

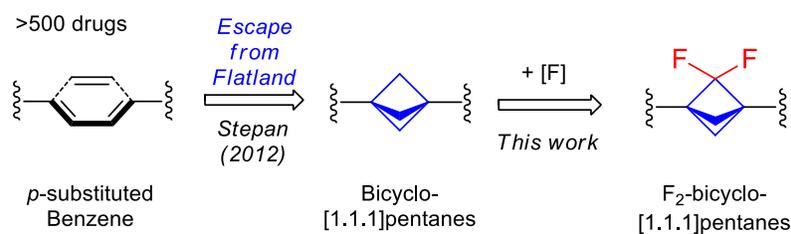
Difluoro-substituted bicyclo[1.1.1]pentanes as novel motifs for medicinal chemistry: design, synthesis and characterization

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ABSTRACT: Herein we developed a practical synthetic approach to the previously unknown difluoro-substituted bicyclo[1.1.1]pentanes. The key step was an addition of difluorocarbene to electron-rich bicyclo[1.1.0]butanes by $\text{CF}_3\text{TMS}/\text{NaI}$ system. The obtained difluoro-bicyclo[1.1.1]pentanes are a new generation of saturated bioisosteres of the benzene ring for drug discovery projects.

INTRODUCTION

Benzene ring is one of the most popular fragments in bioactive compounds.¹ In fact, more than 500 FDA-approved drugs are benzene-containing molecules.² In the context of the recently emerged concept *Escape from Flatland*³ scientists nowadays often replace benzene rings with the saturated bioisosteres⁴ aiming to obtain the patent-free molecules with an improved biological activity and physico-chemical profile. In particular, in 2012 *Stepan* and colleagues replaced a phenyl moiety in a γ -secretase inhibitor with a bicyclo[1.1.1]pentylic skeleton. The obtained analogue showed higher activity, solubility and metabolic stability.⁵ Moreover, the bicyclo[1.1.1]pentylic-containing compound was patent-free, showing a precedent on overcoming patents of pharmaceutical companies on benzene-containing bioactive molecules. Since that moment, bicyclo[1.1.1]pentylic-containing derivatives have been flourishing in chemistry: they are already mentioned in >100 patents by academic groups and commercial companies (Figure 1).⁶

An increasing demand from pharmaceutical institutions, initiated many academic research projects aimed at elaboration of novel synthetic approaches to bicyclo[1.1.1]pentylic-substituted building blocks. Most of the work in this area is devoted to the synthesis of mono- and 1,3-disubstituted derivatives.⁷⁻⁹ At the same time, however, dreams about the new generation of bicyclo[1.1.1]pentanes with a 2-substitution at the side chain are frequently discussed at scientific conferences on medicinal chemistry. Such structures, in turn, would give access into novel 3D-shaped chemical space, and will additionally provide with an opportunity to mimic the *ortho*-substituted benzenes. Although several bridge-substituted propellanes are known,¹⁰ they are obtained through multistep synthetic procedures often employing gaseous reagents and photochemical transformations. It is important to mention that 2,2-dichloro[1.1.1]propellane was reported, but was unstable.¹¹ This suggests that other propellanes with the bridge substituents which can act as leaving groups - fluorine, oxygen, sulphur – might be also unstable. As a result, the

bicyclo[1.1.1]pentanes with the substitution at the bridge positions are very rare.¹² Not surprising that over the years, many pharma-companies initiated internal research projects trying to access these structures; with no success so far, however.

Herein, we present our studies towards the preparation of difluoro-substituted at the bridge position bicyclo[1.1.1]pentanes – a class of compounds unknown before (Figure 1).

