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Morpholinosulfur Trifluoride (Morph-DAST)-Mediated Rearrangement in the Fluorination of Cyclic α,α-Dialkoxy Ketones toward 1,2-Dialkoxy-1,2-difluorinated Compounds

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Abstract: The deoxofluorination of cyclic α,α-dialkoxy ketones with morpholinosulfur trifluoride (Morph-DAST) resulted in 1,2-dialkoxy-1,2-difluorinated carbo- and heterocyclic compounds. The reaction proceeds *via* a 1,2-alkoxy migration leading to mixtures of *cis*- and *trans*-isomers.

Keywords: deoxofluorination; fluorine; ketones; piperidines; rearrangement reactions

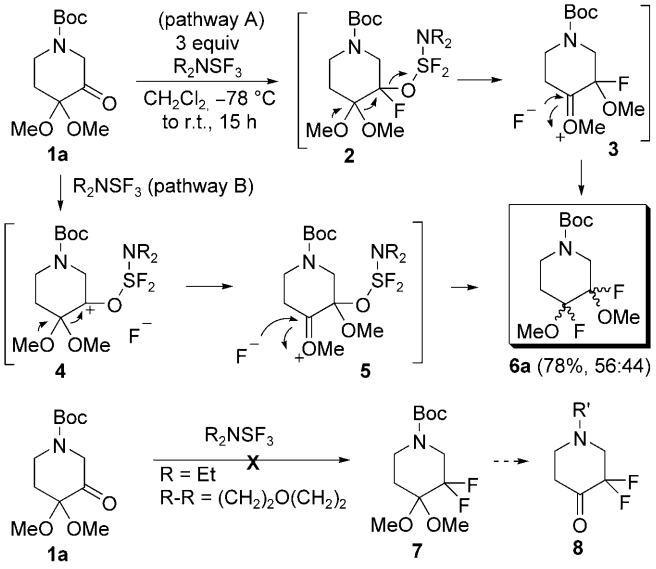
The introduction of fluorine into organic compounds is one of the most simple structural modifications in order to influence their bioactivity. The unique physical, chemical and biological properties of fluorine as a substituent in organic compounds and the success of fluorinated compounds in medicinal chemistry have dramatically intensified the interest and the research in organofluorine chemistry.[1] Especially fluorinated piperidines have become increasingly popular as building blocks toward bioactive compounds. Many fluorinated azasugars have been prepared for biochemical investigations.[2] Recently, we introduced new entries toward valuable 2-substituted 3,3-difluoropiperidines[3] and 3-aminomethyl-3-fluoropiperidines[4] using *N*-fluorodibenzenesulfonimide (NFSI) as electrophilic fluorination reagent and we synthesized new 4-aminomethyl-4-fluoropiperidines *via* a bromofluorination strategy.[5] The commercially available deoxofluorination reagents diethylaminosulfur trifluoride (DAST), bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) and morpholinosulfur trifluoride (Morph-DAST) are powerful nucleophilic fluorination reagents and are frequently used for the conversion of alcohols to alkyl fluorides and of ketones to *gem*-difluorides. In earlier research the use of Morph-DAST was preferred as a result of its higher thermal stability and its better efficiency in the transformation of 3-alkoxy-4-piperidinones toward 3-alkoxy-4,4-difluoropiperidines.[6] In some cases, the use of deoxofluorination reagents can induce the formation of rearranged products. It has been reported that β-hydroxy-α-amino acid esters rearrange to α-fluoro-β-amino acid esters[7] and that 2-alkyl-2-amino alcohols rearrange to 2-alkyl-2-fluoro amines upon treatment with Deoxo-Fluor.[8] Other examples consist of the neighbouring group participation of the indole nucleus in the 3,4-migration of 4-indolyl-3-hydroxypiperidines,[9] the ring expansion of bicyclic epoxy alcohols toward fluorovinyl ethers,[10] the rearrangement of 2-azabicyclo[2.2.0]hexan-6-ols to 5-fluoro-2-azabicyclo-[2.1.1]hexanes[11] and the rearrangement of β-methoxy homoallyl alcohols to α,β-unsaturated aldehydes.[12] The DAST-mediated 1,2-migrations, 1,4-migrations and 1,6-migrations of the anomeric substituent of saccharides, with or without ring contraction, are of special importance in biological studies of deoxofluorinated analogues of carbohydrates.[13] In contrast to alcohols, rearrangements of ketones have been less investigated. Fluorination of the C-2 of aldopyranosid-2-uloses with DAST leads to *gem*-difluorination products or gives 2,5-anhydro-1,2-difluorofuranoses as a result of a ring contraction reaction with concomitant introduction of fluorine at C-

