Fluoro-bicyclo[1.1.1]pentanes

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Dedicated to the people of Ukraine

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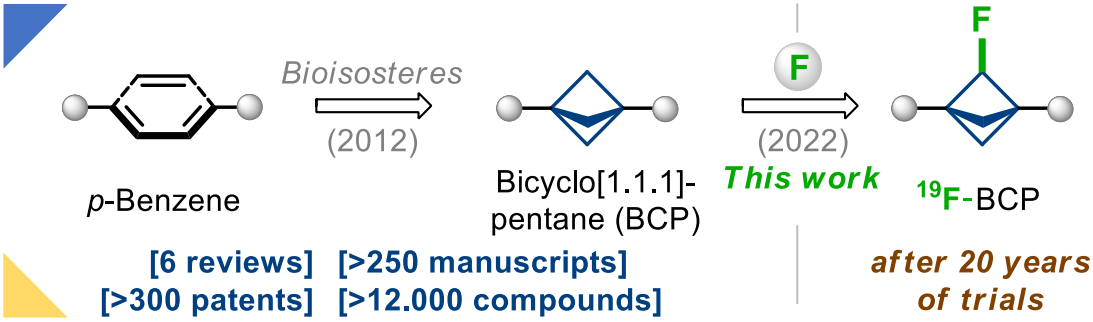
Abstract: After more than 20 years of trials, a practical scalable approach to fluoro-bicyclo[1.1.1]pentanes (^{19}F-BCPs) has been developed. Physico-chemical properties of fluoro-bicyclo[1.1.1]pentanes have been studied, and the core was incorporated into the structure of the anti-inflammatory drug *Flurbiprofen* instead of the fluorophenyl ring.



Introduction. The phenyl ring is one of the most popular structural motifs in natural compounds and synthetic drugs.[1] Ten years ago, Stepan and co-workers replaced the phenyl ring in a γ-secretase inhibitor with the bicyclo[1.1.1]pentyl (BCP) skeleton.[2] The obtained analog showed higher activity and improved physico-chemical properties - that was a starting point for the sunrise of bicyclo[1.1.1]pentanes in various aspects of chemistry: from medicinal chemistry to supramolecular chemistry. Today, bicyclo[1.1.1]pentanes are highly popular in academic and industrial research.[3-5] In fact, at least 6 reviews,[6,7] 250 research manuscripts, 300 patents, and 12.000 BCP-containing compounds appeared during the past decade (Figure 1).[8] Moreover, the number of BCP-containing molecules continues to grow every year almost exponentially (Figure 2).

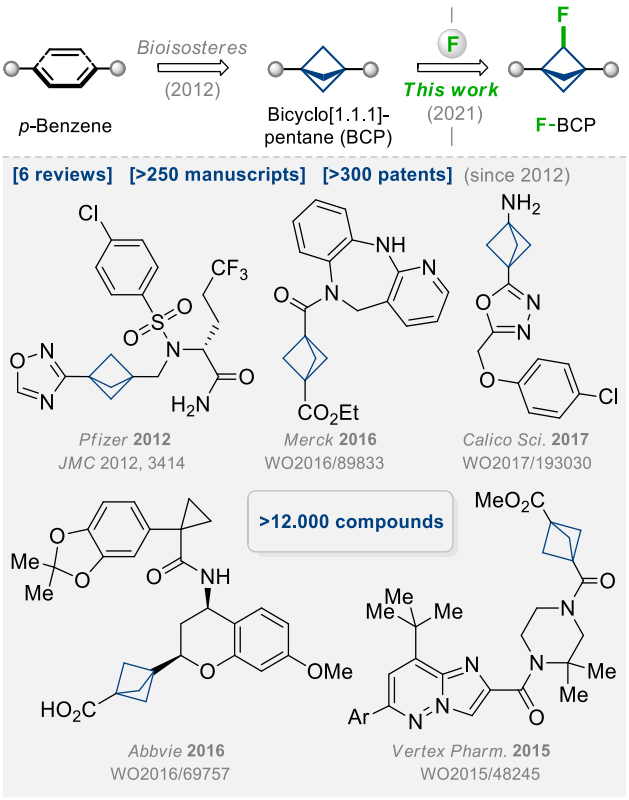


Figure 1. Bicyclo[1.1.1]pentanes (BCPs): state of the art. Aim of this work: fluoro-bicyclo[1.1.1]pentanes (F-BCPs).