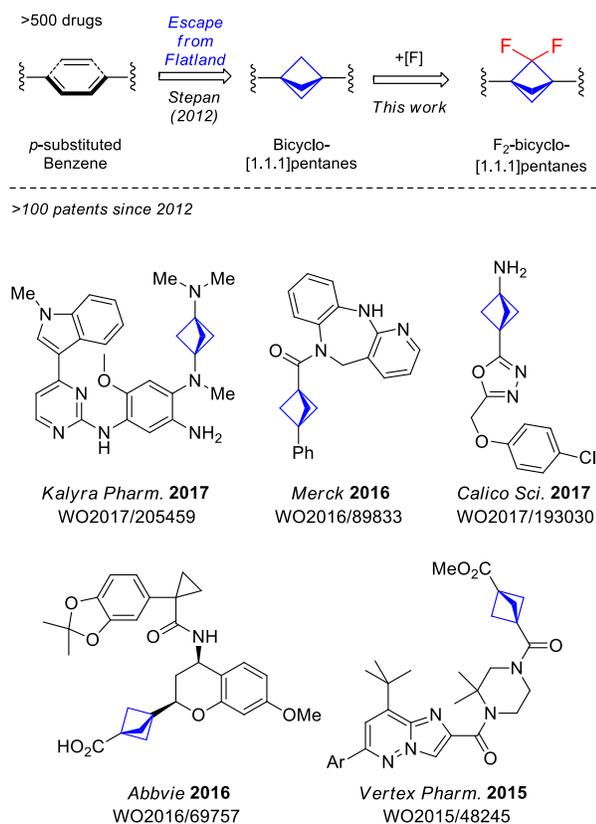


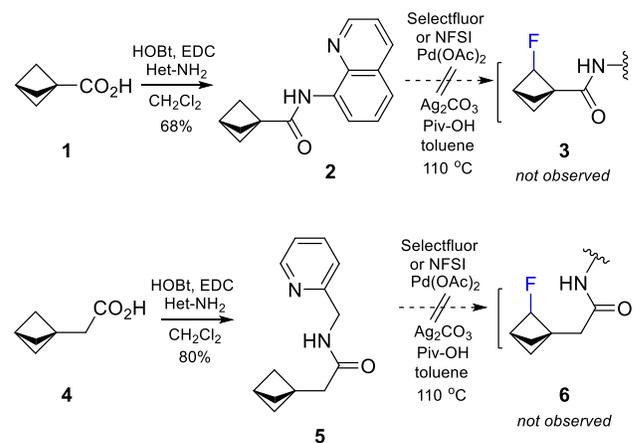
Figure 1. Application of bicyclo[1.1.1]pentanes in medicinal chemistry. Objectives of this work: side-chain fluorinated bicyclo[1.1.1]pentanes.

RESULT AND DISCUSSION

1) **Attempted directed CH-fluorination.** In 2015, *Xu* and coworkers described palladium-catalyzed CH-fluorination of aliphatic amides of 8-aminoquinoline.¹³ Therefore, we first tried to extend this reaction to bicyclo[1.1.1]pentane core. Reaction of acid **1** with 8-aminoquinoline using carbonyldiimidazole EDC as an amide-coupling reagent in dichloromethane as a solvent smoothly gave the needed amide **2** in 71% yield (Scheme 1). Unfortunately, all our attempts to perform directed CH-fluorination of compound **2** following either reported or modified conditions failed. Increasing the reaction temperature and time only led to decomposition of the starting compound. Presumably, compound **2** was too rigid to adopt the proper conformation for the CH-activation.

Previously, we observed similar effect, as several conformationally restricted analogues of proline did not react under the standard directed CH-arylation conditions.¹⁴

In 2016, *Hrdina* and colleagues showed that for the conformationally rigid 1-adamantane-carboxylic acid, 8-aminoquinoline was ineffective directing group in Pd-catalyzed CH-arylation reactions. The authors also found that the more flexible 2-aminomethyl pyridine worked well in this role.¹⁵ We wanted to take advantage of this discovery and to provide our model substrate even with more flexibility: we took a homologue of acid **1** – acid **4** having one additional methylene group (Scheme 1). Reaction of acid **4** with 2-aminomethyl pyridine in the presence of EDC as a condensing reagent in dichloromethane afforded the target model amide **5** in 82% yield. Similar to amide **2**, however, all our efforts to perform Pd-catalyzed CH-fluorination of compound **5** were unsuccessful. We did not observe the formation of the required product under all conditions we tried. Again, prolongation of the reaction time and increasing temperature only led to a decomposition of the starting material.



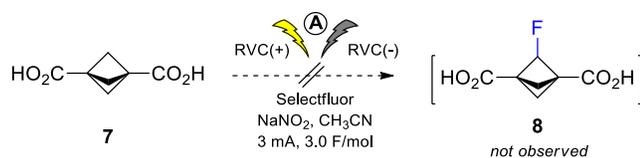
Scheme 1. Attempted Pd-catalyzed directed CH-fluorination of bicyclo[1.1.1]pentanes **2** and **5**.

Worth mentioning, that substrates **2** and **5** also failed to give any arylation product with PhI under the previously developed conditions.^{14, 16} At this point we decided to stop working in this direction and concentrated our efforts onto another approach – electrochemical fluorination.

2) **Attempted electrochemical CH-fluorination.** There are several precedents in the literature on the direct functionalization of bicyclo[1.1.1]dicarboxylate (**7**) with chlorine and fluorine gases. For example, in 1989, *Robinson* and *Michl* reported on the direct chlorination of diacid **7** with chlorine gas under irradiation.¹⁷ The selectivity of the reaction was achieved by careful control of the reaction temperature and time. The reaction with molecular bromine or iodine did not take place. In 1997, the same group treated diacid **7** with

fluorine gas: the reaction was unselective, however, giving a complex mixture of polyfluorinated derivatives.¹⁸ On the other hand, recently *Baran* and coworkers developed a practical electrochemical CH-fluorination protocol of aliphatic compounds.¹⁹ Being involved in this project, we wanted next to expend this methodology onto diacid **7**. In fact, a dilute solution of compound **7**, Selectfluor and mediator NaNO₂ in acetonitrile was electrolyzed under a constant current of 3 mA during different periods of time. The consumed charge was varied between 0.1-3.0 F/mol. Unfortunately, we did not observe the formation of the desired product – ¹⁹F-NMR of the reaction mixture showed no needed signals (Scheme 2). Over the time, only slow decomposition of the starting material took place.

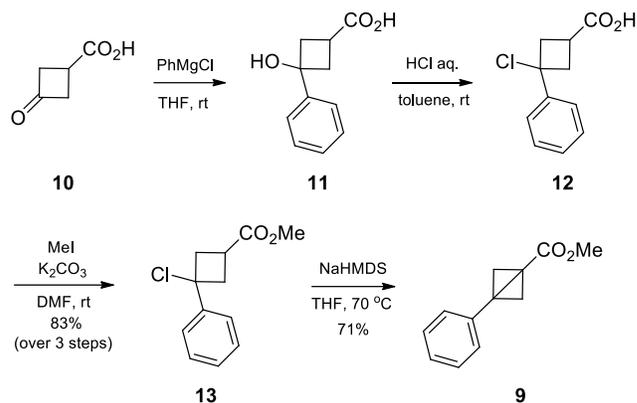
Failure in both CH-activation and electrochemical fluorination prompted us to focus on the third strategy of the synthesis of fluorinated bicyclo[1.1.1]pentanes.