1 and C-2,[14] and does not lead to 2-alkoxy-1,2-difluorotetrahydropyrans *via* a 1,2-alkoxy migration as initially thought.[15] In contrast to the latter monoacetals of α-ketoaldehydes, the deoxofluorination of monoacetals of 1,2-diketones was not investigated before and it was decided to further investigate this reaction. The products formed through *gem*-difluorination should be easily hydrolyzed into α,α-difluorinated ketones. Recently, a convenient synthetic route toward 3,3-difluoro-4-piperidinone **8**, a compound with high potential in medicinal chemistry, starting from ethyl bromodifluoroacetate was developed.[16] Prior to developing this synthetic route, it was considered to evaluate the deoxofluorination of 4,4-dimethoxy-3-piperidinone **1a**.

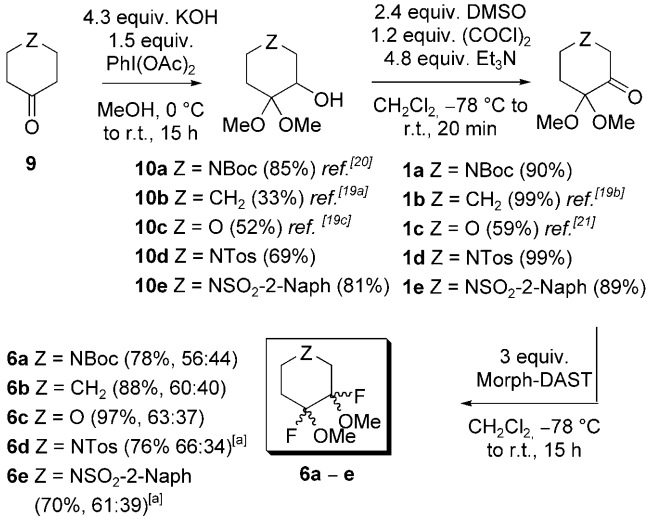
When 4,4-dimethoxy-3-piperidinone **1a** was treated with 3 equivalents of diethylaminosulfur trifluoride or morpholinosulfur trifluoride in dichloromethane at −78 °C, no geminal difluorination toward 3,3-difluoro-4,4-dimethoxypiperidine **7** was observed after 15 h at room temperature. Instead, the obtained product was identified as 3,4-difluoro-3,4-dimethoxypiperidine **6a** as a result of a 1,2-alkoxy migration (Scheme 1).

Gas chromatography-mass spectrometry (GC-MS) and LC-MS analyses of the crude mixture of **6a** revealed that all starting material was converted and that two compounds were formed having the same molecular weight. After studying the ^{13}C NMR spectrum, which does not show a triplet around 110 ppm of about 250 Hz, which is characteristic for a difluoromethylene group, but instead four double doublets with carbon-fluorine coupling constants of ~230 Hz over one bond ($^1J_{F,C}$) and ~35 Hz over two bonds ($^2J_{F,C}$), it was concluded that the obtained mixture contained the *cis*- and the *trans*-isomers of 3,4-difluoro-3,4-dimethoxypiperdine **6a**. The high value for the $^1J_{F,C}$ coupling constant clearly indicates fluoroalkoxy substitution for these two vicinal carbons.[17] The ^{19}F NMR spectrum of the mixture revealed eight signals, which were assigned to eight different fluorine atoms from four structures, namely the *cis*- and *trans*-piperidines **6a**, each with their two Boc-rotamers. Attempts to *N*-deprotect piperidine **6a** in order to avoid the Boc-rotamers and to confirm the structure failed and only gave rise to complex reaction mixtures. The use of Morph-DAST was preferred above DAST for its very clean conversion of 3-piperidinone **1a** into 3,4-difluoro-3,4-dimethoxypiperidine **6a**. Upon purification of 3,4-difluoro-3,4-dimethoxypiperidine **6a** *via* silica gel chromatography no decomposition of the product was observed, resulting in a good yield of 78%. However, the *cis*- and *trans*-isomers could not be separated *via* column chromatography. The mechanism of the reaction of α,α-dialkoxy ketones with deoxofluorination reagents is more complex as compared to the reaction with β,β-dialkoxy alcohols because it involves at least two reactions where different processes can compete. With respect to the obtained ~1:1 mixture of *cis*- and *trans*-**6a**, it cannot be concluded if the fluorine initially attacks the carbonyl group (pathway A), if the 1,2-MeO migration takes place in the first stage of the reaction (pathway B) or if a combination of both pathways occurs.