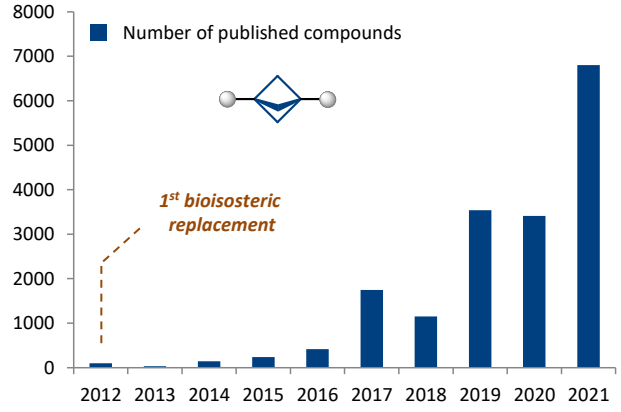
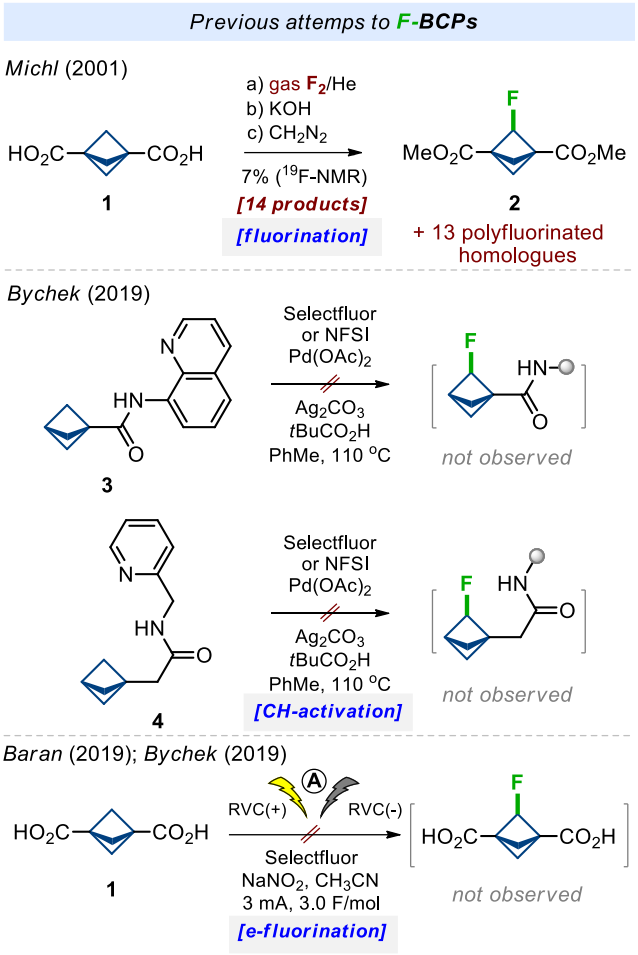


Figure 2. Popularity of bicyclo[1.1.1]pentanes (BCPs) over the years.

Chemists often incorporate a fluorine atom into organic molecules to fine-tune their physicochemical properties,[9] adjust the acidity/basicity of the neighboring functional groups,[10] and control the conformation.[11] Given the high popularity of bicyclo[1.1.1]pentanes, it is not surprising that chemists also tried to selectively decorate them with a fluorine atom. Indeed, previously, synthetic approaches the corresponding bridgehead-,[12,13] gem-[14] and polyfluorinated[15] derivatives had appeared, and these molecules immediately became useful in chemistry. At the same time, bicyclo[1.1.1]pentanes with a single fluorine atom in the bridge position have been remaining a dream.



Scheme 1. Previous attempts to fluoro-bicyclo[1.1.1]pentanes.