Scheme 2. Attempted electrochemical fluorination of diacid **7**.

3) Addition of difluorocarbene to bicyclo[1.1.0]butanes.

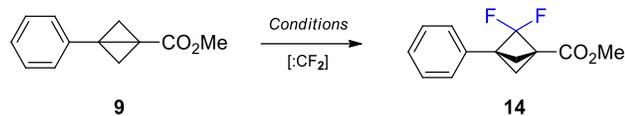
There are several precedents in the literature on the addition of dibromocarbene (:CBr₂) and dichlorocarbene (:CCl₂) to bicyclo[1.1.0]butanes to form the dihalosubstituted bicyclo[1.1.1]pentanes in 16-48% yields.²⁰ Mechanistically, this reaction represents an analogy to the cyclopropanation of alkenes, where a p-rich central bond of bicyclo[1.1.0]butane reacts with electrophilic dibromo- or dichlorocarbenes. Keeping this in mind, we wondered whether the same transformation could occur with (:CF₂). Due to the even higher electrophilicity of difluorocarbene compared with :CCl₂ and :CBr₂, we expected that this reaction would be feasible, and even expected the higher yields of products. There were no examples in the literature on that transformation, however. First, we synthesized a model compound **9** following the experimental procedure published in a patent literature (Scheme 3).²¹ The commercially available and relatively cheap acid **10** (25 g / 60 \$) was treated with PhMgCl in tetrahydrofuran at room temperature to afford alcohol **11** as a mixture of two stereoisomers. Reaction of the latter with concentrated aqueous hydrochloric acid in toluene gave the chloride **12**. Carboxylic function in **12** was alkylated with MeI in dimethylformamide using potassium carbonate as a base. Ester **13** was obtained by column chromatography in 83% isolated yield over three steps starting from acid **10**. Cyclization of compound **13** with NaHMDS gave the needed model substrate **9** in 71% yield.



Scheme 3. Synthesis of the starting substrate **9**.

Finally, we studied an addition of difluorocarbene to bicyclo[1.1.0]butane **9** (Table 1). First, we tried the oldest, and certainly one of the cheapest reagents - sodium chlorodifluoroacetate, - that we successfully used for the difluorocyclopropanation of various alkenes previously.²² Indeed, we observed the formation of product **14**, but in low yields (Table 1, entries 1-3). The use of Hg(CF₃)₂ or Dolbier reagent - FSO₂CF₂CO₂TMS (TFDA) did provide the product in up to 50% yield (Table 1, entries 4-7). Finally, we studied the system CF₃TMS/NaI that was used before for the difluorocyclopropanation of various functionalized alkenes.²³ The reaction already efficiently proceeded with 3 eq. of CF₃TMS, but increasing its amount to 10 equiv allowed the isolation of the difluoro-compound **14** in 68% yield (Table 1, entries 8-11). The use of larger excess of CF₃TMS, modifying amount of NaI or using other solvents did not give any further boost in yield (Table 1, entries 11-15). For further studies on small scale we used ten equivalents of CF₃TMS, but for the subsequent multigram synthesis, this amount could be safely reduced to two-three equivalents.

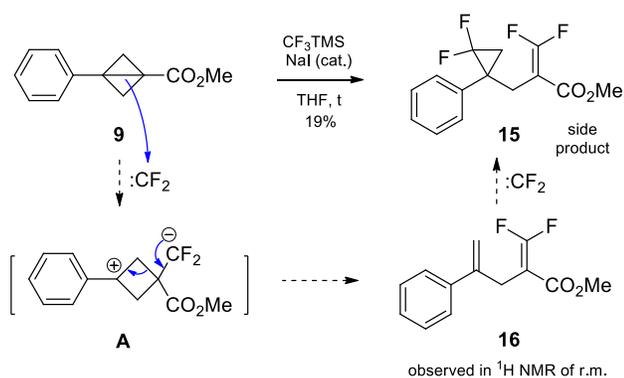
It is worth mentioning that even under the optimized conditions, we also isolated a side product **15** in 19% yield from a reaction mixture (Scheme 4). Compounds of this type are usually formed as the main products in the reaction bicyclo[1.1.0]butanes with carbene obtained by photolysis of diazomethane,²⁴ or with metal-carbenoids under the Simmons-Smith conditions.²⁵ Formation of bicyclo[1.1.1]pentanes was never observed in those reactions. With more electrophilic dibromo- and dichlorocarbenes, bicyclo[1.1.1]pentanes were formed, but only as minor components, whereby dienes of type **15** prevailed.^{20a,b} The highly electrophilic nature of difluorocarbene seems to switch the reactivity of bicyclo[1.1.0]butanes, as the bicyclo[1.1.1]pentane **14** is formed as a main reaction product, while compound **15** – as a minor side product.

Table 1. Optimization of the reaction conditions.