In order to learn more about the generality of this fluorination process, various 6-membered ring derivatives of 3,4-difluoro-3,4-dimethoxypiperidine **6a** were prepared (Scheme 2). The starting materials for fluorination, that is, α,α-dialkoxy ketones **1**, were easily



Scheme 1. Deoxofluorination of 1-Boc-4,4-dimethoxy-3-piperidinone **1a**.



Scheme 2. Synthesis of monocyclic 1,2-difluoro-1,2-dimethoxylated 6-membered rings.
[a] The *cis*- and *trans*-isomers of **6d** and **6e** were separated *via* silica gel chromatography.

obtained from the corresponding ketones **9**[18] *via* an α-hydroxylation, mediated by iodosobenzene diacetate under basic conditions in MeOH toward α-hydroxy ketals **10**,[19] followed by a clean Swern oxidation.[20] It should be noted that the crude α,α-dialkoxy ketones **1a–d** (purity >95%) were used in the next reaction step without further purification because compounds **1** are relatively unstable and decompose on silica gel.[21] In contrast, compound **1e** was successfully purified *via* recrystallization from diethyl ether. The reaction of 2,2-dimethoxycyclohexanone **1b** with Morph-DAST yielded a mixture of *cis*- and *trans*-1,2-difluoro-1,2-dimethoxycyclohexane **6b**, which immediately decomposed after silica gel chromatography. Consequently, the crude compound **6b** (92% purity) was used for spectral analysis and identification. It seems that the presence of a heteroatom at the α-position of dialkoxy ketones **1** stabilizes the fluorinated products **6**, probably due to the inductive effect of the heteroatom slowing down the expulsion of fluoride by methoxide. The same trend was observed in the clean deoxofluorination reaction of 4,4-dimethoxydihydro-2*H*-pyran-3(4*H*)-one **1c** yielding 97% of 3,4-difluoro-3,4-dimethoxytetrahydro-2*H*-pyran **6c** as a stable compound after silica gel chromatography. Also 4,4-dimethoxy-1-tosyl-3-piperidinone **1d** was successfully converted to 3,4-difluoro-3,4-dimethoxy-1-tosylpiperidine **6d** in 76% yield, occurring as a stable 66:34 mixture of isomers. In the case of this tosylated derivative **6d**, the major and the minor isomers were isolated in a pure form *via* silica gel chromatography. As all synthesized vicinal difluorinated derivatives **6a–d** occur as liquids, a final piperidine derivative was synthesized bearing a naphthalene-2-sulfonyl substituent at nitrogen to obtain crystalline derivatives. The mixture of *cis*- and *trans*-3,4-difluoro-3,4-dimethoxypiperidines **6e** was separated *via* silica gel chromatography and each isomer was recrystallized to obtain colourless crystals for the major isomer and white needles for the minor isomer.

Based on detailed 1D NMR spectral analysis, the configuration of the isolated major and minor isomers of **6d** and **6e** could not be assigned with absolute certitude.

Vicinal fluorine-fluorine coupling constants ($^3J_{F,F}$), for example, do not follow the Karplus equation and show different relationships with the dihedral angle depending on the substitution pattern of the compound.[22] However, 2D ^{1}H-^{1}H NOESY NMR and 2D ^{1}H-^{19}F HOESY NMR experiments allowed us to assign a 3,4-*trans* relationship between the two fluorine substituents of the major isomers of **6d** and **6e** (Figure 1). In these cases, NOE correlations were observed between the equatorial fluorine atom F-11 of the *trans*-isomers (major) and the hydrogen atoms H-2a, H-2b, CH_3O-10, CH_3O-13. The equatorial fluorine F-14 of the *trans*-isomers (major) of **6d**, **e** show interaction with the hydrogen atoms H-2b, H-5a, H-5b, CH_3O-10, CH_3O-13.