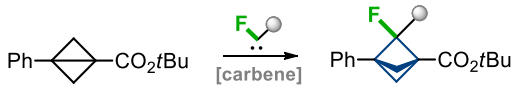
Previously, several attempts to synthesize monofluorinated bicyclo[1.1.1]pentanes (^{19}F-BCPs) were reported in the literature. In 2001, Michl and colleagues performed fluorination of diacid **1** by a mixture of fluorine gas with helium. Saponification and the subsequent esterification with diazomethane gave a mixture of 14 isomeric/homologous polyfluorinated compounds (Scheme 1). The needed diester **2** was present in 7% according to ^{19}F-NMR. It was isolated by a silica gel column and additional preparative GC.[15b] In 2019, our group also tried to synthesize ^{19}F-BCPs by directed-group mediated CH-activation of amides **3** and **4**. In both cases, the formation of the needed products was not observed.[14b] In 2019, Baran and colleagues developed a practical electrochemical C(sp^3)-H fluorination.[16] Being involved in the project at that time, we also

tried to achieve electrochemical fluorination of diacid **1**.[14b] Again, the formation of the needed product was not detected.

In this work, we finally solved this long-standing problem and developed a practical scalable approach to fluoro-bicyclo[1.1.1]pentanes (^{19}F-BCPs).

Optimization. After unsuccessful attempts to access ^{19}F-BCPs by either protecting-group directed CH-activation of BCP-scaffold or its electrochemical fluorination (Scheme 1), we decided to challenge a strain-release addition of carbenes to bicyclo[1.1.0]butanes.[17]

The direct addition of fluorocarbene (:CHF) to bicyclo[1.1.0]butanes is unknown. However, previously practical protocols for the addition of fluorocarbene to activated alkenes were developed.[18,19] These involved the use of freons CHF_2I[18] and CH_2FI.[19] We tried both literature protocols on the model substrate **5**, but the formation of the needed product **6** was not observed (Table 1, entries 1-4). Next, we tried an addition of chlorofluorocarbene (:CClF). Previously, we demonstrated one example of such a reaction between gaseous $CHFCl_2$ and methyl analog of compound **5** in a low yield.[14b] We did observe the formation of the needed product **7**, but despite all efforts, we could not increase the reaction yield significantly (entries 5-7). The addition of bromofluorocarbene (:CBrF) to bicyclo[1.1.0]butanes was unknown in the literature, but out of desperation, we also tried it. First, we did not observe the formation of the product (entries 8-10), but screening of solvents and phase-transfer catalysts (entries 8-15) allowed us to identify the optimal reaction conditions (entry 14). The reaction of substrate **5** with commercially available $CHFBr_2$ and aq. NaOH in the presence of NEt_3BnCl in toluene at room temperature gave the needed product **8** in 71% yield. From the practical standpoint, the protocol was convenient, because $CHFBr_2$ is a liquid at room temperature (b.p. = 65 ºC), in contrast to the previously attempted gaseous freons (CHF_2I, $CHFCl_2$).



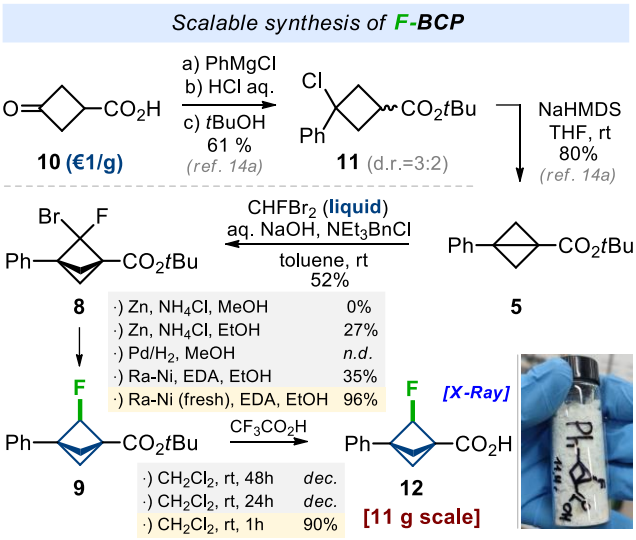
5 **6** (H), **7** (Cl), **8** (Br)

