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Efficient synthesis of 5-fluoroalkylated 1*H*-1,2,3-triazoles and application of the bromodifluoromethylated triazole to the synthesis of novel bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds

Weimin Peng and Shizheng Zhu*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

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Abstract—A series of 5-fluoroalkylated 1*H*-1,2,3-triazoles were synthesized in good yield by the regiospecific 1,3-dipolar cycloaddition reaction of (*Z*)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylates with aryl or benzyl azides. In the cases of benzyl azides, addition of Na_2CO_3 was crucial for a high yield of the triazoles. Tetrakis(dimethylamino)ethylene (TDAE) promoted reaction of bromodifluoro-methylated triazole with aldehydes affording a new class of β,β-difluoro-β-triazolyl alcohol derivatives, which were lactonized with catalytic amount of *p*-toluenesulfonic acid in toluene at 80–90°C to give a series of novel bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds in good yield. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Up to now, no natural products containing 1*H*-1,2,3-triazole heterocycle moiety have been isolated because it is difficult for biochemical systems to produce molecules with three vicinal nitrogen atoms in a cyclic arrangement.[1] However, the multifunctional 1*H*-1,2,3-triazoles and benzotriazoles (Fig. 1) have found numerous applications[2] in organic synthesis,[3] as well as in medicine and industry as biologically active systems,[4] dyestuffs[5] and fluorescent compounds,[6] corrosion inhibitors,[7] photostabilizers[8] and agrochemicals.[9]

One of the two well established approaches to 1*H*-1,2,3-triazoles is through the 1,3-dipolar cycloaddition reaction of a wide variety of organic azides with acetylenic compound (Fig. 2a),[1,2]which are poorly or moderately regioselective, and two regioisomers are normally obtained.[10] By contrast, another powerful methodology is through the regioselective reaction of azides with 'push–pull' alkenes with a leaving group (LG) at one side of the double bond (Fig. 2b).[11] We had interest in the synthesis of fluorine-containing 1*H*-1,2,3-triazoles and *gem*-difluorinated benzotriazole analogues since fluorine in those compounds might impart profound influences on their chemical, physical and biological properties.[12] Although several trifluoromethylated starting materials have been reported to react with phenyl or benzyl azides,[13] there are no general methods to the synthesis of fluoroalkylated 1*H*-1,2,3-triazoles, especially the halogeno-difluoromethylated 1*H*-1,2,3-triazoles. In an earlier report,[14] we demonstrated the facile synthesis of (*Z*)-ethyl 3-fluoro-alkyl-3-pyrrolidino-acrylate and its reaction with nitrile oxide to prepare a series of 5-fluoroalkyl substituted isoxazoles in high yield. Herein, we wish to report its regiospecific reaction with aryl azide and benzyl azide in the synthesis of 5-fluoroalkyl 1*H*-1,2,3-triazoles, especially the halogeno-difluoromethylated 1*H*-1,2,3-triazoles, under the thermal and solvent free condition which is very amiable to the environment and highly economic. There has been an increasing interest in the synthesis of new *gem*-difluorinated compounds in view of the potential biological properties of such molecules.[15] For the anticipation of the high reactivity of the resulting halogeno-difluoromethylated 1*H*-1,2,3-triazole in the single electron transfer (SET) reaction,[16] we further employed them in reactions with aldehydes, using tetrakis(dimethylamino)ethylene (TDAE) as SET reaction initiator, to prepare a new class of β,β-difluoro-β-triazolyl alcohol derivatives. The hydroxy group of these alcohols was readily lactonized with the ester group attached at 4-position of triazole cycle by treatment with catalytic amount of *p*-toluenesulfonic acid in toluene at 80–90°C, to give a series of novel benzotriazole analogues

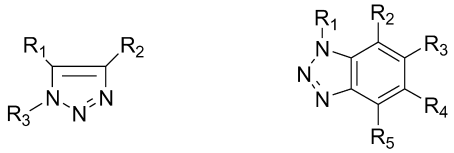

Figure 1.

Keywords: acrylates; 1,3-dipolar cycloaddition; fluoroalkylated 1*H*-1,2,3-triazole; tetrakis-(dimethylamino)ethylene; *gem*-difluorinated compounds.

* Corresponding author. Tel.: +86-21-64163300-3525; fax: +86-21-64166128; e-mail: zhusz@pub.sioc.ac.cn

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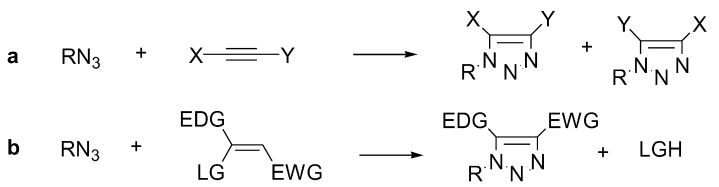
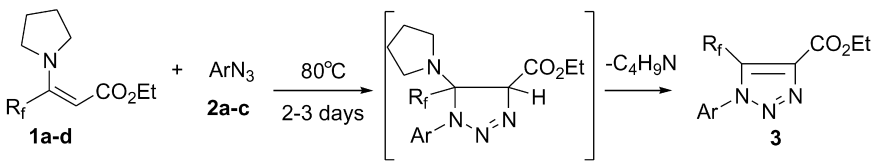


Figure 2. The synthetic strategy of 1*H*-1,2,3-triazoles.

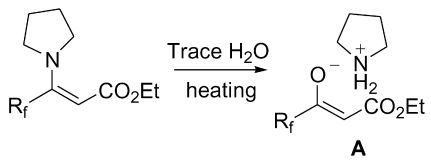


Scheme 1.

Table 1. Synthesis of 1-aryl-5-fluoroalkyl-1*H*-1,2,3-triazoles **3**

Entry	Acrylate	Azide	Temperature (°C)	Time (d)	Product (%)[a]
1	**1a**	**2a**	78	2	**3aa** (84)
2	**1b**	**2a**	78	2.5	**3ba** (79)
3	**1c**	**2a**	78	2	**3ca** (76)
4	**1a**	**2b**	78	2	**3ab** (79)
5	**1a**	**2c**	86	1.5	**3ac** (97)
6	**1c**	**2b**	78	1	**3cb** (66)
7	**1c**	**2c**	78	1.5	**3cc** (89)
8	**1d**	**2a**	78	9	**3da** (92)

[a] Isolated yield.



Scheme 2.

and *gem*-difluorinated bicyclic 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds.

2. Results and discussion

2.1. Preparation of 5-fluoroalkylated 1*H*-1,2,3-triazoles

2.1.1. Through the reaction of acrylate 1 with aryl azide 2. The synthesis of 1-arylated 5-fluoroalkyl-1*H*-1,2,3-triazole was achieved by a very simple procedure. After heating a mixture of (*Z*)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylate **1** and excess aryl azides **2** at 80°C for 2–3 days, the TLC analysis and ^{19}F NMR spectroscopy showed that the acrylate had converted completely, flash chromatography of the reaction mixture afforded the expected 1*H*-1,2,3-triazoles **3** in high yield (Scheme 1 and Table 1). Although the reaction of acrylate **1d** with phenyl azide **2a** (Table 1, entry 8) needed prolonged heating time (more than one week) due to the steric hindrance and the greater electron-withdrawing nature of long chain fluoroalkyl group ($ClCF_2$-CF_2CF_2–),[17] the yield was not diminished.