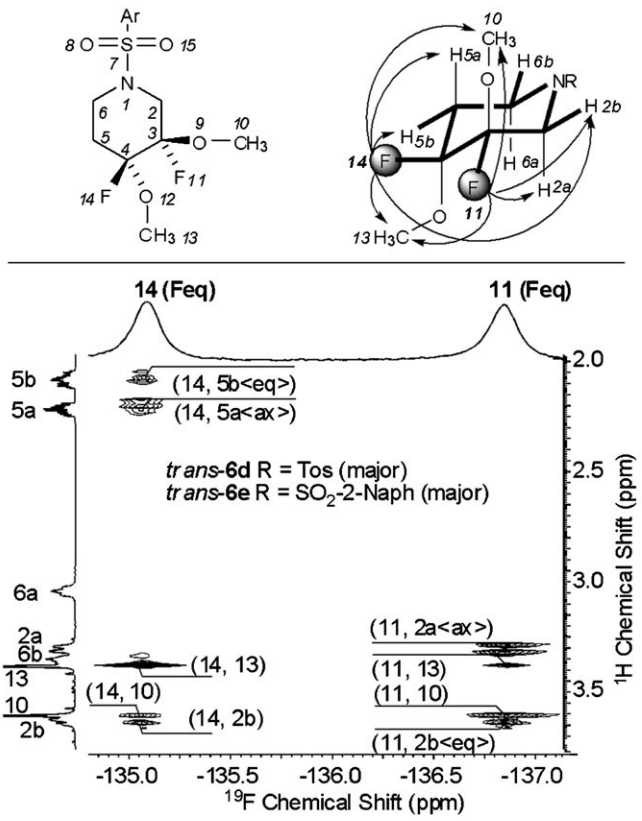


Figure 1. Assignment of the *trans*-configuration of the major isomers of **6d** and **6e**.

Furthermore, the 2D ^{1}H-^{1}H NOESY NMR and 2D ^{1}H-^{19}F HOESY NMR analysis of the isolated minor isomers of **6d** and **6e** proved that these minor isomers possess the *cis*-configuration (Figure 2). The observed NOE interactions of fluorine atom F-11 of the *cis*-isomers (minor) do not change compared to the interactions of fluorine atom F-11 of the *trans*-isomers (major), because both are in equatorial positions. In contrast, fluorine atom F-14 is now axial in the case of the *cis*-isomers (minor of **6d**, **e**) and shows interaction with the axial hydrogen atoms H-2a and H-6a and with H-5b, CH_3O-13. The axial fluorine atom F-14 of the *cis*-isomers (minor) does not couple anymore with H-5a, H-2b and CH_3O-10.

In order to study the stereoselectivity of the fluorination, spirocyclic starting materials **1f** and **1g** were synthesized from the corresponding β-hydroxy-dimethoxy acetals **10a** and **10d** by reaction with propane-1,3-diol and ethane-1,2-diol, respectively, followed by Swern oxidation (Scheme 3). When 9-Boc-7-oxo-1,5-dioxa-9-azaspiro[5.5]undecane **1f** was treated with Morph-DAST, a 67:33 mixture of *cis*- and *trans*- (or *trans*- and *cis*-) 3,4-dialkoxy-3,4-difluoropiperidine **6f** was obtained, which is a relatively small improvement

