6, 30.4, 27.8, 26.5, 24.0, 21.5, 13.0 ppm. IR (neat) $\tilde{\nu}_{max}$ = 2960, 2930, 2861, 1706, 1431, 1213, 1183, 1148, 990 cm^{-1}. EI-MS (70 eV): *m/z* = 443 $[M]^+$ (15), 181 (100), 166 (25), *123* (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-(Nona-1,3-dienyl)-2-(trifluoromethyl)-1-(trifluoromethylcarbonyl)piperidin-4-one (41):** HCl (4 M, 6 mL) was added to a stirred solution of ketal **40** (593 mg, 1.3 mmol) in acetone (20 mL). The resulting mixture was stirred at room temperature for 4 days, and was then quenched with an excess of NaOH (4 M). Acetone was eliminated under reduced pressure and the residue was diluted with diethyl ether (50 mL). The two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried, filtered, and concentrated. The residue, after purification by column chromatography (ethyl acetate/cyclohexane, 1:9), afforded compound **41** (335 mg, 65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, complex spectrum due to the coexistence of amide rotamers): δ = 6.29–5.06 (m, 4 H), 2.88–2.72 (m, 4 H), 2.18–2.05 (m, 2 H), 1.59 (br. s, 1 H), 1.42–1.23 (m, 7 H), 0.88 (t, J = 8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 157.7, 138.6, 134.7, 128.4, 125.5, 122.7 (q, J_{C-F} = 215.5 Hz), 115.2 (q, J_{C-F} = 287 Hz), 54.4, 54.1, 42.5, 32.5, 31.3, 28.6, 22.4, 13.9 ppm. IR (neat) $\tilde{\nu}_{max}$ = 3026, 2960, 2931, 2861, 1732, 1709, 1430, 1274, 1227, 1178, 1149, 993 cm^{-1}. EI-MS (70 eV): *m/z* = 385 $[M]^+$ (30), 215 (30), 202 (30), 175 (30), *123* (100), 91 (70), 79 (70), 55 (30), 41 (40).

(±)-(2*R,4*S**,6*S**)-6-(Nona-1,3-dienyl)-2-(trifluoromethyl)piperidin-4-ol (42):** By starting from compound **41** (150 mg, 0.39 mmol) in anhydrous methanol (10 mL) and sodium borohydride (29 mg, 0.78 mmol), as described in the procedure employed for the synthesis of compound **37**, compound **42** (84 mg, 74%) was obtained after purification by column chromatography (ethyl acetate/cyclohexane, 1:4) as a white solid. M.p. 93–95 °C. ^{1}H NMR ($CDCl_3$): δ = 6.17 (dd, J = 15 and 10 Hz, 1 H), 6.00 (dd, J = 15 and 10 Hz, 1 H), 5.68 (m, 1 H), 5.55 (dd, J = 15 and 7 Hz, 1 H), 3.74 (m, 1 H), 3.23 (m, 2 H), 1.95–2.20 (m, 4 H), 1.60 (br. s, 3 H), 1.43–1.21 (m, 8 H), 0.88 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.9, 131.5, 131.4, 129.2, 125.2 (q, J_{C-F} = 279 Hz), 67.9, 56.4 (q, J_{C-F} = 29 Hz), 56.3, 41.1, 33.6, 32.6, 31.4, 28.9, 22.5, 14.0 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3263, 1658, 1266, 1190, 1157, 1086, 988, 886 cm^{-1}. EI-MS (70 eV): *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.

(±)-(2*R,4*S**,6*R**)-6-Nonyl-2-(trifluoromethyl)piperidin-4-ol (Trifluoro-241 D) (22):** By starting from compound **42** (65 mg, 0.22 mmol) in anhydrous methanol (10 mL), ammonium formate (70 mg, 1.1 mmol), and $Pd(OH)_2$/C (20%, 20 mg), as described in the procedure employed for the synthesis of compound **23**, compound **22** (61 mg, 93%) was obtained as a white solid without need for purification. M.p. 78.4–80.9 °C. ^{1}H NMR ($CDCl_3$): δ = 3.71 (m, 1 H), 3.18 (m, 1 H), 2.58 (m, 1 H), 2.14 (dQ, J = 12 and 2.5 Hz, 1 H), 2.0 (dQ, J = 12.5 and 2 Hz, 1 H), 1.56 (br. s, 2 H), 1.49–1.26 (m, 17 H), 1.07 (q, J = 11.5 Hz, 1 H), 0.88 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 125.3 (q, J_{C-F} = 279 Hz), 68.2, 56.7 (q, J_{C-F} = 29 Hz), 54.4, 41.2, 36.5, 34.2, 31.9, 29.6, 29.5, 29.3, 25.8, 22.7, 14.1 ppm. IR (KBr) $\tilde{\nu}_{max}$ = 3269, 2964, 1264, 1191, 1146, 1089, 1043 cm^{-1}. EI-MS (70 eV): *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.

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