The economically and environmentally benign solvent free conditions, which could also raise reaction rate vigorously,[18] were crucial for the efficiency of the synthesis. When tried in refluxing benzene, chloroform and carbon tetrachloride, this reaction did not occur, but the acrylate became partially hydrated as shown by ^{19}F NMR spectroscopy and TLC analysis of the reaction mixture (Scheme 2).[19] When tried in toluene and *p*-oxylene, the formation of triazole could be detected, however the reaction was too slow and the acrylate hydrated vigorous. By contrast, the reaction under heating without solvent was

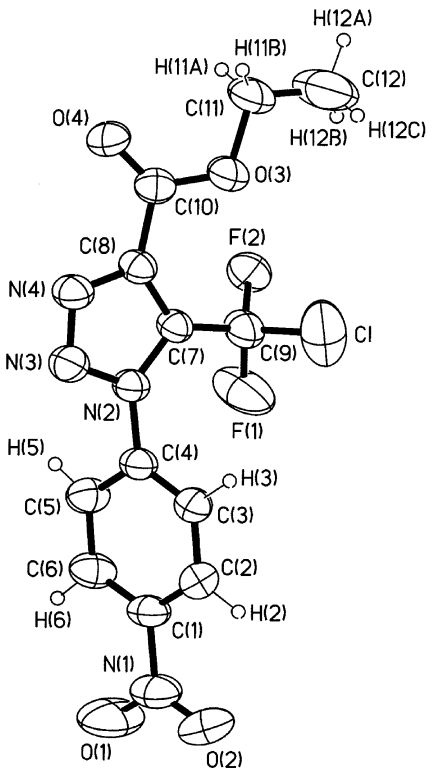
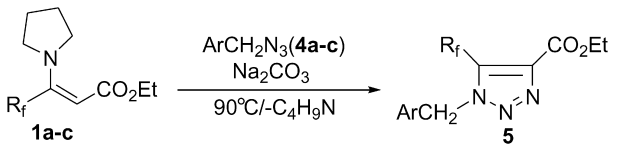


Figure 3. Molecular structure of compound **3ac**.



Scheme 3.

Table 2. Synthesis of 1-benzyl-5-fluoroalkylated 1*H*-1,2,3-triazoles **5**

Entry	Acrylate	Azide	Temperature (°C)	Time (d)	Product (%)[a]
1	**1a**	**4a**	90	4	**5aa** (88)
2	**1a**	**4b**	90	5	**5ab** (88)
3	**1c**	**4a**	95	3	**5ca** (85)
4	**1a**	**4c**	Toluene/reflux[b]	10	**5ac** (66)
5	**1b**	**4a**	85	5	**5ba** (32)[c]

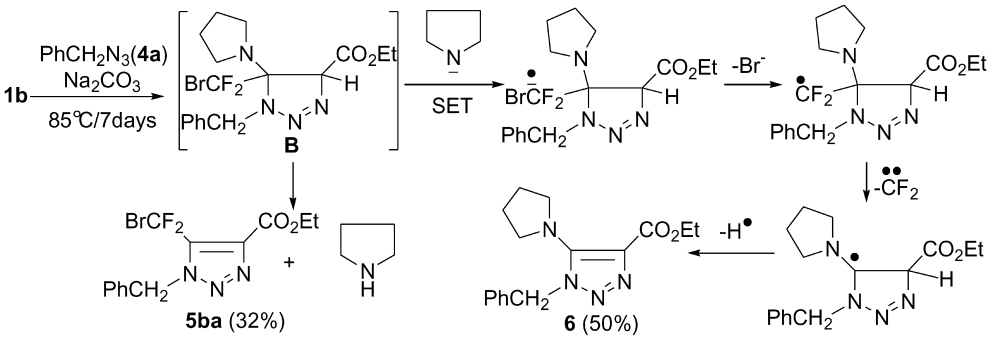
[a] Isolated yield.
[b] Using toluene as solvent, due to reaction mixture solidifying during heating without solvent.
[c] Yield was low due to defluorination.

smooth and no hydrolysis of the acrylates was detected. Furthermore, it was found that this reaction was regiospecific without the formation of 4-fluoroalkylated regioisomer. The regiochemistry obtained was unambiguously confirmed by the X-ray diffraction of triazole **3ac**, showing the fluoroalkyl group at the triazole 5-position (Fig. 3). It was noteworthy that pyrrolidino group plays two important roles in the course of the reaction: (1) acting as a electron-donating group (EDG) to completely control the regioselectivity in the initial 1,3-dipolar cycloaddition reaction of the acrylate with azide;[20] (2) acting as a leaving group (LG) to prevent the triazoline intermediate from decomposing, by ready extrusion of pyrrolidine.[21]

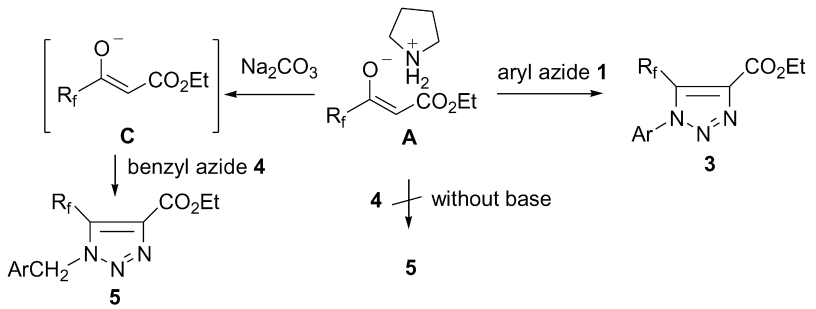
2.1.2. Through the reaction of acrylate 1 with benzyl azide 4. Compared to its reaction with aryl azides, there were some differences in the reaction of fluoroalkylated acrylate **1** with benzyl azide **4**: (1) addition of 1–2 equimolar Na_2CO_3 was necessary for a high yield of the triazole (Scheme 3). About half of the acrylate hydrated and some unknown by-products appeared in the absence of Na_2CO_3; (2) higher temperature for thermolysis was needed to raise the reaction rate (90–100°C); (3) reaction time doubled albeit under this more forcing conditions. The results of reaction of benzyl azide **4** with acrylate **1** are summarized in Table 2.