entry	conditions		yield (%)[a]
1	CHF_2I, EtZnI·Et_2O, CH_2Cl_2, -40 ºC	H	*n.d.*
2	*— same as above* ——, rt		*n.d.*
3	CH_2FI, LDA, THF, -50 ºC		*n.d.*
4	*— same as above*, rt		*n.d.*
5	$CHFCl_2$ (*gas*), aq. NaOH, NBu_4Br, CH_2Cl_2, rt	Cl	<20
6	*— same as above* ——, PhMe, rt	(*ref. 14b*)	<20
7	*— same as above* ——, 15-crown-5, CH_2Cl_2, rt		<10
8	*— same as below* ——, THF, rt	Br	*n.d.*
9	*— same as below* ——, MeO*t*Bu, rt		*n.d.*
10	*— same as below* ——, dioxane, rt		*n.d.*
11	*— same as below* ——, Et_2O, rt		<10
12	*— same as below* ——, C_6H_6, rt		56
13	*— same as below* ——, CH_2Cl_2, rt		43
14	$CHFBr_2$ (*liquid*), aq. NaOH, NEt_3BnCl, PhMe, rt		71
15	*— same as above* ——, db-18-crown-5, pinacol, CH_2Cl_2, rt		<20

[a] Isolated yield. 2 mmol scale.

Table 1. Optimization of synthesis of F-BCP **8**.

Scalable synthesis. Having an optimized procedure in hand, we studied its scalability. The synthesis commenced from the commercially available ketoacid **10** (ca. 1€/g, Scheme 2). Chloride **11** was obtained from acid **10** in three steps yield following the literature protocol.[14a] Cyclization of **11** was performed with NaHMDS in THF at room temperature to provide bicyclo[1.1.0]pentane **5** in 80% yield. The scaled-up reaction of **5** with $CHFBr_2$ under the previously developed conditions gave bicyclo[1.1.1]pentane **8** in a slightly lower yield of 52%. However, 21 g of product **8** was obtained in one run. Cleavage of C-Br bond was developed next (Scheme 2). Reduction with either Zn/NH_4Cl or Pd/H_2 gave only traces of the product. However, the reaction of bromide **9** with the freshly prepared Raney nickel in the presence of ethylenediamine (EDA) in ethanol smoothly afforded the desired monofluoro-bicyclo[1.1.1]pentane **9** in 96% yield. Finally, cleavage of the *tert*-butyl ester was performed with a catalytic amount of trifluoroacetic acid in dichloromethane at room temperature for one hour. The needed acid **12** was obtained as a crystalline solid in 90% yield in an 11 g amount.



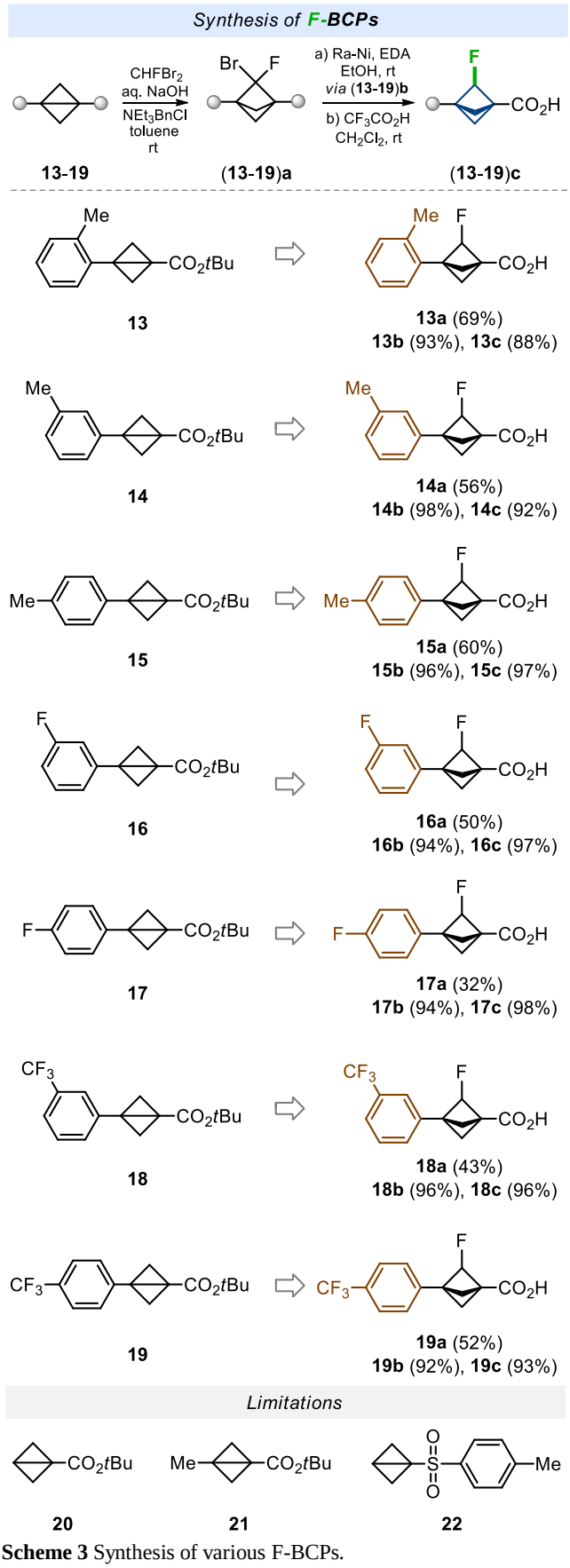
Scheme 2. Scalable synthesis of F-BCP carboxylic acid **12**.