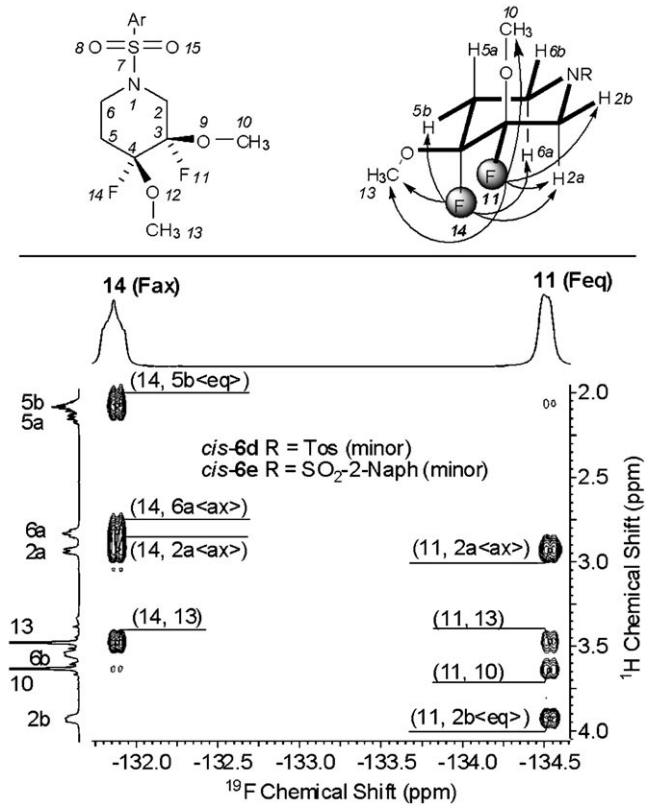
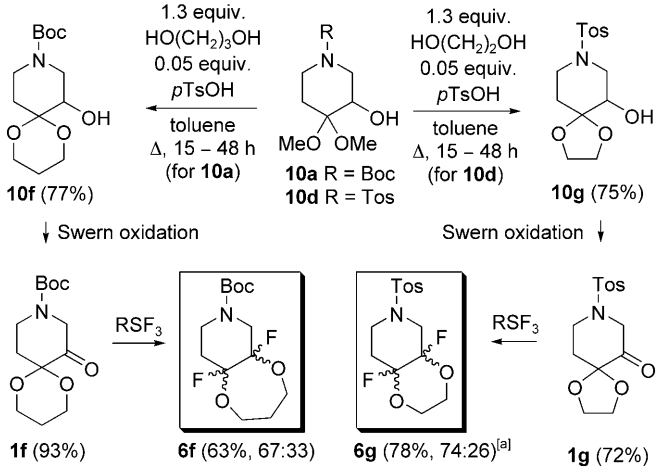
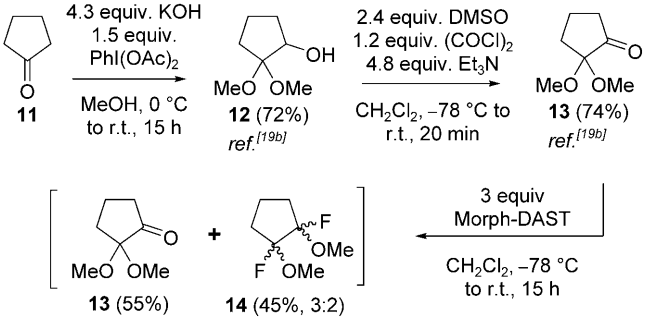


Figure 2. Assignment of the *cis*-configuration of the minor isomers of **6d** and **6e**.



Scheme 3. Synthesis of bicyclic 3,4-difluoropiperidines. [a] *trans*-**6g** (major isomer) and *cis*-**6g** (minor isomer) were separated *via* silica gel chromatography. RSF_3 = Morph-DAST.

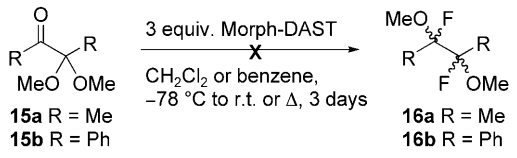
of the stereoselectivity compared to the reaction of the corresponding monocyclic 1-Boc-4,4-dimethoxy-3-piperidinone **1a** with Morph-DAST (56:44 mixture). The *cis*- and *trans*-isomers of compound **6f** could not be separated *via* silica gel chromatography. Reaction of the bicyclic derivative 8-tosyl-6-oxo-1,4-dioxa-8-azaspiro[4.5]decane **1g** with Morph-DAST resulted in a ring expansion of the 1,3-dioxolane toward difluorinated 1,4-dioxane **6g** as a 74:26 mixture of isomers, which is also a small improvement of the stereoselectivity compared to the fluorination of the monocyclic 1-tosylpiperidine **1d** (66:34 mixture). In analogy to the monocyclic compounds **6d** and **6e**, the 2D ^{1}H-^{1}H NOESY NMR and 2D ^{1}H-^{19}F HOESY NMR experiments indicated that the major isomer of the bicyclic 1,4-dioxane **6g** is the *trans* isomer and that the minor isomer possesses the *cis*-configuration.



Scheme 4. Deoxofluorination of 2,2-dimethoxycyclopentanone **13**.

In an attempt to extend the rearrangement methodology to 5-membered rings, 2,2-dimethoxycyclopentanone **13** was first synthesized from cyclopentanone **11** *via* hydroxy acetal **12** and subsequent oxidation. The obtained cyclopentanone **13** was then reacted with Morph-DAST under the same reaction conditions as described for the 6-membered rings (Scheme 4). The reaction proceeded sluggishly, and after 15 h, the reaction mixture contained 55% of starting material **13** and only 45% of 1,2-difluoro-1,2-dimethoxycyclopentane **14** in a 3:2 ratio of *cis*/*trans* isomers (determined by GC-MS analysis). The slower deoxofluorination of cyclopentanone **13** as compared cyclohexanone **6b** is most probably due to the increase in torsional strain when hybridization changes from sp^2 to sp^3 in the five-membered ring. This is in accordance with the quite general higher reactivity of cyclohexanones during carbonyl addition reactions. In addition, analogously to the unstable 1,2-difluoro-1,2-dimethoxycyclohexane **6b**, 1,2-difluoro-1,2-dimethoxycyclopentane **14** decomposed rapidly and could not be purified.