The reaction of acrylate **1b** with benzyl azide **4a** gave the expected 5-bromodifluoromethylated triazole **5ba** in low yield (Table 2, entry 5) along with a defluorinated product **6** in 50% yield (Scheme 4). A pyrrolidine anion promoted defluorination mechanism is proposed to explain the formation of the defluorination products. Substantial amount of pyrrolidine is producing during the formation of the triazole, under the effect of Na_2CO_3, a pyrrolidine anion could acted as a single electron donor to transfer an electron to the bromodifluoromethyl group of the intermediated triazoline **B**, because bromodifluoromethyl is a better single electron acceptor than other fluoroalkyl groups.[22] The triazoline intermediate successively loss a bromide anion, difluoromethene carbene, and β-hydrogen to give the unexpected defluorination triazole **6**.[23]

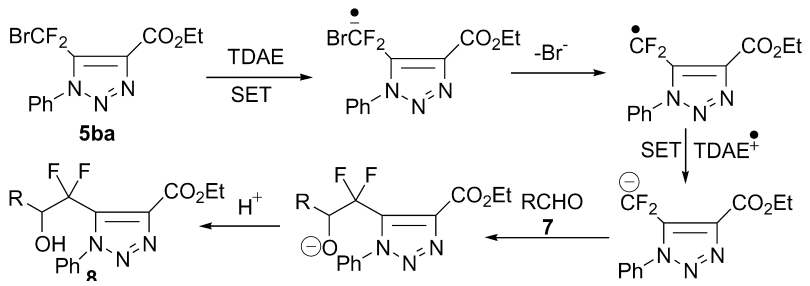
Due to the fact that Na_2CO_3 was unnecessary in the reaction of aryl azides **2** with acrylates **1**, the mechanism shown in Scheme 5 was proposed to explain the function of Na_2CO_3. Through heating, some of the acrylate could react with both benzyl and aryl azide to give the expected corresponding triazoles **3** and **5**. However, some of acrylate hydrated to produce **A** (shown in Schemes 2 and 5) in both cases.



Scheme 4.

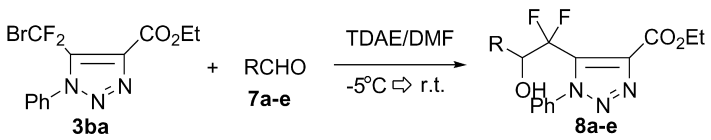


Scheme 5.



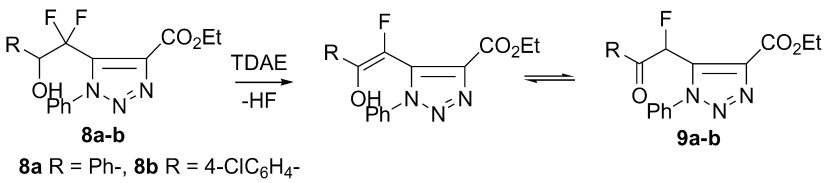
Scheme 6.

Table 3. The reaction of triazole **3ba** with aldehydes **7**



Entry	Aldehyde	Time at −5°C (h)	Time at room temperature (h)	Product (%)[a]
1	**7a** R=Ph	1	17	**8a** (68)[b]
2	**7b** R=4-ClC_6H_4–	3	6	**8b** (55)[b]
3	**7c** R=4-MeOC_6H_4–	2	5	**8c** (62)
4	**7d** R=*trans*-CH_3CH=CH–	3	13	**8d** (65)
5	**7e** R=$PhCH_2CH_2$–	2	7	**8e** (28)[c]

[a] Isolated yield.
[b] The further dehydrofluorinated products **9a** and **9b** (Scheme 7) were also obtained in 13 and 18% yield, respectively.
[c] The reaction was not clean, although the product was obtained in poor yield.



Scheme 7.

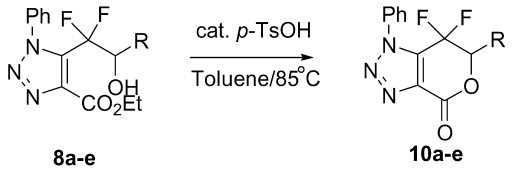
Because aryl azide is more reactive than benzyl azide, it could react directly with hydration product **A** to afford the triazoles **3**, while the benzyl azide only reacts with anion intermediate **C**, produced from the reaction of **A** and Na_2CO_3, to give the expected triazole **5** (Scheme 5).[24]

2.2. Preparation of the β,β-difluoro-β-triazolyl alcohol derivatives

It is well known that halogeno-difluoromethyl, especially bromodifluoromethyl, is an excellent electron acceptor in the SET reaction and the formed difluoromethyl anion is strongly nuleophilic to aldehydes and other electrophiles.[25] With the halogeno-difluoromethylated triazoles in hand, we explored their reactions with aldehydes promoted by SET initiators. It was found that the procedure developed by Dolbier Jr. et al. using tetrakis(dimethylamino)ethylene (TDAE) as initiator could be successfully applied to our system.[26] In the presence of TDAE, the bromodifluoromethyl triazole **3ba** reacted with aldehyde in DMF at −5°C to room temperature to give the β,β-difluoro-β-triazolylated alcohol derivatives in satisfactory yield, along with an amount of the reduced product formed by protonation of the difluoromethyl anion (shown in Scheme 6). The reaction results and a plausible reaction mechanism are shown in Table 3 and Scheme 6, respectively.

The reaction with aromatic and α,β unsaturated aldehydes generally afforded the expected *gem*-difluorinated alcohol derivatives in satisfactory yield (Table 3, entries 1–4). However, the reaction with 1-phenyl-propaldehyde was not clean, the alcohol **8e** was obtained in poor yield (Table 3, entry 5) possibly due to the enolizable potential of this aldehyde. The chlorodifluoromethyl substituted triazole **3aa** was inert to TDAE under the same reaction conditions, which might be attributed to the higher reduction potential of chlorodifluoromethyl. Raising reaction temperature was not effective, only a small amount of the substrate reacted and only trace product was detected by TLC analysis after heating for 8 h at 90°C. It was noteworthy that in addition to the desired difluorinated alcohols **8a** and **8b**, their further TDAE mediated dehydrofluorination products **9a** and **9b**

Table 4. Synthesis of the bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*]-[1,2,3]-triazol- 4-one compounds **10**



8a-e **10a-e**

Entry	Alcohol	Reaction time	Product (%)[a]
1	**8a** R=Ph–	**72h**	**10a** (68)
2	**8b** R=4-ClC_6H_4–	**5d**	**10b** (68)
3	**8c** R=4-$MeOC_6H_4$–	**72h**	**10c** (41)
4	**8d** R=*trans*-CH_3CH=CH–	**5d**	**10d** (94)
5	**8e** R=Ph$(CH_2)_2$–	**4d**	**10e** (87)

[a] Isolated yield.

(Scheme 7) were also obtained in 13 and 18% yield (Table 3, entries 1 and 2), respectively. These two products were well characterized by spectroscopy and macroanalysis.

2.3. Synthesis of the bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds

Cyclization of β,β-difluoro-β-triazolylated alcohol derivatives **8** could be smoothly achieved by simple treatment of the alcohol with catalytic *p*-toluenesulfonic acid in toluene at 85°C.[27] After 3–5 days heating, evaporation of solvent under reduced pressure followed by flash chromatography afforded the *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds in good yield (Table 4), except alcohol **8c** (R=4-$MeOC_6H_4$–) which gave the compound **10c** in moderate yield. We anticipated that these *gem*-difluorinated benzotriazole analogous compounds potentially might have biological activities. The work to evaluate their bioactivity is now in progress and will be reported in due course.

