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The Synthesis and Acid-base Properties of α-(Fluoromethyl)- and α-(Difluoromethyl)-substituted Cyclobutane Building Blocks

Abstract

Aim. To synthesize cyclobutane-derived amines and carboxylic acids bearing CH_2F or CHF_2 groups in the α position; to determine the regularities of the effect of fluoroalkyl substituents on the acid-base properties of the title compounds.

Results and discussion. Synthetic approaches to 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanamines, 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanecarboxylic acids have been developed. It has been found that the pK_a (pK_a(H)) values measured for the title compounds, as well as for their non-substituted and CF_3-substituted analogues, are consistent with the electron-withdrawing effect of the corresponding fluoroalkyl substituents.

Experimental part. The synthesis of the title compounds commenced from the known ethyl 1-(hydroxymethyl)cyclobutanecarboxylate or the product of its Swern oxidation (the corresponding aldehyde) and included fluorination, alkaline ester hydrolysis (for carboxylic acids), and modified Curtius rearrangement (for amines). The pK_a value was determined from the pre-equivalence point part of the titration curve using the standard acid-base titration.

Conclusions. A newly developed synthetic approach to 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanamines, 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanecarboxylic acids allows to obtain the title compounds in multigram quantities (up to 97 g). With a single exception, the acid-base properties of these products, as well as their parent non-substituted and CF_3-substituted analogues, change in a monotonous manner in accordance with inductive electronic effect of the fluorine atom(s).

Keywords: cyclobutane; fluorine; acidity/basicity; amine; carboxylic acid

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Синтез та кислотно-основні властивості α-(флуорометил)- та α-(дифлуорометил)заміщених циклобутанових будівельних блоків

Анотація

Мета. Синтезувати аміни та карбонові кислоти на основі циклобутану із групами CH_2F або CHF_2 в α-положенні; визначити закономірності впливу флуороалкільних замісників на кислотно-основні властивості цільових сполук.

Результати та їх обговорення. Було розроблено синтетичні підходи до 1-(флуорометил)- та 1-(дифлуорометил)циклобутанамінів, 1-(флуорометил)- та 1-(дифлуорометил)циклобутанкарбонових кислот. Було визначено, що виміряні показники pK_a (pK_a(H)) одержаних сполук, а також їх незаміщених та CF_3-заміщених аналогів узгоджуються з електроноакцепторним ефектом відповідних фтороалкільних замісників.

Експериментальна частина. Синтез цільових сполук виходив з відомого етил-1-(гідроксиметил)циклобутанкарбоксилату або продукту його окиснення за Сверном (відповідного альдегіду) та передбачав флуорування, лужний гідроліз естеру (для карбонових кислот) та модифіковане перегрупування Курціуса (для амінів). Показники pK_a було визначено із частини кривої титрування до точки еквівалентності шляхом стандартного кислотно-основного титрування.

Висновки. Новий розроблений синтетичний підхід до 1-(флуорометил)- та 1-(дифлуорометил)циклобутанамінів, 1-(флуорометил)- та 1-(дифлуорометил)циклобутанкарбонових кислот дозволяє одержувати цільові сполуки в багатограмових кількостях (аж до 97 г). За єдиним винятком – кислотно-основні властивості цих продуктів, а також відповідних родоначальних незаміщених та CF_3-заміщених аналогів змінюються монотонним чином згідно з індуктивним електронним ефектом атома(ів) фтору.

Ключові слова: циклобутан; флуор; кислотність/основність; амін; карбонова кислота

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■ Introduction

Introducing fluorinated substituents into the molecules of interest is a well-recognized design approach in modern drug discovery, and it is supported by numerous recent success stories [1–5]. Fluorine atoms or fluoroalkyl groups can improve the compound potency, physicochemical properties relevant to medicinal chemistry, or the metabolic stability. On the other hand, cyclobutane derivatives have become increasingly popular in drug discovery [6, 7] as small sp^3-rich three-dimensional structural motifs fully compliant with recent trends in this area [8]. Therefore, it is not surprising that functionalized cyclobutanes containing fluoroalkyl substituents have become very promising building blocks that have already confirmed their value for medicinal chemistry. For example, they were used in the discovery of cannabinoid receptor type 2 (CB_2) antagonists [9], FMS-like tyrosine kinase 3 (FLT3) inhibitors [10], or interleukin-1 receptor-associated kinase 4 (IRAK-4) inhibitors [11] (Figure 1).