Entry ^a	Reagent	Solvent	Addit.	T (°C) ^b	Yield (%) ^c
1	CF ₂ ClCO ₂ Na (3 eq.)	toluene		110	12
2	CF ₂ ClCO ₂ Na (5 eq.)	xylene		150	16
3	CF ₂ ClCO ₂ Na (10 eq.)	glyme		170	23
4	TFDA (3 eq.)	toluene	LiF (5%)	110	32
5	TFDA (5 eq.)	toluene	LiF (10%)	110	44
6	TFDA (10 eq.)	toluene	LiF (20%)	110	51
7	(CF ₃) ₂ Hg (2 eq.)	THF	NaI (200%)	70	21
8	CF ₃ TMS (1 eq.)	THF	NaI (20%)	70	44
9	CF ₃ TMS (3 eq.)	THF	NaI (20%)	70	61
10	CF ₃ TMS (5 eq.)	THF	NaI (20%)	70	66
11	CF ₃ TMS (10 eq.)	THF	NaI (20%)	70	73(68) ^d
12	CF ₃ TMS (20 eq.)	THF	NaI (20%)	70	71
13	CF ₃ TMS (10 eq.)	THF	NaI (40%)	70	70
14	CF ₃ TMS (10 eq.)	THF	NaI (10%)	70	72
15	CF ₃ TMS (10 eq.)	CH ₃ CN	NaI (20%)	70	62

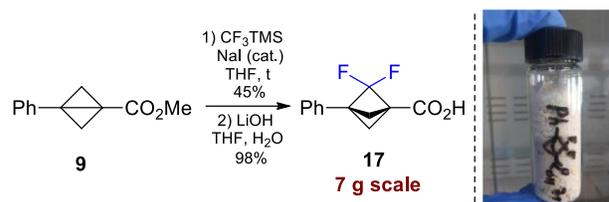
^a Reactions were performed on 0.1 mmol scale. ^b Temperature in the oil bath. Yield determined by ¹H-NMR with CH₂Br₂ as an internal standard. ^d Yield of isolated product. Abbreviations: nd = not detected.

Mechanistically, it seems reasonable to assume that the central *p*-rich bond in compound **9** attacks the electrophilic :CF₂ to form a stable benzylic carbocation **A**. The rearrangement of the latter gives a putative alkene **16** (Scheme 4). Although we did not isolate alkene **16** in the individual state, we did observe in ¹H NMR of the reaction mixture the formation of characteristic alkene protons at 5.5-6.0 ppm that disappeared over the time in a course of the reaction. Indeed, styrene **16** rapidly reacted with an excess of difluorocarbene to give the side product **15**. Acrylic double bond in **15** is far less reactive towards difluorocarbene, however, upon prolonged reaction times we did also observe its slow difluorocyclopropanation.

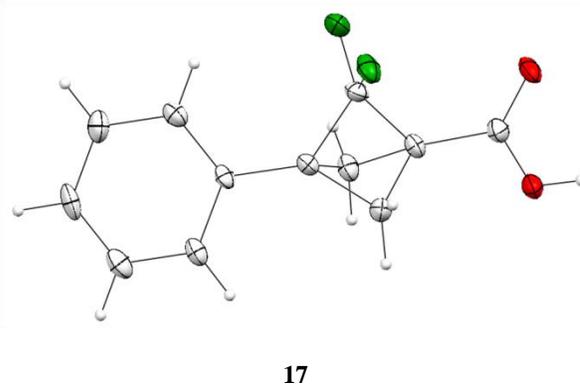
**Scheme 4.** Proposed mechanism for the formation of the side product **15**.

Hydrolysis of the ester group in compound **9** smoothly gave acid **17** which is a valuable building block for medicinal

chemistry projects (Scheme 5). Next, we challenged its gram-scale synthesis. The only modification to the previously elaborated procedure was the amount of CF₃TMS in the addition of difluorocarbene. To reduce the costs of the synthesis, we decreased an excess of CF₃TMS from 10 equiv. to 3 equiv. This affected the reaction yield, but not dramatically - product **14** was isolated in 45% yield. Significant formation of the side product **15** was also observed. Finally, hydrolysis of the ester group in **14** gave acid **17** as a white solid in 7 g scale.

**Scheme 5.** Gram-scale synthesis of acid **17**.

The molecular structure acid **17** was confirmed by X-Ray analysis (Figure 2).

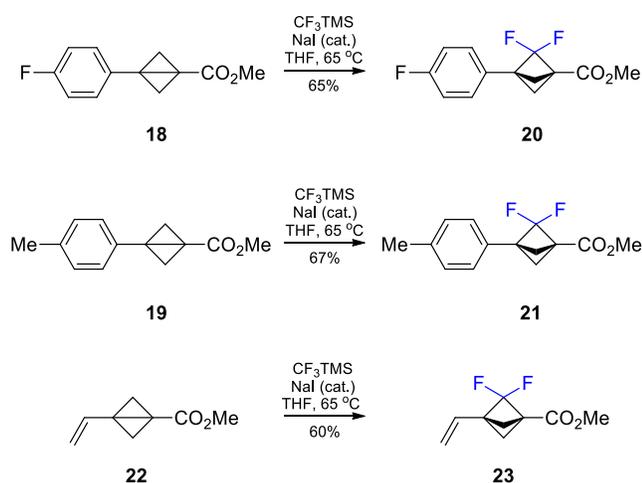
**Figure 2.** X-Ray crystal structure of acid **17**. Atoms are shown as ellipsoids at 25% probability level. Atoms of fluorine – green, oxygen – red.²⁶

Having elaborated a practical procedure to phenyl-substituted bicyclo[1.1.1]pentane **14**, we wanted to understand how sensitive the reaction was to the substituents at the phenyl ring. Although, a detailed scope of this transformation is beyond the scope of this communication, we synthesized two representative key starting compounds bearing either the electron-withdrawing *para*-fluorine substituent at the phenyl ring (**18**), or an electron-donating methyl-group (**19**). The both compounds were easily synthesized in several steps from acid **10** following the previously described strategy (Scheme 3). Compounds **18** and **19** smoothly reacted with CF₃TMS/NaI to form the needed fluorinated bicyclo[1.1.1]pentanes **20** and **21** (Scheme 6).