3. Conclusions

A general and efficient procedure to synthesize the 5-fluoroalkylated (especially the halogeno-difluoromethylated) 1*H*-1,2,3-triazoles by the regiospecific 1,3-dipolar cycloaddition reaction of (*Z*)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylate with organic azides was described. Via the further reaction of the bromodifluomethylated triazoles with aldehydes, mediated by TDAE, a new class of β,β-difluoro-β-triazolylated alcohol derivatives were conveniently prepared. These alcohols were smoothly cyclized by treatment with catalytic *p*-TsOH in toluene, to give the novel *gem*-difluorinated bicyclic 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds in good to excellent yields.

4. Experimental

4.1. General methods

Unless otherwise noted, solvents and reagents were commercial available and used as received. DMF was distillated from calcium hydride, and toluene from P_2O_5. All the aryl and benzyl azides were prepared according to the references.[28] The preparation of (*Z*)-ethyl 3-fluoroalkyl-3-pyrrolidino-acrylate **1** was previously reported in this journal.[14] IR spectra were obtained with a Perkin-Elmer 983G spectro-photometer on KBr disks. NMR spectra were recorded either on Varian-360L, or Bruker AM-300 spectrometer with $CDCl_3$ as solvent, unless otherwise stated. The ^{1}H NMR chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard tetramethylsilane (TMS). In ^{19}F NMR spectra, upfield shifts from external standards ($CFCl_3$) are quoted as negative. Coupling constants are given in Hertz (Hz). Spectra splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were taken on a HP 5989a spectrometer, and accurate mass measurements were performed on Finngan MAT instrument, while elemental analyses were performed by this institute. TLC analysis was performed on silica gel plate and column chromatography over silica gel (30–40 μm), which were both obtained from Qingdao Ocean Chemicals.

4.2. Preparation of 5-fluoroalkylated 1*H*-1,2,3-triazoles 3 and 5 through the reaction of acrylate 1 with aryl azide 2 (general procedure)

(*Z*)-Ethyl 3-fluoroalkyl-3-pyrrolidino-acrylate **1** (1 mmol) was added to about 1 mL liquid aryl azide **2**, the mixture was heated at about 80°C for the time specified in Table 1 to convert the acrylate **1** completely. Then without work-up, direct flash chromatography of the reaction mixture using *n*-hexane/EtOAc as eluent gave 5-fluoroalkylated 1*H*-1,2,3-triazoles **3**, in addition to recovery of excess aryl azide.

4.2.1. 5-Chlorodifluoromethyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3aa). Through the general procedure starting from acrylate **1a** and phenyl azide **2a**, flash chromatography using *n*-hexane/EtOAc (20:1 followed by 10:1) as eluent afforded triazole **3aa** (253 mg, 84%) as a yellow solid, mp 69.5–70.5°C. [Found: C, 47.80; H, 3.35; N, 14.24. $C_{12}H_{10}ClF_2N_3O_2$ requires C, 47.78; H, 3.34; N, 13.93%]; ν_{max} (film) 2982, 1723, 1593, 1560, 1497, 1375, 1296, 1254, 1238, 1153, 1094, 1058, 1008, 906, 771 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.47 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 4.52 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.34–7.74 (5H, m, Ph); δ_F (56.4 MHz, $CDCl_3$) −44.5; *m/z* (EI) 302/304 (10/3, M^++1), 256/258 (12/4), 245/247 (10/3), 189 (42), 170 (33), 144 (19), 77 (100%, Ph^+).

4.2.2. 5-Bromodifluoromethyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3ba). Through the general procedure starting from acrylate **1b** and phenyl azide **2a**, flash chromatography using *n*-hexane/EtOAc (20:1 followed by 10:1) as eluent afforded triazole **3ba** (273 mg, 79%) as a pale yellow solid, mp 72.5–73.0°C. [Found: C, 41.73; H, 3.05; N, 12.15. $C_{12}H_{10}BrF_2N_3O_2$ requires C, 41.64; H, 2.91; N, 12.14%]; ν_{max} (film) 2982, 1722, 1592, 1559, 1497, 1253, 1229, 1153, 1055, 1019, 1007, 930, 770 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.49 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 4.50 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.38–7.76 (5H, m, Ph). δ_F (56.4 MHz, $CDCl_3$) −41.3; *m/z* (EI) 346/348 (30/28, M^+), 300/302 (10/10), 266 (4), 244/246 (24/23), 222/224 (6/5), 190 (30), 170 (54), 77 (100%, Ph^+).

4.2.3. 5-Trifluoromethyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3ca). Through the general procedure starting from acrylate **1c** and phenyl azide **2a**, flash chromatography using *n*-hexane/EtOAc (20:1 followed by 15:1) as eluent afforded triazole **3ca** (216 mg, 76%) as a clear oil; ν_{max} (film) 2984, 1738, 1594, 1558, 1499, 1301, 1232, 1161, 1089, 1041, 1007, 797, 771 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.47 (3H, t, J=7.5 Hz, OCH_2CH_3), 4.55 (2H, q, J=7.5 Hz, OCH_2CH_3), 7.35–7.78 (5H, m, Ph); δ_F (56.4 MHz, $CDCl_3$) −54.5; *m/z* (EI) 286 (31, M^++1), 240 (18), 212 (21), 189 (100, M^+−Ph−F), 185 (25), 165 (49), 77 (78), 69 (6), 51 (29%); HRMS (EI): M^+, found 285.07683. $C_{12}H_{10}^{9}F_3N_3O_2$ requires 285.07251.

4.2.4. 5-Chlorodifluoromethyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3ab). Through the general procedure starting from acrylate **1a** and 4-methoxyphenyl azide **2b**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 5:1) as eluent afforded triazole **3ab** (262 mg, 79%) as a brown oil. [Found: C, 47.19; H, 3.88; N, 12.63. $C_{13}H_{12}ClF_2N_3O_3$ requires C, 47.07; H, 3.65; N, 12.67%]; ν_{max} (film) 2938, 1736, 1607, 1589, 1514, 1456, 1305, 1176, 1114, 840, 792 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.61 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.07 (3H, s, O*Me*), 4.67 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.21 (2H, B of AB-system, J=9.0 Hz, Ar*H*), 7.58 (2H, A of AB-system, J=9.0 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −44.7; *m/z* (EI) 332/334 (42/14, M^+), 286/288 (13/5), 258/260 (21/8), 219 (100, M^+−$ClCF_2$−N_2), 200 (80), 180 (26), 77 (16%).

4.2.5. 5-Chlorodifluoromethyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3ac). Through the general procedure starting from acrylate **1a** and 4-nitrophenyl azide **2c**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 5:1) as eluent afforded triazole **3ac** (336 mg, 97%) as a pale white solid, mp 123.5–125.0°C. [Found: C, 41.78; H, 2.58; N, 16.37. $C_{12}H_9ClF_2N_4O_4$ requires C, 41.58; H, 2.62; N, 16.16%]; ν_{max} (film) 2997, 1732, 1611, 1596, 1524, 1500, 1350, 1250, 1221, 1049, 855, 790 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.48 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.55 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.81 (2H, B of AB-system, J=9.0 Hz, Ar*H*), 7.99 (2H, A of AB-system, J=9.0 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −44.1; *m/z* (EI) 346/348 (5/2, M^+), 301/303 (19/6), 290/292 (69/23) 274/276 (5/3), 189 (79), 165 (40), 85/87 (57/33), 76 (100%, Ph^+−1).