Meanwhile, the simplest fluoroalkyl-substituted cyclobutane-derived amines and carboxylic acids have been insufficiently represented in the literature until recently. The corresponding α-, β-, and γ-CF_3-substituted building blocks have been studied most thoroughly (Figure 2) [12–17]. Among the CH_2F- and CHF_2-substituted analogues,

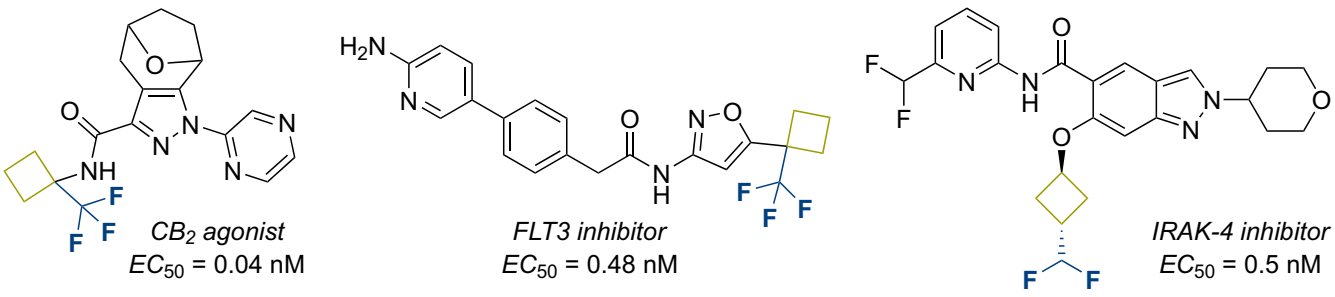

Figure 1. Representatives of MedChem relevant molecules with the α-fluoroalkyl-substituted cyclobutane moiety