The reactivity of substrate **22** (prepared also from acid **10**) towards the difluorocarbene is noteworthy. The reaction

occurred first selectively at the central bond of bicyclo[1.1.0]butane (Scheme 6). The present $-\text{CH}=\text{CH}_2$ double bond started to react only when the reaction of the central bond was finished. Therefore, control of the reaction by TLC and NMR allowed the isolation of the needed vinyl-substituted product **23** in 60% yield.

Despite the advantages outlined herein, the developed strategy is not without limitation: the aryl/vinyl-substituents at the bicyclo[1.1.0]butane core were found to be crucial for the formation of bicyclo[1.1.1]pentanes. Unfortunately, none, of the tested substrates **24-26** gave the expected products. In every case, the compounds were unreactive. Increasing the reaction temperature in the external oil bath, and the prolonged reaction time led to the formation of complex mixtures. Some signals corresponding to the alkene fragment in ^1H NMR indicated the formation of alkenes of the type **16** apart from other side products.



Limitations:

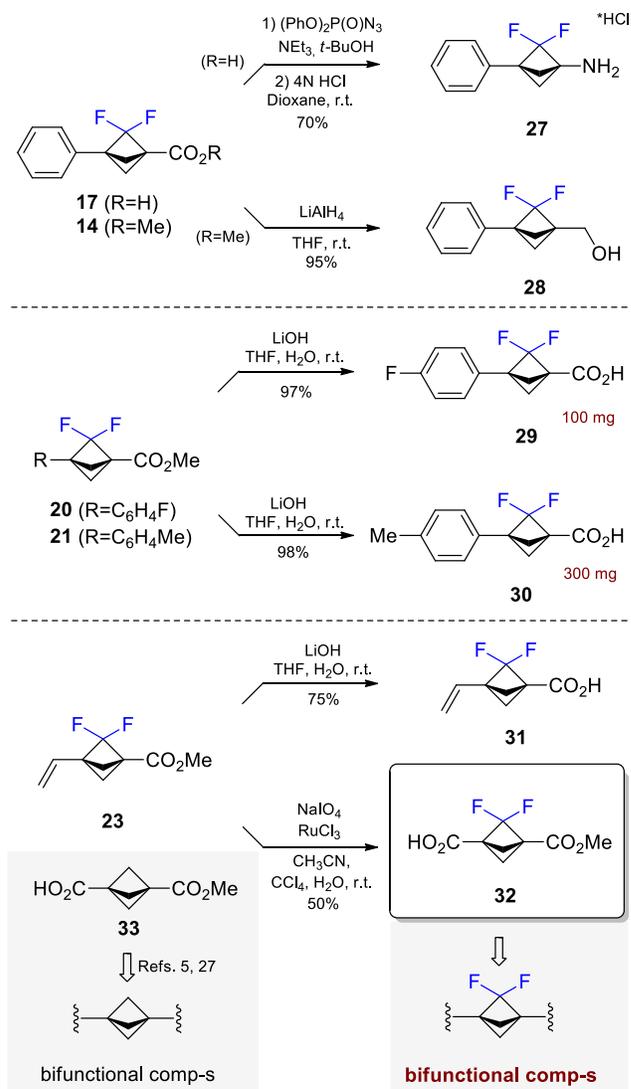


Scheme 6. Synthesis of difluoro-substituted bicyclo[1.1.1]pentanes **21-23**. Unreactive substrates **24-26**.

Synthesis of building blocks. Next, we performed several representative postmodifications of difluoro-substituted bicyclo[1.1.1]pentanes to obtain the corresponding building blocks for the direct use in drug discovery projects. For example, Curtius rearrangement of acid **17** with $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ in *tert*-butanol, followed by acidic *N*-Boc deprotection gave amine **27** in the form of hydrochloride as a white solid (Scheme 7). Reduction of the ester group in **14** with LiAlH_4 in tetrahydrofuran smoothly provided alcohol **28**

in 95% yield. Hydrolysis of esters **20**, **21** and **23** with LiOH at room temperature gave acids **29-31** in 100-300 mg scale.

All previously described difluoro-substituted bicyclo[1.1.1]pentanes contained aryl-substituents. Therefore, we also oxidized the vinyl group in compound **23** with NaIO_4 and the catalytic amount of RuCl_3 to obtain mono-acid **32**. Compound **32** opens up a way to synthesize various bifunctional derivatives: amino acids, amines, diamines *etc.* This tactic is being used routinely these days to synthesize difunctional bicyclo[1.1.1]pentyl derivatives from non-fluorinated acid **33** (Scheme 7).^{5, 27}



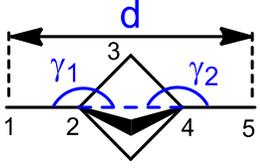
Scheme 7. Synthesis of mono- (**27-31**) and bifunctional difluoro-substituted bicyclo[1.1.1]pentane **32**.