The structure of product **12** was proven by X-Ray analysis.[20]

Scope. Next, we studied the generality of the developed protocol. First, we synthesized representative starting compounds bearing simple methyl (**13**–**15**), fluorine (**16**, **17**), and trifluoromethyl (**18**, **19**) substituents on the phenyl ring (Scheme 3). All bicyclo[1.1.0]butanes were prepared from ketoacid **10** analogously to the initial substrate **5** (Scheme 2, please see SI). Bicyclo[1.1.0]butanes **13**-**15** with methyl groups reacted with $CHFBr_2$ in 56-69% yield. Interestingly to note, the ortho-substituted substrate **13** gave the highest yield of 69%. Fluorine-substituted substrates **16**, **17** gave the corresponding derivatives **16a** and **17a** in 50% and 32% yield, correspondingly. Trifluoromethyl-substituted bicyclo[1.1.0]butanes **18**, **19** gave products **18a** and **19a** in 43% and 52% yield. All compounds **13a**-**19a** were next converted in two steps (via esters **13b**-**19b**) into the desired acids **13c**-**19c** in high yields. Most of the final acids were obtained on a gram scale.

The developed approach was not without limitations, however. Substrates **20**-**22** having no phenyl substituents failed to react with $CHFBr_2$ (Scheme 3).

Modifications. Some key modifications of key fluoro-bicyclo[1.1.1]pentanes **5** and **12** were undertaken to show their high synthetic value (Scheme 4). Reduction of the ester group with $LiAlH_4$ in tetrahydrofuran at room temperature gave alcohol **23** in 92% yield. Reduction of C-F bond was not observed. Oxidation of the phenyl ring in **5** with $NaIO_4$/$RuCl_3$ (cat.) in acetonitrile-water-

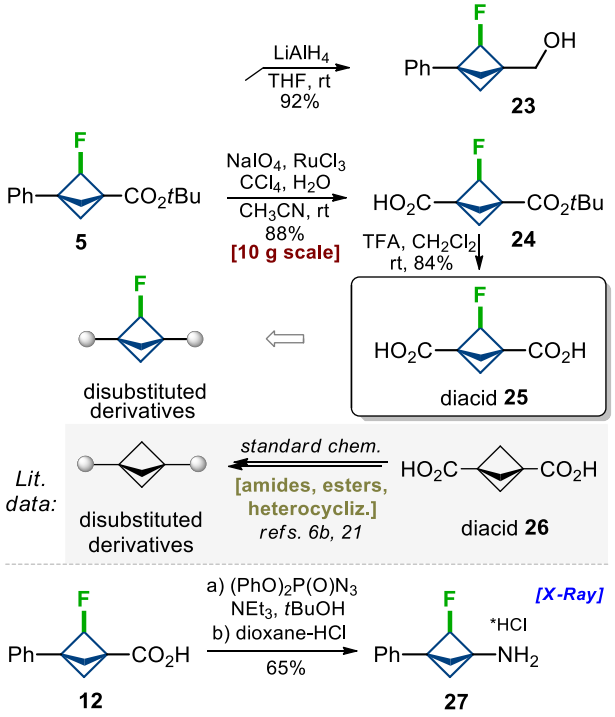


Scheme 3 Synthesis of various F-BCPs.