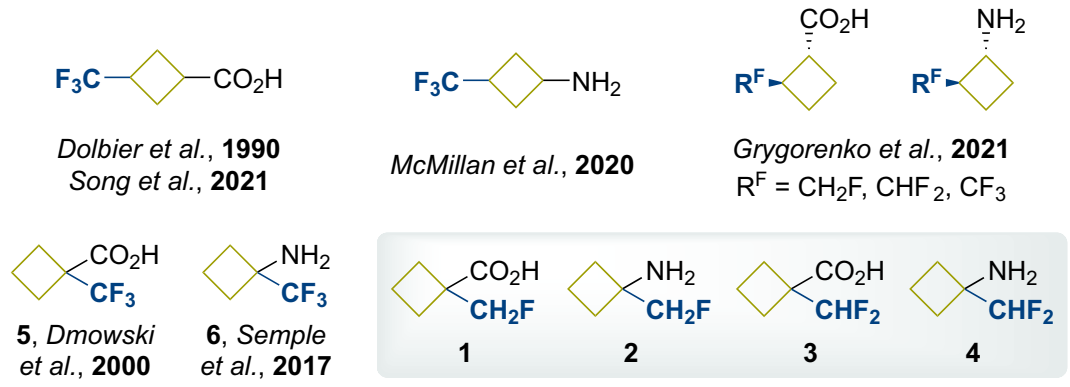

Figure 2. Status quo for fluoroalkylcyclobutanes

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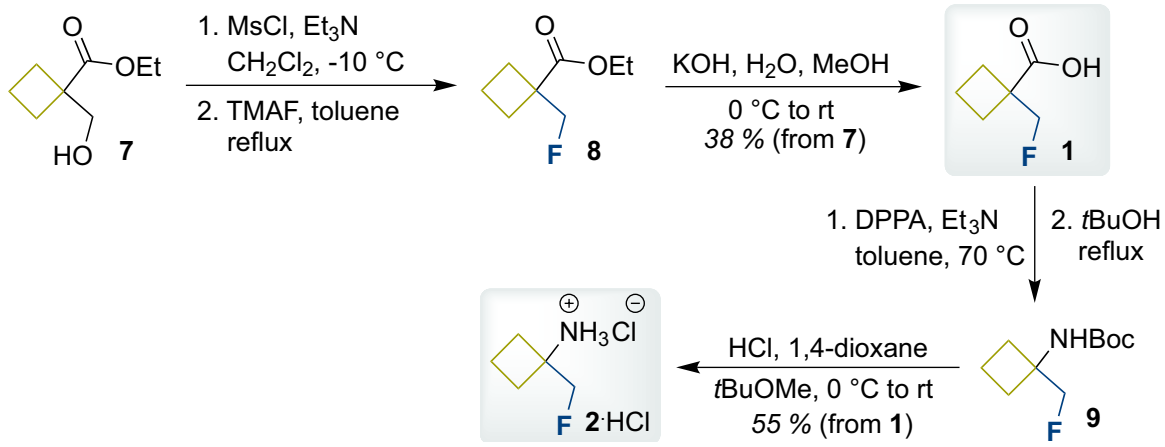
β-substituted derivatives were described by our group recently [16]. On the contrary, cyclobutane-derived amines and carboxylic acids bearing CH_2F or CHF_2 groups in the α position (compounds **1**–**4**) are unknown in the literature to date.

In this work, we were focused on the development of an efficient approach to the synthesis of compounds **1**–**4** allowing for their preparation on a multigram scale. In addition to that, acid-base properties of the products synthesized, as well as their CF_3-substituted analogues **5** and **6** were evaluated and compared to the parent non-substituted compounds to determine the effects of CH_2F, CHF_2, and CF_3 groups in the series studied.