4.2.6. 5-Trifluoromethyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3cb). Through the general procedure starting from acrylate **1c** and 4-methoxyphenyl azide **2b**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 4:1) as eluent afforded triazole **3cb** (208 mg, 66%) as a pale white solid, mp 82.0–83.0°C. [Found: C, 49.52; H, 3.91; N, 13.45. $C_{13}H_8F_3N_3O_3$ requires C, 49.53; H, 3.84; N, 13.33%]; ν_{max} (film) 2989, 1738, 1607, 1592, 1518, 1458, 1374, 1352, 1256, 1239, 1195, 1180, 1140, 1082, 1035, 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.48 (3H, t, J=7.2 Hz, OCH_2CH_3), 3.93 (3H, s, OMe), 4.54 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.08 (2H, B of AB-system, J=8.7 Hz, Ar*H*), 7.41 (2H, A of AB-system, J=8.7 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −55.6; *m/z* (EI) 315 (29, M^+), 242 (25), 219 (100, M^+−OMe−OEt−F), 176 (13), 77 (16), 69 (7%).

4.2.7. 5-Trifluoromethyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3cc). Through the general procedure starting from acrylate **1c** and 4-nitrophenyl azide **2c**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 5:1) as eluent afforded triazole **3cc** (294 mg, 89%) as a yellow solid, mp 120.0–122.0°C. [Found: C, 43.57; H, 2.83; N, 17.12. $C_{12}H_9F_3N_4O_4$ requires C, 43.65; H, 2.75; N, 16.97%]; ν_{max} (film) 3094, 2991, 1741, 1615, 1598, 1561, 1528, 1503, 1450, 1352, 1303, 1226, 1153, 1085, 856 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.49 (3H, t, J=7.2 Hz, OCH_2CH), 4.55 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.77 (2H, B of AB-system, J=8.7 Hz, Ar*H*), 8.51 (2H, A of AB-system, J=8.7 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −53.8; *m/z* (EI) 330 (14, M^+), 302 (1), 285 (32), 257 (19), 234 (100, M^+−CF_3−OEt+2), 122 (26), 76 (36), 69 (7%).

4.2.8. 5-(3-Chloro-1,1,2,2,3,3-hexafluoropropyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (3da). Through the general procedure starting from acrylate **1d** and phenyl azide **2a**, flash chromatography using *n*-hexane/EtOAc (20:1 followed by 10:1) as eluent afforded triazole **3da** (369 mg, 92%) as a colorless oil. [Found: C, 42.07; H, 2.71; N, 10.68. $C_{14}H_{10}ClF_6N_3O_2$ requires C, 41.86; H, 2.51; N, 10.46%]; ν_{max} (film) 2984, 1739, 1593, 1541, 1496, 1374, 1297, 1223, 1192, 1153, 1219, 1085, 988, 774, 613 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.45 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.50 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.87–8.11 (5H, m, Ph); δ_F (56.4 MHz, $CDCl_3$) −117.0 (2F, s), −101.8 (2F, s), −66.5 (2F, s); *m/z* (EI) 401 (1, M^+), 356/358 (5/1), 328/330 (5/1), 265 (6), 215 (6), 166 (88), 144 (23), 77 (100%, Ph^+).

4.3. Preparation of 5-fluoroalkylated 1*H*-1,2,3-triazoles 3 and 5 through the reaction of acrylate 1 with benzyl azide 4 (general procedure)

Into a mixture of Na_2CO_3 (120 mg, 1.1 mmol) and about 1 mL benzyl azide **4**, was added (*Z*) ethyl 3-fluoroalkyl-3-pyrrolidino-acrylate **1** (1 mmol). The resultant mixture was heated at about 90°C for the time specified in Table 2 to convert the acrylate **1** completely. The reaction mixture was filtered, the solid was washed with CH_2Cl_2 (5 mL×3). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography using *n*-hexane/ EtOAc as eluent to give 5-fluoroalkylated 1*H*-1,2,3-triazoles **5**, in addition to recovery of excess benzyl azide **4**.

4.3.1. 5-Chlorodifluoromethyl-1-benzyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (5aa). Through the general procedure starting from acrylate **1a** and benzyl azide **4a**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 5:1) as eluent afforded triazole **5aa** (278 mg, 88%) as a slightly yellow solid, mp 58.0–59.5°C. [Found: C, 49.61; H, 3.67; N, 13.59. $C_{13}H_{12}ClF_2N_3O_2$ requires C, 49.46; H, 3.83; N, 13.31%]; ν_{max} (film) 2988, 1738, 1634, 1465, 1332, 1262, 1241, 1209, 1130, 1065, 1043, 921, 793, 731, 696 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.48 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.54 (2H, q, J=7.2 Hz, OCH_2CH_3), 5.80 (2H, s, CH_2Ar), 7.10–7.59 (5H, m, Ph); δ_F (56.4 MHz, $CDCl_3$) −44.8; *m/z* (EI) 316/318 (5/1, M^+), 286/288 (2/1), 270/272 (7/2), 258/260 (2/1), 243/245 (10/3), 214/216 (22/8), 91 (100%, $PhCH_2^+$).

4.3.2. 5-Chlorodifluoromethyl-1-[(4-methoxyphenyl)-methyl]-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (5ab). Through the general procedure starting from acrylate **1a** and 4-methoxybenzyl azide **4b**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 4:1) as eluent afforded triazole **5ab** (304 mg, 88%) as a slightly yellow oil. [Found: C, 48.45; H, 4.06; N, 12.25. $C_{14}H_{14}ClF_2N_3O_3$ requires C, 48.64; H, 4.08; N, 12.15%]; ν_{max} (film) 2981, 2937, 2906, 1738, 1610, 1585, 1544, 1511, 1464, 1370, 1335, 1305, 1295, 1251, 1202, 1178, 1117, 1066, 1045, 845 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.48 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 3.86 (3H, s, O*Me*), 4.55 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.79 (2H, s, CH_2Ar), 6.95 (2H, B of AB-system, *J*=8.1 Hz, Ar*H*), 7.32 (2H, A of AB-system, *J*=8.1 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −45.8; *m/z* (EI) 345/347 (3/1, M^+), 316 (1), 282 (1), 252 (1), 121 (100, 4-methoxy $PhCH_2^+$), 91 (7), 77 (14%).

4.3.3. 5-Trifluoromethyl-1-benzyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (5ca). Through the general procedure starting from acrylate **1c** and benzyl azide **4a**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 7:1) as eluent afforded triazole **5ca** (254 mg, 85%) as a brown oil. [Found: C, 52.36; H, 4.20; N, 14.04. $C_{13}H_{12}F_3N_3O_2$ requires C, 52.18; H, 4.04; N, 14.04%]; ν_{max} (film) 2984, 1737, 1602, 1553, 1495, 1454, 1435, 1342, 1217, 1162, 1126, 751, 728, 694 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.42 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.46 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.77 (2H, s, CH_2Ar), 7.22–7.37 (5H, m, Ph); δ_F (282 MHz, $CDCl_3$) −56.2; *m/z* (EI) 270 (1, M^+), 254 (2), 242 (2), 222 (2), 198 (13), 91 (100, $PhCH_2^+$), 77 (5).