Chemical stability. Indeed, because the donor-acceptor cyclobutanes sometimes undergo ring-fragmentation,²⁸ we next checked a chemical stability of difluoro-bicyclo[1.1.1]pentanes, being strained cyclobutanes. Luckily,

treatment of acid **17** and amine **27** with aq. 1M hydrochloric acid, or aq. 1M sodium hydroxide at room temperature for 24 hours did not lead to any decomposition of the starting materials. These experiments indicate that described herein products possess sufficient chemical stability and, indeed, can be used as building blocks in medicinal chemistry.

Crystallographic analysis. In 2011, *O'Hagan* and coworkers showed that *gem*-difluorination of cycloalkanes altered significantly their geometry.²⁹ We next checked whether incorporation of fluorine atoms would have an effect on the geometry of the bicyclo[1.1.1]pentane skeleton. Luckily, there are two related non-fluorinated compounds **34** and **35** reported in the literature with the known crystallography data.³⁰ Therefore, we compared geometric parameters of all three molecules **17**, **34** and **35** (Table 2). Incorporation of *gem*-difluoro unit slightly shortened C(2)-C(3) and C(3)-C(4) bonds: 1.515-1.529 Å (**17**) vs 1.540-1.560 Å (**34**, **35**). Also, it increased the internal C(2)-C(3)-C(4) angle: 78.2° (**17**) vs 74.5-75.3° (**34**, **35**). The factors describing the collinearity of substituents - angles γ_1 and γ_2 , - did not deviate significantly from the ideal value of 180°: 178.0-179.1° (**17**) vs 178.3-179.6° (**34**, **35**). The distance between the bridgehead carbon atom C(2)-C(4) of the bicyclo[1.1.1]pentane was somewhat elongated: 1.919 Å (**17**) vs 1.882-1.891 Å (**34**, **35**).

Table 2. Selected parameters of bicyclo[1.1.1]pentanes **17**, **34**, **35** according to X-Ray crystal data: bond lengths (Å), angles (°), and distances (Å).



Compound	17	34	35 ^a
Bond (Å)			
C(2)-C(3)	1.529	1.546-1.556	1.540-1.557
C(3)-C(4)	1.515	1.553-1.560	1.542-1.552
C(1)-C(2)	1.491	1.493	1.489
C(4)-C(5)	1.491	1.517	1.518
Angle (°)			
C(2)-C(3)-C(4)	78.2	75.2-74.9	74.5-75.3
C(1)-C(2)-C(4), γ_1	178.0	178.6	178.3
C(2)-C(4)-C(5), γ_2	179.1	179.2	179.6
Distance (Å)			
C(2)-C(4), d	1.919	1.891	1.882
C(1)-C(5), d	4.901	4.901	4.889

^a Ar = 4-TMS-C₆H₄.

Importantly, however, that the key parameter, distance between the substituents - **d**, - was not changed at all: 4.901 Å (**17**) vs 4.889-4.901 Å (**34**, **35**).

In short summary, although *gem*-difluorination slightly changed some bond lengths and internal angles of the bicyclo[1.1.1]pentane core, it did not affect its key characteristics that are important for medicinal chemistry: overall 3D-shape, collinearity of the substituents (178-179°) and distance between them (4.9 Å).

Acidity/basicity of functional groups. Incorporation of fluorine atoms into organic molecules changes significantly acidity/basicity of the neighboring functional groups.³¹ For this reason we experimentally measured pK_a values of acids **17**, **35** and amine hydrochlorides **27**, **36** (Figure 3). Thus, *gem*-difluorination of acid **35** increased its acidity by one magnitude of order: pK_a (**35**) = 4.0 vs pK_a (**17**) = 3.0. On the other hand, *gem*-difluorination of amine **36** reduced its basicity by already three magnitudes of order: pK_a (**36***HCl) = 7.9 vs pK_a (**27***HCl) = 4.9. The much bigger impact of fluorination on the basicity than on the acidity can be explained in terms of -(I)-inductive effect of fluorine atoms. In acid **17**, fluorine atoms and the acidic hydrogen atom are distanced by five single bonds. At the same time, in amine **27**, fluorine atoms and the basic nitrogen atom are distanced by three single bonds; hence an effect of fluorination on the basicity is bigger.

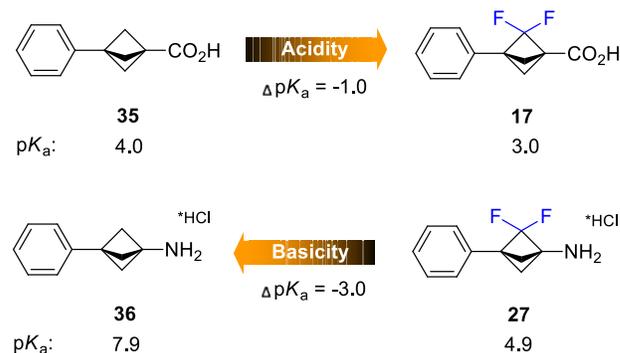


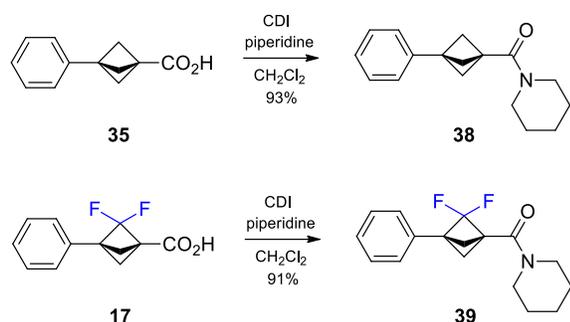
Figure 3. Experimental pK_a values of acids **17**, **35**; and conjugated amines **27***HCl and **36***HCl.