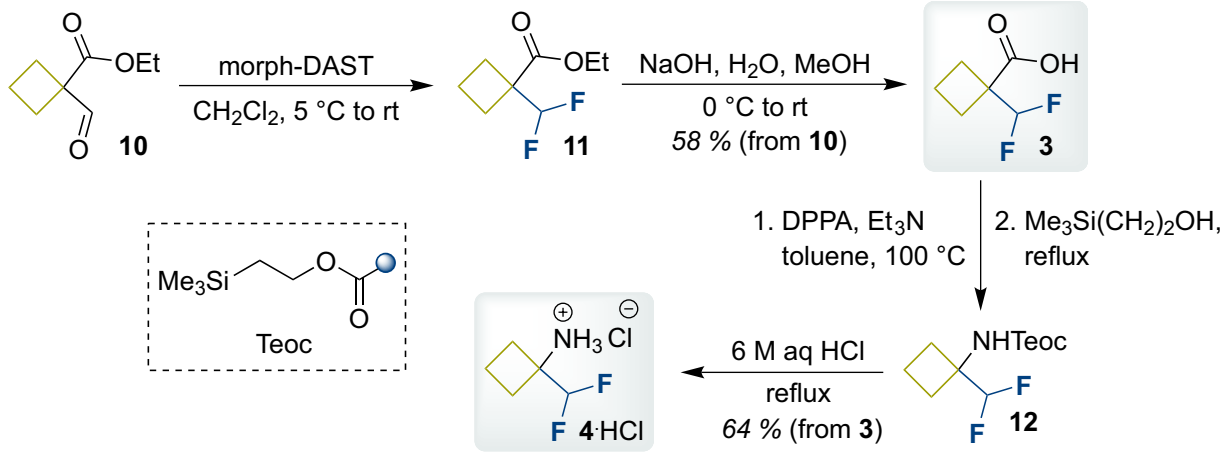
Results and discussion

The synthetic part of our work commenced from hydroxy ester **7** that was prepared on a 100-g scale starting from ethyl cyclobutanecarboxylate using the method reported [18]. To obtain the CH_2F-substituted series, compound **7** was mesylated and then subjected to the reaction with tetramethylammonium fluoride (TMAF) in refluxing toluene to give an fluoroorganic intermediate **8** (Scheme 1). Compound **8** was not isolated in a pure form, but subjected to the next step, namely the alkaline hydrolysis, to provide target carboxylic acid **1** (38% yield from **7**). The reaction of compound **1** with diphenyl phosphoryl azide (DPPA) in the presence of triethylamine and then with *tert*-butanol (the modified Curtius reaction protocol) gave carbamate **9** that was immediately subjected to acid-promoted deprotection resulting in amine **2** in the form of hydrochloride (55% yield from **1**).

The synthesis of CHF_2-substituted analogues included a similar reaction sequence commencing from aldehyde **10** – a product of the Swern oxidation of compound **7** according to the reported procedure [18]. In particular, deoxoflurionation of compound **10** with morph-DAST in CH_2Cl_2 gave intermediate ester **11** that was subjected to alkaline hydrolysis providing carboxylic acid **3** (58% yield from **10**) (Scheme 2). Surprisingly, the modified Curtius rearrangement protocol described above did not work well with compound **3** when



Scheme 1. Synthetic approach to α-(fluoromethyl)cyclobutanecarboxylic acid and α-(fluoromethyl)cyclobutaneamine



Scheme 2. S ynthetic approach to α-(difluoromethyl)cyclobutanecarboxylic acid and α-(difluoromethyl)cyclobutaneamine

Table 1. The pK_a (pK_a(H)) values of compounds **1**–**6** (21 °C)

Compound	R^F	pK_a (pK_a(H))	ΔpK_a [a]
1	CH_2F	3.66	0.84
3	CHF_2	3.08	1.42 / 0.71
5	CF_3	2.90	1.60 / 0.53
c-C_4H_7COOH	H	4.50 [19]	–
2×HCl	CH_2F	8.10	1.76
4×HCl	CHF_2	6.62	3.24 / 1.62
6×HCl	CF_3	5.00	4.86 / 1.62
c-$C_4H_7NH_2$	H	9.86 [19]	–

Note: [a] Compared to the parent non-fluorinated compound; the second number is per one fluorine atom

tert-butanol was used as the reagent for the intermediate isocyanate quenching, possibly due to the steric effects. Meanwhile, Teoc-protected derivative **12** (Teoc – 2-(trimethylsilyl)ethoxycarbonyl) was formed efficiently when *tert*-butanol was replaced with 2-(trimethylsilyl)ethanol. After acid-promoted deprotection, amine **4** was obtained as hydrochloride in 64% yield (from **3**).

The pK_a values of carboxylic acids **1**, **3**, and **5**, as well as the pK_a(H) values of amines **2**, **4**, and **6** were determined by the acid-base titration according to the previously reported protocol [19]. It was found that, generally, the pK_a values followed rules-of-thumb reported previously for the analogous acyclic series ($\Delta pK_a \approx 1.7$ and 0.7 per each fluorine atom in the positions β and γ to the (de)protonation site, respectively) [20] (Table 1). These results confirm that the inductive effect of the fluorine atoms is the main factor governing acidic/basic properties within the series studied. The only exception was compound **5** that was somewhat less acidic than might be expected (Figure 3); perhaps, some intramolecular interactions (e.g., H···F or F···C=O) might be responsible for this behavior.