4.3.4. 5-Chlorodifluoromethyl-1-[(4-nitrophenyl)-methyl]-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (5ac). Into a solution of (*Z*) ethyl 3-chlorodifluoromethyl-3-pyrrolidino-acrylate **1a** (167 mg, 0.66 mmol) and 4-nitrobenzyl azide **4c** (800 mg, 4.5 mmol) in 10 mL toluene, was added Na_2CO_3 (120 mg, 1.1 mmol), the mixture was refluxed for 10 days. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Following flash chromatography using *n*-hexane/EtOAc (5:1 followed by 2:1) as eluent afforded triazole **5ac** (156 mg, 0.44 mmol, 66%) as a slightly yellow solid, mp 113.5–115.0°C. [Found: C, 43.23; H, 3.01; N, 15.81. $C_{13}H_{11}ClF_2N_4O_4$ requires C, 43.29; H, 3.07; N, 15.53%]; ν_{max} (film) 2982, 1733, 1607, 1558, 1525, 1471, 1433, 1371, 1347, 1317, 1299, 1264, 1250, 1211, 1107, 847, 731 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.40 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.51 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.92 (2H, s, CH_2Ar), 7.39 (2H, B of AB-system, *J*=8.0 Hz, Ar*H*), 8.17 (2H, A of AB-system, *J*=8.0 Hz, Ar*H*); δ_F (56.4 MHz, $CDCl_3$) −46.5; *m/z* (EI) 331 (1), 315/317 (38/12), 297 (48), 288/290 (100/34, M^+-CO_2Et), 136 (90), 91 (8), 78 (67%).

4.3.5. 5-Bromodifluoromethyl-1-benzyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (5ba) and 5-pyrrolidino-1-benzyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (6). Through the general procedure starting from acrylate **1b** and benzyl azide **4a**, flash chromatography using *n*-hexane/EtOAc (10:1 followed by 5:1) as eluent firstly afforded 5-bromodifluoromethylated 1*H*-1,2,3-triazole **5ba** (115 mg, 32%) as a yellow solid, mp 62.0–63.0°C; ν_{max} (film) 2991, 1736, 1564, 1467, 1334, 1263, 1210, 1128, 1042, 1015, 884, 790, 730 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.46 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.76 (2H, s, CH_2Ar), 7.24–7.38 (5H, m, Ph); δ_F (282 MHz, $CDCl_3$) −44.1; *m/z* (EI) 359/361 (1/1), 314/316 (2/2), 280 (8), 252 (5), 208 (34), 91 (100, $PhCH_2^+$), 77 (3), 65 (15), 51 (3%); HMRS (EI): M^+, found 359.01224. $C_{13}H_{12}^{79}Br^{19}F_2N_3O_2$ requires 359.00809. Subsequent chromatography using *n*-hexane/EtOAc (2:1) as eluent afforded the defluorination product **6** (150 mg, 50%) as brown oil. [Found: C, 64.25; H, 6.55; N, 18.19. $C_{16}H_{20}N_4O_2$ requires C, 63.98; H, 6.71; N, 18.65%]; ν_{max} (film) 3065, 3043, 2977, 2144, 1710, 1563, 1456, 1194, 1138, 1052, 847, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.41 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 1.88–1.93 (4H, m, $2\times NCH_2CH_2$), 3.13–3.17 (4H, m, $2\times NCH_2CH_2$), 4.40 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 5.47 (2H, s, CH_2Ar), 7.16–7.32 (5H, m, Ph); *m/z* (EI) 391 (42, M^++Bn), 301 (100, M^++1), 300 (9, M^+), 299 (65, M^+-1), 271 (43), 255 (61), 243 (5), 227 (12), 209 (48), 200 (17), 186 (8), 158 (4), 135 (20), 91 (90%); HRMS (EI): M^+, found 300.15869. $C_{16}H_{20}N_4O_2$ requires 300.15862.

4.4. Preparation of the β,β-difluoro-β-triazolyl alcohol derivatives 8 (general procedure)

Into a solution of triazole **3ba** (277 mg, 0.8 mmol) and aldehyde **7** (4 mmol) in 8 mL anhydrous DMF, cooled at ice-salt bath under nitrogen, was added TDAE (176 mg, 0.21 mL, 0.88 mmol) dropwise via a syringe over half an hour. A red color immediately developed with the formation of fine white precipitate. The mixture was further vigorously stirred for the time specified in Table 3 under cooling, and then warmed up to room temperature for the time specified also in Table 3. The orange red turbid solution was filtered and hydrolyzed with 8 mL saturated NH_4Cl solution, followed by extraction with ethyl acetate (3×20 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue which was purified by flash chromatograph using *n*-hexane/EtOAc as eluent to give the expected *gem*-difluoronated alcohols **8** as white solids.

4.4.1. 5-(1,1-Difluoro-2-hydroxy-2-phenyl-ethyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (8a) and 5-(1-fluoro-2-phenyl-2-oxo-ethyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (9a). Through the general procedure starting from triazole **3ba** and benzaldehyde **7a** (0.424 g, 4 mmol), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent firstly afforded product **9a** (37 mg, 13%) as a slightly brown heavy oil; ν_{max} (film) 3065, 2982, 2936, 1746, 1711, 1596, 1569, 1501, 1449, 1379, 1296, 1238, 1085, 1070, 1006, 850, 765, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.45 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.49–4.54 (2H, m), 7.27–7.69 (11H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −177.6 (d, *J*=45.1 Hz); *m/z* (EI) 353 (2, M^+), 308 (3), 296 (1), 280 (1), 252 (3), 232 (2), 204 (2), 172 (3), 144 (5), 105 (100, $PhCO^+$), 77 (50); HRMS (EI): M^+, found 353.12097. $C_{19}H_{16}FN_3O_3$ requires 353.11757. Then gave *gem*-difluorinated alcohol **8a** (203 mg, 68%) as a white powder, mp 146.0–148.0°C. [Found: C, 61.41; H, 4.78; N, 10.97. $C_{19}H_{17}F_2N_3O_3$ requires C, 61.12; H, 4.59; N, 11.25%]; ν_{max} (film) 3445, 3065, 2984, 1778, 1717, 1595, 1546, 1497, 1249, 1231, 1170, 1077, 1014, 766, 738, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.51 (3H, t, *J*=7.2 Hz,

OCH_2CH_3), 4.01 (1H, d, J=3.9 Hz, O*H*), 4.55 (2H, q, J=7.2 Hz, OCH_2CH_3), 5.63 (1H, ddd, J=12.7, 8.7, 3.9 Hz, C*H*OH), 6.89–7.49 (10H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −97.7 (1F, dd, J=273.0, 8.7 Hz), 102.9 (1F, dd, J=273.0, 12.7 Hz); m/z (EI) 373 (8, M^+), 353 (15), 328 (1), 300 (3), 281 (1), 104 (25), 77 (100, Ph^+), 51 (20%).