Finally the 1,2-migration reaction was evaluated on acyclic α,α-dimethoxy ketone derivatives (Scheme 5).



Scheme 5. Deoxofluorination of acyclic α,α-dimethoxy ketones **15**.

3,3-Dimethoxy-2-butanone **15a** and 2,2-dimethoxy-1,2-diphenylethanone **15b** were treated with Morph-DAST at room temperature or at reflux temperature in dichloromethane or benzene for various numbers of days, but in these cases, no fluorinated reaction products were obtained.

In conclusion, we have developed a new method for 1,2-difluorination of monoacetals of cyclic 1,2-diketones *via* a Morph-DAST-mediated 1,2-alkoxy migration reaction. The *cis*-and *trans*-1,2-dialkoxy-1,2-difluorinated products are obtained in good yields and are stable in the case of piperidines and tetrahydropyrans.

Experimental Section

General Procedure for the Deoxofluorination of α,α-Dialkoxy Ketones 1

In a 50-mL flask, 0.50 g (1.93 mmol, 1.0 equiv.) of *tert*-butyl 4,4-dimethoxy-3-oxopiperidine-1-carboxylate **1a** was dissolved in 25 mL of dry CH_2Cl_2. The solution was cooled to −78 °C under N_2 atmosphere and 1.01 g (5.79 mmol, 3.0 equiv., 0.7 mL) of Morph-DAST (morpholinosulfur trifluoride) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 15 h. The mixture was diluted with 20 mL of CH_2Cl_2 and was carefully quenched with 20 mL of aqueous saturated $NaHCO_3$ at 0 °C. The separated aqueous phase was extracted with CH_2Cl_2 (2×20 mL) and the combined organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the concentrate was purified by flash chromatography over silica gel (hexane/EtOAc 9:1, R_f=0.38) affording ***tert*-butyl 3,4-difluoro-3,4-dimethoxypiperidine-1-carboxylate 6a** (yield: 0.42 g, 1.51 mmol; 78%; *cis-trans* isomerism: major/minor 56:44 + each isomer consists of two Boc-rotamers). Colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.42 (9H, s, 3×CH_3), 1.74–2.10 (2H, m, CH_2), 3.11–3.37 (2H, m, NCH_2), 3.45, 3.48, 3.50 (2×MeO), 3.53–3.89 (2H, m, NCH_2); ^{19}F NMR ($CDCl_3$): δ=−130.6, −132.4, −132.7, −133.4, −137.0, −137.8, −138.4, −139.2 (2F, 8 × s, 2×CF); ^{13}C NMR ($CDCl_3$): δ=28.2 (3×CH_3), 29.5, 30.0, 30.4, 31.3 (4×d, J=27.7 Hz, 27.7 Hz, 27.7 Hz, 23.1 Hz, CH_2), 39.5, 40.5 (2×s, NCH_2CH_2), 43.9, 44.5, 45.6, 45.9 (4×d, J=45.0 Hz, 38.1 Hz, 35.8 Hz, 35.8 Hz, NCH_2CF), 50.4 (m, MeO), 51.3 (m, MeO); 80.5 (OC_q); 109.0 (ddm, J=231.3 Hz, 26.0 Hz, CF); 110.3 (ddm, J=230.8 Hz, 26.0 Hz, CF), 154.1, 154.2 (2×s, C=O); IR (ATR): ν=2977, 1697 (C=O), 1421, 1366, 1279, 1233, 1204, 1153, 1102, 1072, 1051, 936, 890, 822, 767, 718 cm^{-1}; GC-MS (EI): m/z (%)=281 (M^+, 5), 266 (M^+−Me, 1); 241 (M^+−2HF, 1), 222 (16), 210 (13), 206 (17), 190 (12), 186 (23), 176 (9), 161 (22), 146 (16), 131 (56), 118 (23), 104 (4), 93 (11), 89 (10), 76 (15), 57 (100), 42 (18); MS (ES^+): m/z (%)=182 (M−Boc$^+$+2H$^+$, 5), 186 (M−2HF−$(CH_3)_3C^+$+2H$^+$, 100), 206 (M−HF−$(CH_3)_3C^+$+H$^+$, 7), 300 (M−HF+K$^+$, 20).

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