Water solubility and lipophilicity. Fluorination is known also to affect the physico-chemical properties of organic compounds, such as water solubility and lipophilicity.³¹ Therefore, we first synthesized model amides **37-39** (Scheme 8) and measured their experimental logD and water solubility values.

As it was expected,^{5, 6a, 32} replacement of the benzene ring in compound **37** by bicyclo[1.1.1]pentane increased the water solubility by almost 4-times: 104 uM (**37**) vs 370 uM (**38**) (Table 3). *Gem*-fluorination of compound **38** slightly reduced its water solubility: 370 uM (**38**) vs 250 uM (**39**). Nevertheless,

the water solubility of gem-difluorinated bicyclo[1.1.1]pentane **39** was almost 2.5-times higher than that of the benzene-containing containing compound **37**: 250 μM (**39**) vs 104 μM (**37**).

An effect of benzene substitution and fluorination of bicyclo[1.1.1]pentane onto lipophilicity was less profound (Table 3). The replacement of the benzene ring in compound **37** by bicyclo[1.1.1]pentane slightly reduced its lipophilicity, as measured by logD(7.4) index: 3.6 (**37**) vs 3.4 (**38**). Gem-difluorination of bicyclo[1.1.1]pentane again increased the lipophilicity, logD(7.4): 3.4 (**37**) vs 3.6 (**38**).



Scheme 8. Synthesis of model amides **38** and **39**.

Table 3. Experimental lipophilicity and solubility data of model compounds **37-39**.

Model compound	LogD(7.4) ^a	Sol(7.4) ^b
37	3.6	104
38	3.4	370
39	3.6	250

^aExperimental *n*-octanol/water distribution coefficient (log) at pH 7.4;

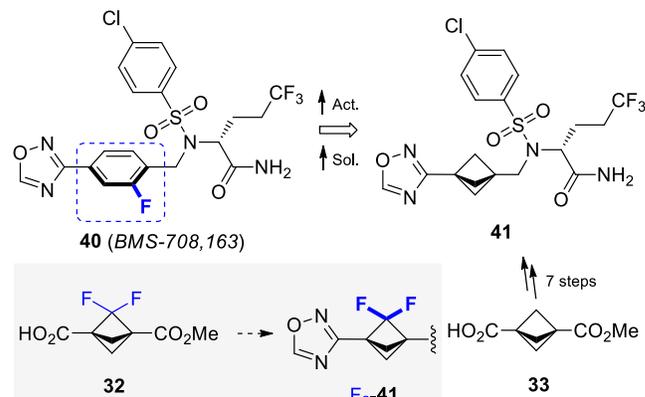
^bKinetic aqueous solubility (μM) in 50 mM phosphate buffer (pH 7.4).

In short summary, gem-difluorination of bicyclo[1.1.1]pentane decreased its water solubility, and slightly reduced lipophilicity (logD). On the other hand, replacement of the benzene ring (**37**) with gem-difluoro bicyclo[1.1.1]pentane (**39**) selectively increased significantly its water solubility and did not affect its lipophilicity, which might be beneficially used in medicinal chemistry programs.

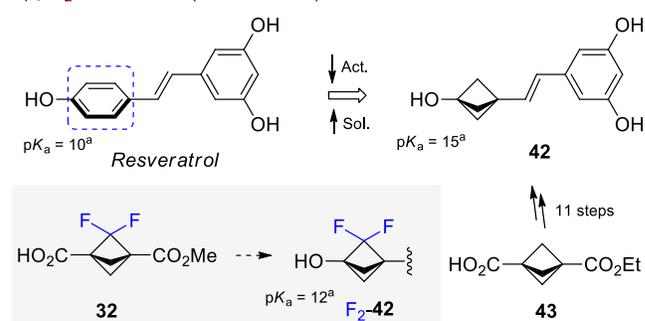
Possible application areas. After a practical synthesis of gem-difluorinated bicyclo[1.1.1]pentanes, and demonstration that their chemical and physico-chemical properties are compatible with medicinal chemistry requirements, we also

wanted to suggest areas, where these building blocks might be useful. Indeed, they can be considered as advanced mimics for the substituted benzene rings, but there are some particular cases that in our opinion are worth mentioning (Scheme 9).