4.4.2. 5-[1,1-Difluoro-2-hydroxy-2-(4-chlorophenyl)-ethyl]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (8b) and 5-[1-fluoro-2-(4-chlorophenyl)-2-oxo-ethyl]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (9b). Through the general procedure starting from triazole **3ba** and 4-chlorobenzaldehyde **7b** (0.562 g, 4 mmol), flash chromatography using *n*-hexane/EtOAc (3:1 followed by 2:1) as eluent firstly afforded product **9b** (56 mg, 18%) as a slightly yellow heavy oil; ν_{max} (film) 3067, 2982, 1741, 1713, 1588, 1500, 1401, 1379, 1247, 1218, 1091, 1014, 764, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.46 (3H, t, J=6.9 Hz, OCH_2CH_3), 4.47–4.55 (2H, m, OCH_2CH_3), 7.27–7.70 (10H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −176.9 (d, J=45.1 Hz); m/z (EI) 387/389 (3/2, M^+), 342/344 (3/1), 286/288 (4/1), 249 (2), 220 (15), 192 (10), 139 (100, $ClC_6H_4CO^+$), 111 (24), 77 (73%); HRMS (EI): M^+, found 387.07922. $C_{19}H_{15}^{35}ClFN_3O_3$ requires 387.07859; Then gave *gem*-difluorinated alcohol **8b** (179 mg, 55%) as a white powder; mp 193.0–195.0°C. [Found: C, 55.97; H, 4.09; N, 10.21. $C_{19}H_{16}^{35}Cl^{19}F_2N_3O_3$ requires C, 55.96; H, 3.95; N, 10.30%]; ν_{max} (film) 3443, 2985, 1719, 1596, 1548, 1497, 1251, 1229, 1179, 1017, 774, 693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.31 (1H, d, J=4.2 Hz, O*H*), 4.54 (2H, q, J=7.2 Hz, OCH_2CH_3), 5.62 (1H, ddd, J=13.6, 6.8, 4.2 Hz, C*H*OH), 7.06–7.53 (9H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −94.5 (1F, dd, J=275.0, 6.8 Hz), 103.9 (1F, dd, J=275.0, 13.6 Hz); m/z (EI) 407/409 (1/1, M^+), 387/389 (13/4), 361/363 (12/3), 332/335 (8/2), 267 (25), 165 (96), 139 (17), 104 (24), 77 (100%, Ph^+).

4.4.3. 5-[1,1-Difluoro-2-hydroxy-2-(4-methoxyphenyl)-ethyl]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (8c). Through the general procedure starting from triazole **3ba** and 4-methoxybenzaldehyde **7c** (0.544 g, 4 mmol), flash chromatography using *n*-hexane/EtOAc (2:1) as eluent afforded the *gem*-difluorinated alcohol **8c** (200 mg, 62%) as a white powder, mp 170.0–172.0°C. [Found: C, 59.75; H, 4.87; N, 10.38. $C_{20}H^{19}F_2N_3O_4$ requires C, 59.55; H, 4.75; N, 10.42%]; ν_{max} (film) 3357, 3068, 3004, 2907, 1734, 1612, 1518, 1500, 1371, 1347, 1305, 1263, 1226, 1173, 1085, 1026, 793, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (3H, t, J=7.5 Hz, OCH_2CH_3), 3.81 (3H, s, OMe), 3.92 (1H, d, J=3.9 Hz, O*H*), 4.54 (2H, q, J=7.5 Hz, OCH_2CH_3), 5.57 (1H, ddd, J=13.1, 8.1, 3.9 Hz, C*H*OH), 6.81–7.50 (9H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −97.4 (1F, dd J=272.4, 8.1 Hz), 103.6 (1F, dd, J=272.4, 13.1 Hz); m/z (EI) 383 (14), 355 (43), 338 (2), 309 (3), 267 (43), 165 (100), 137 (65), 109 (29), 77 (69, Ph^+), 51 (14%).

4.4.4. 5-(1,1-Difluoro-2-hydroxy-3-pentenyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (8d). Through the general procedure starting from triazole **3ba** and crotonaldehyde **7d** (0.28 g, 4 mmol), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent afforded the *gem*-difluorinated alcohol **8d** (175 mg, 65%) as a white powder, mp 88.0–90.0°C. [Found: C, 57.09; H, 5.16; N, 12.65. $C_{16}H_{17}^{19}F_2N_3O_3$ requires C, 56.97; H, 5.08; N, 12.46%]; ν_{max} (film) 3359, 2997, 1737, 1726, 1679, 1596, 1560, 1500, 1444, 1377, 1351, 1277, 1263, 1224, 1189, 1133, 1081, 1022, 969, 850, 765, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.47 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.73 (3H, d, J=6.9 Hz, =CHCH_3), 3.25 (1H, d, J=6.0 Hz, O*H*), 4.50 (2H, q, J=7.2 Hz, OCH_2CH_3), 4.93 (1H, dddd, J=17.4, 6.0, 6.0, 5.7 Hz, C*H*OH), 5.45 (1H, dd, J=15.3, 5.7 Hz, =C*H*CHOH), 5.92 (1H, dq, J=15.3, 6.9 Hz, =CHCH_3), 7.47–7.58 (5H, m, Ph); δ_F (282 MHz, $CDCl_3$) −94.5 (1F, dd, J=274.4, 6.0 Hz), 106.7 (1F, dd, J=274.4, 17.4 Hz); m/z (EI) 338 (34, M^++1), 292 (6), 265 (19), 166 (41), 104 (49), 77 (100, Ph^+), 71 (27), 69 (18), 41 (22%).

4.4.5. 5-(1,1-Difluoro-2-hydroxy-4-phenyl-butyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester (8e). Through the general procedure starting from triazole **3ba** and 1-phenyl propanal **7e** (0.54 g, 4 mmol), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent afforded the *gem*-difluorinated alcohol **8e** (90 mg, 28%) as a white powder, mp 168.0–171.0°C. [Found: C, 63.05; H, 5.40; N, 10.17. $C_{21}H_{21}F_2N_3O_3$ requires C, 62.84; H, 5.27; N, 10.47%]; ν_{max} (film) 3474, 3028, 2985, 2960, 1724, 1595, 1547, 1497, 1253, 1236, 1095, 1073, 1012, 764, 752, 703, 688 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.63–2.05 (2H, m, CH_2CH_2CHOH), 2.71–2.92 (2H, m, CH_2CH_2CHOH), 3.46 (1H, brs, O*H*), 4.34–4.44 (3H, m, OCH_2CH_3 and C*H*OH), 7.18–7.56 (10H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −95.0 (1F, d, J=274.7 Hz), 109.5 (1F, dd, J=274.7, 20.1 Hz); m/z (EI) 402 (1, M^++1), 356 (22), 329 (21), 194 (18), 166 (38), 144 (23), 115 (12), 105 (28), 91 (100, $PhCH_2^+$), 77 (82%).