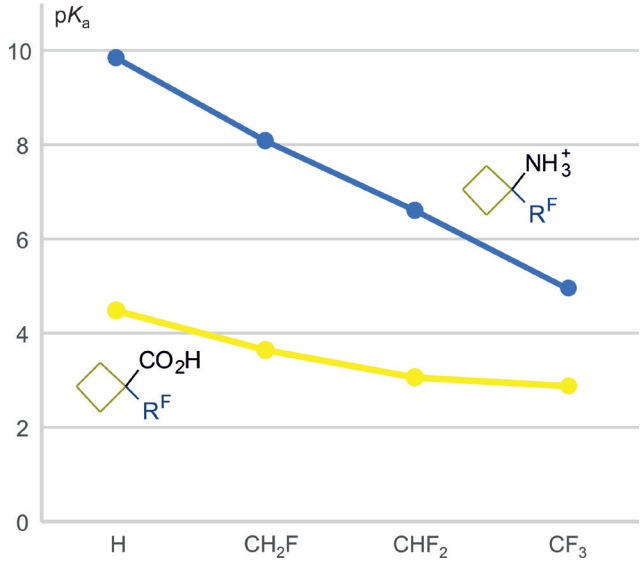


Figure 3. Change in the pK_a (pK_a(H)) values of compounds **1**–**6**

■ Conclusions

A newly developed synthetic approach to 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanamines, 1-(fluoromethyl)- and 1-(difluoromethyl)cyclobutanecarboxylic acids allows to obtain the title compounds in multigram quantities (up to 97 g). The acid-base properties of these products, as well as their parent non-substituted and CF_3-substituted analogues, change in a monotonous manner in accordance with inductive electronic effect of the fluorine atom(s). In particular, the ΔpK_a values were *ca.* 0.7 and 1.7 units per single fluorine atom for carboxylic acids and amines, respectively. The only exception was 1-(trifluoromethyl)cyclobutanecarboxylic acid that was somewhat less acidic than might be expected; perhaps, some intramolecular interactions might be responsible for this behavior.

■ Experimental part

The solvents were purified according to the standard procedures [21]. All starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on a MPA100 OptiMelt automated melting point system. ^1H, $^{13}C\{H\}$ and $^{19}F\{H\}$ NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, and 126 MHz for $^{13}C\{H\}$ NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{H\}$ NMR, and 376 MHz for $^{19}F\{H\}$ NMR). NMR chemical shifts were reported in ppm (δ scale) upfield from TMS as an internal standard and were referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and $^{13}C\{^1H\}$ in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and $^{13}C\{^1H\}$ in DMSO-d_6, 4.79 for ^1H in D_2O. Coupling constants (*J*) were given in Hz. Spectra were reported as follows: chemical shift (δ, ppm), integration, multiplicity, and coupling constants (Hz).

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Table 2. Yields, melting points, HRMS data for compounds **1**–**4** synthesized

Compound	Yield, %	M. p., °C	HRMS
1	38 (from **7**)	liquid	Calculated for $[C_6H_9FO_2–H]^-$ 131.0508. Found 131.0509
2×HCl	58 (from **1**)	178–181 (dec.)	Calculated for $[C_5H_{10}FN+H]^+$ 104.0876. Found 104.0871
3	58 (from **10**)	liquid	Calculated for $[C_6H_8F_2O_2–H]^-$ 149.0414. Found 149.0412
4×HCl	64 (from **3**)	188–192 (dec.)	Calculated for $[C_5H_9F_2N+H]^+$ 122.0781. Found 122.0776

Table 3. ^{1}H NMR spectra data for compounds **1**–**4** synthesized

Compound	Solvent	^{1}H NMR (400 MHz), δ, ppm
1	$CDCl_3$	1.95–2.22 (4H, m); 2.52 (2H, dd, *J* = 8.8, 7.8 Hz); 4.66 (2H, d, *J* = 47.2 Hz); 11.04 (1H, s)
2×HCl[a]	DMSO-d_6	1.78–1.94 (2H, m); 1.94–2.09 (2H, m); 2.27–2.36 (2H, m); 4.66 (2H, d, *J* = 47.2 Hz); 8.81 (3H, s)
3	$CDCl_3$	1.96–2.21 (2H, m); 2.36–2.65 (4H, m); 6.11 (1H, t, *J* = 56.5 Hz); 10.66 (1H, br. s)
4×HCl	DMSO-d_6	1.76–1.93 (1H, m); 1.91–2.07 (1H, m); 2.19–2.32 (2H, m); 2.32–2.46 (2H, m); 6.43 (1H, t, *J* = 54.6 Hz); 9.15 (3H, s)