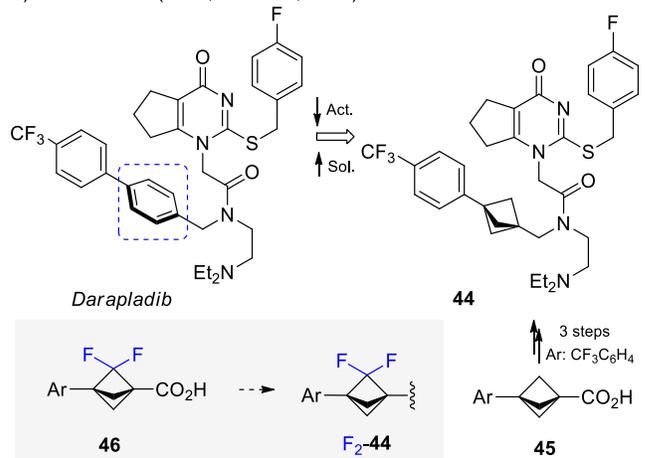
a) C-F benzene (2012, *Stepan*):⁵



b) pK_a modulation (2017, *Adsool*):^{27c}



c) Ar-Ar motifs (2017, *Measom, Hirst*):^{27d}



Scheme 9. Possible application areas for gem-difluorinated bicyclo[1.1.1]pentanes. ^aCalculated pK_a values.

For example, in 2012, *Stepan* and colleagues made an intriguing discovery: the authors replaced a fluorophenyl moiety in the γ -secretase inhibitor **40** (BMS-708,163) with a bicyclo[1.1.1]pentyl skeleton to obtain compound **41** (Scheme

9a).⁵ Synthetically, compound **41** was obtained from acid **33** in 7 steps. Compound **41** showed better activity, and higher solubility than **40**. On the other hand, the original compound **40** possessed a fluoro-substituted phenyl ring, and it is strategically reasonable also to test the fluorinated analogues of compound **41**, because fluorine atoms are often involved in the specific ligand-protein interactions.³³ In particular, the synthesis of F₂-**41** could have been realized from acid **32** (Scheme 7).

Resveratrol is a natural compound exhibiting anticancer activity (Scheme 9b). In 2017, *Adsool* and co-workers replaced the phenyl ring in Resveratrol by bicyclo[1.1.1]pentyl skeleton (**42**).^{27c} Compound **42** was synthesized in 11 steps from acid **43**. Compared to Resveratrol, compound **42** had 40-times better water solubility and almost identical activity against cancer cells. However, replacement of the aromatic phenol moiety by aliphatic bicyclo[1.1.1]pentan-ol led to decrease in OH-acidity: pK_a = 10 (Resveratrol) vs 15 (**42**). From the strategic standpoint it would have been desirable also to synthesize and test the fluorinated compound F₂-**42** that might have a much closer acidity of the OH-group to that of Resveratrol: pK_a (F₂-**42**) = 12. The synthesis could have been also started from acid **32**.

Finally, in 2017, *Measom*, *Hirst* and colleagues replaced the central biphenyl moiety of Darapladib – an agent for the treatment of atherosclerosis, - with Ar-BCP motif (**44**, Scheme 9c).^{27d} The obtained compound **44** was more water-soluble than Darapladib, but slightly less active. The synthesis of **44** was undertaken from acid **45** in three steps. Indeed, bioactive compounds with the biphenyl motif, like Darapladib, seem to be the most obvious targets for the incorporation of Ar-F₂-BCP fragments described herein. For example, the synthesis of F₂-**44** could have been realized from the corresponding acid **46**.

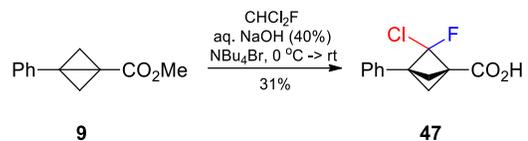
CONCLUSIONS

Herein, we developed a practical synthesis of the previously unknown gem-difluorinated bicyclo[1.1.1]pentanes (F₂-BCPs). The key synthetic step was an addition of :CF₂-carbene, generated *in situ* from CF₃TMS/NaI mixture, to aryl/vinyl-substituted bicyclo[1.1.0]butanes. The synthesis was optimized to obtain up to 7 g of the target compounds (acid **17**) in one run. Experimental physico-chemical properties, - acidity, basicity, lipophilicity and water solubility, - were measured for the obtained compounds. Based on this data, gem-difluorinated bicyclo[1.1.1]pentanes are suggested as novel saturated mimics for the benzene ring in medicinal chemistry projects.

The described herein synthetic approach gives access to mono- and bifunctional F₂-BCPs. Starting from the corresponding aryl-substituted bicyclo[1.1.0]butane one could obtain Ar-substituted F₂-BCPs, - like acid **17**, amine **27**, alcohol **28** (Schemes 6, 7) - suitable for the replacement of

biphenyl cores in bioactive compounds. On the other hand, acid **32** (Scheme 7) gives an access to a wide range of bifunctional compounds, - amino acids, diamines, amino alcohols, *etc.*, - by stepwise standard modifications of the carboxylic groups. This work is currently in progress in our laboratory.

Also, the successful addition of :CF₂-carbene to compound **9** (Table 1, Scheme 5) suggests that other carbenes of type :CF(R) might also be used. To prove this hypothesis, we also want to disclose our first results in this area: addition of :CFCl-carbene to compound **9** under the basic conditions allowed to obtain Cl,F-disubstituted acid **47** in 31% non-optimized yield (Scheme 10).



Scheme 10. Synthesis of Cl,F-acid **47** by an addition of :CFCl-carbene to substrate **9**.

We do believe that with the practical synthetic protocol in hand and appropriate physico-chemical properties, gem-difluorinated bicyclo[1.1.1]pentanes (F₂-BCPs) will find practical application in drug discovery projects very soon.³⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the website.

Copies of spectra, X-Ray and experimental lipophilicity and solubility data.

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