4.5. Synthesis of the bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds 10 (general procedure)

Into a solution of alcohol **8** (0.2 mmol) in 10 mL toluene, was added a catalytic amount of *p*-toluenesulfonic acid (10 mg), the solution was then heated at 85°C for the time specified in Table 4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography using *n*-hexane/EtOAc or CH_2Cl_2 as eluent to afford compound **10** in the yields shown in Table 4.

4.5.1. 7,7-Difluoro-6-phenyl-1-phenyl-6,7-dihydro-1*H*-pyrano[3,4-*d*][1,2,3]triazol-4-one (10a). Following the general procedure starting from difluorinated alcohol **8a** (56 mg, 0.15 mmol), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent afforded compound **10a** (34 mg, 0.1 mmol, 69%) as a white powder, mp 192.0–195.0°C. [Found: C, 62.58; H, 3.74; N, 12.46. $C_{17}H_{11}F_2N_3O_2$ requires C, 62.39; H, 3.39; N, 12.84%]; ν_{max} (film) 3087, 1770, 1598, 1575, 1513, 1457, 1393, 1200, 1154, 1124, 1085, 1074, 1022, 762, 729, 709, 688 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.76 (1H, dd, J=20.4, 5.1 Hz, C*H*O–), 7.47–7.74 (10H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −96.2 (1F, dd, J=276.8, 20.4 Hz), 115.6 (1F, dd, J=276.8, 5.3 Hz); m/z (EI) 327 (13, M^+), 165 (100), 105 (3), 77 (28), 51 (12%).

4.5.2. 7,7-Difluoro-6-(4-chlorophenyl)-1-phenyl-6,7-dihydro-1*H*-pyrano[3,4-*d*] [1,2,3]triazol-4-one (10b).

Following the general procedure starting from difluorinated alcohol **8b** (55 mg, 0.14 mmol), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent afforded compound **10b** (24 mg, 0.07 mmol, 69%) as a white powder, in addition to recovery of 16 mg starting material. Mp 159.0–161.0°C; ν_{max} (film) 2924, 2853, 1768, 1708, 1599, 1577, 1511, 1497, 1397, 1200, 1159, 1126, 1086, 1034, 1016, 793, 757, 688 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.75 (1H, dd, J=20.7, 5.1 Hz, C*H*O–), 7.46–7.72 (9H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −95.8 (1F, dd, J=276.7, 21.7 Hz), 116.3 (1F, dd, J=276.7, 5.1 Hz); m/z (EI) 361/363 (8/3, M^+), 165 (100), 139 (6), 111 (5), 77 (36); [HRMS (EI): M^+, found 361.04258. $C_{17}H_{10}^{35}Cl^{19}F_2N_3O_2$ requires 361.04296].

4.5.3. 7,7-Difluoro-6-(4-methoxyphenyl)-1-phenyl-6,7-dihydro-1*H*-pyrano[3,4-*d*] [1,2,3]triazol-4-one (10c). Following the general procedure starting from difluorinated alcohol **8c** (149 mg, 0.37 mmol) catalyzed by *p*-TsOH (25 mg), flash chromatography using *n*-hexane/EtOAc (3:1) as eluent afforded compound **10c** (54 mg, 0.15 mmol, 41%) as a white powder, mp 192.0–194.0°C. [Found: C, 60.41; H, 3.89; N, 11.49. $C_{18}H_{13}F_2N_3O_3$ requires C, 60.51; H, 3.67; N, 11.76%]; ν_{max} (film) 3022, 2970, 2937, 2841, 1759, 1613, 1574, 1518, 1388, 1290, 1253, 1180, 1154, 1122, 1065, 1013, 800, 765, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, O*Me*), 5.69 (1H, dd, J=20.7, 5.4 Hz, C*H*O–), 6.96–7.73 (9H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −97.8 (1F, dd, J=276.2, 20.7 Hz), 116.9 (1F, dd, J=276.2, 5.4 Hz); m/z (EI) 357 (20, M^+), 284 (3), 222 (7), 165 (100), 135 (4), 77 (20), 51 (7%).

4.5.4. 7,7-Difluoro-6-(1-propenyl)-1-phenyl-6,7-dihydro-1*H*-pyrano[3,4-*d*][1,2,3] triazol-4-one (10d). Following the general procedure starting from difluorinated alcohol **8d** (53 mg, 0.16 mmol) catalyzed by *p*-TsOH (13 mg), flash chromatography using CH_2Cl_2 as eluent afforded compound **10d** (43 mg, 0.15 mmol, 94%) as a white powder, mp 103.0–106.0°C; ν_{max} (film) 2961, 2920, 2853, 1761, 1675, 1596, 1507, 1398, 1205, 1178, 1147, 1126, 1075, 1009, 973, 965, 784, 761, 689 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.84 (3H, d, J=6.9 Hz, =CHC*H*$_3$), 5.12 (1H, ddd, J=16.8, 7.8, 6.9 Hz, C*H*O–), 5.66 (1H, dd, J=15.6, 7.8, 1.2 Hz, =CHCHO–), 6.15 (1H, dq, J=15.6, 6.9, 0.9 Hz, =C*H*CH$_3$), 7.63–7.77 (5H, m, Ph); δ_F (282 MHz, $CDCl_3$) −102.1 (1F, dd, J=278.1, 16.8 Hz), 110.4 (1F, dd, J=278.1, 6.9 Hz); m/z (EI) 291 (10, M^+), 165 (100), 145 (6), 104 (16), 77 (55), 51 (7), 41 (10%); HRMS (EI): M^+, found 291.08053. $C_{14}H_{11}^{19}F_2N_3O_2$ requires 291.08193.

4.5.5. 7,7-Difluoro-6-(2-phenylethyl)-1-phenyl-6,7-dihydro-1*H*-pyrano[3,4-*d*] [1,2,3]triazol-4-one (10e). Following the general procedure starting from difluorinated alcohol **8e** (39 mg, 0.10 mmol) catalyzed by *p*-TsOH (10 mg), flash chromatography using CH_2Cl_2 as eluent afforded compound **10d** (30 mg, 0.08 mmol, 87%) as a white powder, mp 137.0–140.0°C; ν_{max} (film) 2961, 2931, 1767, 1596, 1570, 1504, 1399, 1204, 1153, 1130, 1089, 1047, 947, 795, 787, 766, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.24–2.38 (2H, m, CH_2CH_2CHO–), 2.84–3.12 (2H, m, CH_2CH_2CHO), 4.53–4.63 (1H, m, CH_2CH_2CHO), 7.21–7.72 (10H, m, Ar*H*); δ_F (282 MHz, $CDCl_3$) −100.8 (1F, dd, J=278.9, 22.6 Hz), 115.5 (1F, dd, J=278.9, 3.4 Hz); m/z (EI) 355 (29, M^+), 194 (10), 166 (22), 144 (13), 105 (6), 91 (77), 77 (100), 65 (18), 51 (40%); FTMS-HR (EI): M^+, found 355.1127. $C_{19}H_{15}^{19}F_2N_3O_2$ requires 355.1136.

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