Note: [a] At 500 MHz

Table 4. ^{13}C NMR spectra data for compounds **1**–**4** synthesized

Compound	Solvent	$^{13}C\{^1H\}$ NMR (126 MHz), δ, ppm
1[a]	$CDCl_3$	15.6; 26.0 (d, *J* = 6.4 Hz); 47.2 (d, *J* = 19.6 Hz); 85.3 (d, *J* = 173 Hz); 180.9 (d, *J* = 4.1 Hz)
2×HCl	DMSO-d_6	14.0; 27.5 (d, *J* = 6.3 Hz); 55.4 (d, *J* = 18.3 Hz); 84.8 (d, *J* = 171 Hz)
3	$CDCl_3$	15.2; 23.4 (t, *J* = 4.5 Hz); 49.3 (t, *J* = 23.4 Hz); 115.0 (t, *J* = 242 Hz); 178.2
4×HCl	DMSO-d_6	13.8; 25.8 (t, *J* = 3.8 Hz); 56.0 (t, *J* = 22.8 Hz); 115.2 (t, *J* = 244 Hz)

Note: [a] At 151 MHz

High-resolution mass spectra were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

For compounds **1**–**4** synthesized, the yields, melting points, data of high-resolution mass spectra (HRMS) (Table 2), ^{1}H NMR spectra (Table 3), ^{13}C NMR spectra (Table 4), and ^{19}F NMR spectra (Table 5) were given in a tabular format.

1-(Fluoromethyl)cyclobutanecarboxylic acid (1)

To a pre-cooled (–15 °C) solution of compound **7** [18] (120 g, 0.76 mol) and Et_3N (125 mL, 0.90 mol) in CH_2Cl_2 (1000 mL), MsCl (65.8 mL, 0.85 mol) was added in a dropwise manner while keeping the internal temperature below –10 °C. After additional stirring for 30 min, the thick suspension obtained was washed with ice-cold water (3×150 mL), the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a crude mesylate (*ca.* 185 g), which was immediately used in the next step without purification.

The amount of the mesylate obtained and freshly dried TMAF (119 g, 1.28 mol) were mixed in toluene (900 mL), and the resulting mixture was stirred at reflux overnight. The progress of the reaction was monitored by ^{1}H NMR; in case of incomplete conversion an additional portion of TMAF was added. After the reaction completion, the resulting mixture was cooled to room temperature, diluted with hexanes (700 mL), washed with ice-cold water (3×200 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give a crude compound **8** (*ca.* 110 g).

Table 5. ^{19}F NMR spectra data for compounds **1**–**4** synthesized

Compound	Solvent	$^{19}F\{^1H\}$ NMR (376 MHz), δ, ppm
1	$CDCl_3$	–223.5
2×HCl	DMSO-d_6	–226.9
3	$CDCl_3$	–129.5
4×HCl	DMSO-d_6	–133.0

The amount of compound **8** obtained was dissolved in MeOH (800 mL), and the solution was cooled to 0 °C on an ice-water bath. An aqueous solution of KOH (47.6 mL, 0.50 M, 0.85 mol) was added while keeping the internal temperature below 5 °C. The resulting turbid solution was stirred for 2 h, and most of the organic solvent was evaporated under reduced pressure. The residue was washed with CH_2Cl_2 (2×100 mL), *t*BuOMe (2×100 mL), diluted with a fresh portion of CH_2Cl_2 (300 mL), and acidified with 10% aq $NaHSO_4$ (1100 mL). The aqueous layer was additionally

washed with CH_2Cl_2 (2×300 mL) and discarded. The combined organic layers were washed with brine (2×100 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give compound **1** as a beige solid (38.2 g, 0.29 mol, 38% yield over three steps).