tetrachloromethane mixture gave monoacid **24** in 88% yield. The product was obtained in 10 g amount in one run. Cleavage of the *tert*-butyl ester with a catalytic amount of trifluoracetic acid in dichloromethane at room temperature gave diacid **25** in 84% yield. Both compounds **24** and **25** open a way to synthesize various mono- and bifunctional derivatives fluoro-bicyclo[1.1.1]pentanes by standard stepwise modifications of carboxylic groups: synthesis of amides, esters, heterocyclizations *etc*. This approach, for example, is commonly used to prepare bis-substituted derivatives of bicyclo[1.1.1]pentanes from diacid **26** and its monoesters (Scheme 4).[6b,21] Curtius reaction of acid **12** with $(PhO)_2P(O)N_3$/NEt_3 in *tert*-butanol gave, after acidic cleavage of *N*-Boc group in the intermediate, the final fluoroamine **27** as a hydrochloride salt in 65% yield. The structure of amine **27** was proven by X-Ray analysis.[20]

Stability. All acids **12**, **13c**-**19c**, **25**, alcohol **23,** and amine **27** were obtained as crystalline solids. We stored them at room temperature in closed vials on the shelf and did not observe any detectable decomposition according to ^{1}H NMR for at least three months.

Characterization. *Acidity/Basicity*. The incorporation of a fluorine atom into organic compounds could dramatically alter the acidity/basicity of the neighboring functional groups.[10] Therefore, to study the influence of the fluorine atom on the electronic properties of the bicyclo[1.1.1]pentane skeleton, we experimentally measured pK_a values of acids **28** and **12** and amine hydrochlorides **29** and **27** (Figure 3). Bridge-fluorination of acid **28** significantly increased its acidity from pK_a (**28**) = 4.2 to pK_a (**12**) = 3.5. On the other hand, bridge-fluorination of amine **29** reduced its basicity even more - by more than one order of magnitude: pK_a (**29***HCl) = 8.2 vs pK_a (**27***HCl) = 6.5. Because



Scheme 4. Chemical modifications of F-BCPs.

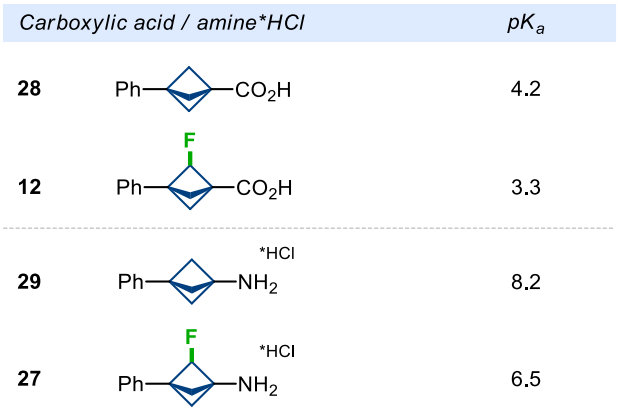


Figure 3. Experimental pK_a values of F-BCP carboxylic acids and amines.

basic nitrogen atoms could cause toxicity of bioactive compounds,[22] the incorporation of a fluorine atom at BCP-containing amines could be a solution here.

Lipophilicity. Fluorination is known also to affect the physicochemical properties of organic compounds, such as lipophilicity.[red] Therefore, we next calculated lipophilicity as measured by logP index of model BCP-compounds **9**, **30**, and isomeric aromatic compounds **31**, **32** (Figure 4).[23] Incorporation of a fluorine atom into the bicyclo[1.1.1]pentane slightly decreased lipophilicity, clogP: 3.5 (**30**) vs 3.3 (**9**) (Table 3). On the other hand, lipophilicity of F-BCP scaffold was almost 2 orders of magnitude lower than that of F-Ph, clogP: 3.3 (**9**) *vs* 4.9 (**31**) *vs* 5.4 (**32**).

In a short summary, bridge-fluorination of bicyclo[1.1.1]-pentane seems to slightly decrease its lipophilicity (clogP). While the replacement of the fluorophenyl ring (**31**, **32**) with fluoro-bicyclo[1.1.1]pentane (**9**) dramatically reduced lipophilicity (clogP) by almost two orders of magnitude, which might be beneficially used in medicinal chemistry programs.