1-(Fluoromethyl)cyclobutanamine hydrochloride (2×HCl)

To a solution of compound **1** (38.2 g, 0.29 mol) in toluene (500 mL), Et_3N (61.4 mL, 0.44 mol) was added in one portion. The resulting solution was cooled to 0 °C on an ice-water bath, and DPPA (87.8 g, 0.32 mol) was added portionwise while keeping the internal temperature below 5 °C. After the addition, the reaction mixture was slowly heated to 70 °C and then stirred at the same temperature for 3 h. After the gas evolution ceased, the mixture was heated to intensive reflux, and *tert*-butanol (83 mL, 0.87 mol) was added in a dropwise manner, following by additional stirring at reflux overnight. The resulting solution was cooled to room temperature, diluted with *t*-BuOMe (300 mL), washed successively with 10% aq $KHSO_4$ (2×100 mL), saturated aq $NaHCO_3$ (2×100 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give a crude compound **9** (*ca.* 43.3 g).

To a solution of the amount of **9** obtained in *t*BuOMe (250 mL), 10 M HCl in 1,4-dioxane (35 mL) was added in one portion at 0 °C, and the resulting mixture was stirred overnight. The resulting suspension was filtered, the precipitate was washed with *t*BuOMe (3×75 mL) and dried *in vacuo* (0.1 mbar) to give target product **2**×HCl as a colorless solid (22.7 g, 0.16 mol, 55% yield over two steps).

1-(Difluoromethyl)cyclobutanecarboxylic acid (3)

To an ice-cold solution of aldehyde **10** [18] (174 g, 1.11 mol) in CH_2Cl_2 (2 L), a solution of morph-DAST (291 g, 1.67 mol) in CH_2Cl_2 (300 mL) was added dropwise while maintaining the temperature below 5 °C. When the addition was complete, the resulting mixture was left to stir at room temperature overnight. The reaction mixture was slowly poured into saturated aq $NaHCO_3$, the aqueous phase was separated and extracted with CH_2Cl_2 (500 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by distillation (b. p. 51 °C / 5 mbar) to give crude ester **11** (*ca.* 125 g) as a colorless liquid.

To a solution of the amount of compound **11** obtained in MeOH (1 L), NaOH (84.3 g, 2.11 mol) was added portionwise (an exotherm was observed during the addition). After 2 h of stirring, the reaction mixture was evaporated *in vacuo* and partitioned between water (1 L) and CH_2Cl_2 (1 L). The organic phase was discarded, and the aqueous phase was acidified with 6 M aq HCl to to pH *ca.* 3, extracted with CH_2Cl_2 (2×1 L). The combined organic phases were washed with brine (300 mL), dried over Na_2SO_4, and evaporated to give carboxylic acid **3** (97.0 g, 58% from **10**) as a colorless oil.

1-(Difluoromethyl)cyclobutanamine hydrochloride (4×HCl)

To a solution of carboxylic acid **3** (97.0 g, 0.646 mol) in toluene (1 L), Et_3N (99.0 g, 0.711 mol) was added, and the resulting mixture was heated to 100 °C. DPPA (179 g, 0.65 mol) was added dropwise at such a rate to maintain a gentle reflux. When the gas evolution ceased, 2-(trimethylsilyl)ethanol (84.1 g, 0.711 mol) was added in one portion, and the heating was continued for 18 h. The reaction mixture was allowed to cool to room temperature, washed with saturated aq K_2CO_3 (300 mL), brine (300 mL), dried over Na_2SO_4, and evaporated in vacuo to give carbamate **12** (*ca.* 141 g) as a brown solid used in the next step without further purification.

The amount of compound **12** obtained was suspended in 6 M aq HCl and refluxed until all solids dissolved. The resulting mixture was evaporated to dryness and triturated with *t*BuOMe (1 L). The precipitate was filtered, washed with *t*BuOMe (2×400 mL), and dried in vacuo to give **4**×HCl (84.1 g, 64% yield) as a colorless solid.

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