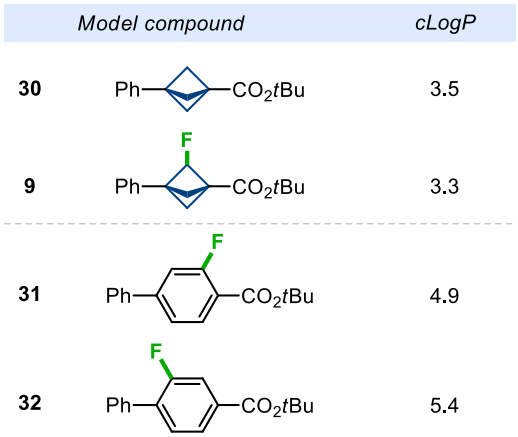
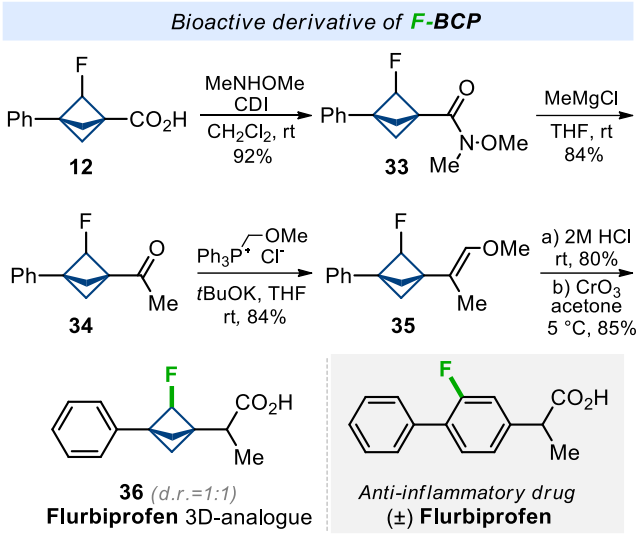


Figure 4. Calculated lipophilicity (cLogP) for compounds **9**, **30**-**32**.

Applications. To demonstrate a practical utility of F-BCP scaffold, we incorporated it into the structure of Flurbiprofen, a commercialized nonsteroidal anti-inflammatory drug, instead of fluorophenyl core (Scheme 5). Worth noting, that Flurbiprofen is used in practice as a racemic mixture. The synthesis started from carboxylic acid **12**. Weinreb amide **33** was easily obtained in one step in 92% yield. Treatment of the latter with MeMgCl gave ketone **34** in 84% yield. Wittig reaction of the keto group with (Ph_3PCH_2OMe)Cl in tetrahydrofuran in the presence of KO*t*Bu gave alkene **35**. Acidic hydrolysis of the vinyl ether moiety followed by oxidation of the intermediate aldehyde with CrO_3 gave the needed acid **36** as a non-separable mixture of two stereoisomers. Compounds **36** can be viewed as 3D-shaped saturated analogue of Flurbiprofen.



Scheme 5. Synthesis of F-BCP **36** – a saturated analogue of a nonsteroidal anti-inflammatory drug Flurbiprofen.

Summary. Since the pioneering work of Stepan and colleagues ten years ago,[2] bicyclo[1.1.1]pentanes (BCPs) have become extremely popular in chemistry (Figure 2). At least 6 reviews, 250 research manuscripts, 300 patents are devoted to them.[3-8] Different research groups, including ours, tried to selectively incorporate a single fluorine atom into the bridge-position of bicyclo[1.1.1]pentane for more than 20 years. Here, we finally solved this long-standing problem: a practical scalable method to fluoro-bicyclo[1.1.1]pentanes (^{19}F-BCP) has been developed. Crystallographic analysis of the obtained compounds was performed, and their physico-chemical properties have been studied. Finally, ^{19}F-BCP core was incorporated into the structure of the nonsteroidal anti-inflammatory drug Flurbiprofen, instead of the fluorophenyl core.

We believe that with a practical scalable protocol, ^{19}F-BCPs will soon find a solid practical application in medicinal chemistry[7a] and supramolecular chemistry.[7b]

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Keywords: bicyclo[1.1.1]pentane • BCP • fluorine • bicyclo[1.1.0]butane • bioisosteres

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