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Synthesis of New γ-Lactams with *gem*-Difluorinated Side Chains

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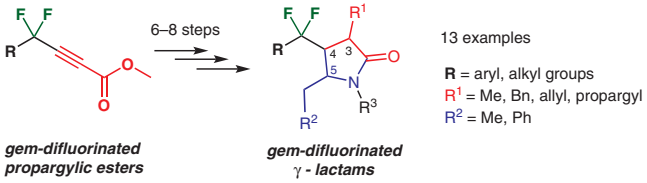

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Abstract A short and efficient approach has been designed for the synthesis of new γ-lactams that feature *gem*-difluorinated side-chains in position 4. The key steps involve 1,4-addition of nitroalkane anions on electrophilic *gem*-difluoroalkenes, followed by a cascade nitro reduction–heterocyclization. This flexible strategy also allows easy introduction of substituents in positions 3 or 5.

Key words fluorine, gamma lactams, *gem*-difluoropropargyl, heterocycles, synthesis

The γ-lactam ring is part of the core structure of a large number of natural and non-natural compounds covering a broad spectrum of biological activities. This privileged scaffold is widely present in important pharmaceuticals, such as (*R*)-Rolipram, a selective phosphodiesterase-4 inhibitor developed as a potential antidepressant drug, the antitussive Cynometrine, and Brivaracetam, which exhibits anticonvulsant properties (Figure 1).[1] Furthermore, γ-lactams also serve as versatile intermediates for the synthesis of other medicinally relevant molecules and complex natural products.[2]

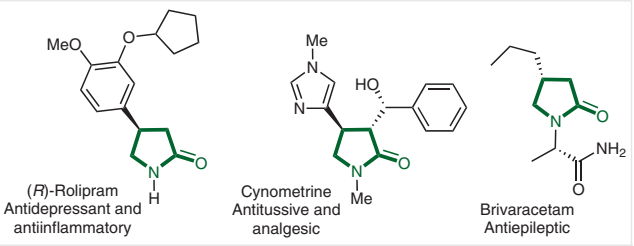
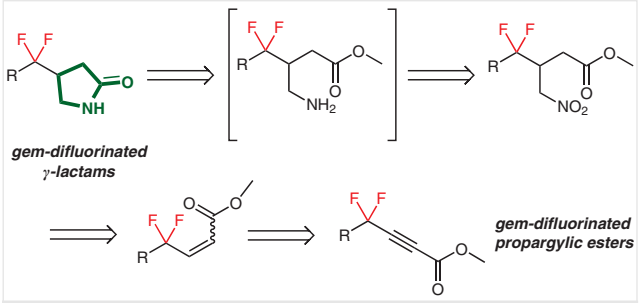


Figure 1 Some biologically active γ-lactam containing molecules

On the other hand, it is known that the introduction of fluorine to organic molecules strongly modifies their physical, chemical and biological properties, and this topic has been covered in many reviews.[3] However, to our knowledge, only a few fluorinated γ-lactams have been described to date.[4] Thus, based on the previous experience gained in our laboratories in the synthesis and uses of propargylic fluorides, we have designed a strategy for the preparation of novel γ-lactams with *gem*-fluorinated side chains (Scheme 1). This takes advantage of readily accessible and versatile *gem*-difluoro propargylic derivatives.[5] The target molecules could be obtained by cyclization of amino ester intermediates with the desired fluorinated side chains. These derivatives could be prepared by reduction of the corresponding nitro compounds. These intermediates could, in turn, be obtained by a Michael addition of the nitromethane anion on electrophilic alkenes possessing the *gem*-difluoro chains. The latter derivatives could be prepared by reduction of the corresponding *gem*-difluoro propargylic esters.

The fluorinated alkynes **4a–h** were prepared in three steps, as indicated in Scheme 2 and Table 1.



Scheme 1 Retrosynthetic analysis for the preparation of γ-lactams with fluorinated side chains in position 4

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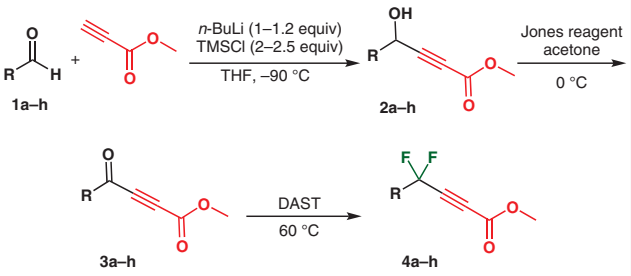
The addition of methyl propiolate to a range of aldehydes (aromatic and alkyl) afforded propargylic alcohols **2a–h** in fair to good yields. Subsequent oxidation with Jones reagent gave the ketones **3a–h**, also in excellent yields.



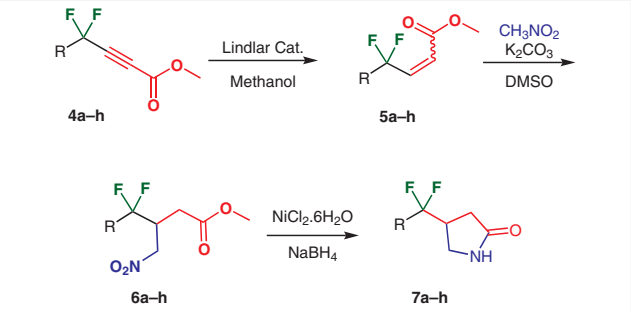
Scheme 2 Synthesis of alkynes **4a–h** with the *gem*-difluoroalkylated chains

Table 1 Synthesis of Alkynes **2a–h**, **3a–h**, and **4a–h** with *gem*-Difluoroalkylated Chains

Entry	SM	R	Yield (%)		
			2	**3**	**4**
1	**1a**	Ph	**2a** (90)	**3a** (80)	**4a** (65)
2	**1b**	$PhCH_2CH_2$	**2b** (69)	**3b** (74)	**4b** (91)
3	**1c**	$4\text{-}ClC_6H_4$	**2c** (70)	**3c** (79)	**4c** (62)
4	**1d**	$2\text{-}BrC_6H_4$	**2d** (64)	**3d** (84)	**4d** (76)
5	**1e**	$4\text{-}FC_6H_4$	**2e** (81)	**3e** (95)	**4e** (70)
6	**1f**	$4\text{-}MeOC_6H_4$	**2f** (77)	**3f** (93)	**4f** (25)
7	**1g**	$4\text{-}F_3CC_6H_4$	**2g** (70)	**3g** (77)	**4g** (79)
8	**1h**	$n\text{-}C_8H_{17}$	**2h** (60)	**3h** (82)	**4h** (60)

Fluorination with diethylaminosulfur trifluoride (DAST) then afforded the target intermediates **4a–h** in satisfactory yields, except for **4f**, for which some decomposition occurred.

The conversion into the target γ-lactams was achieved in three more straightforward steps (Scheme 3). First, the semi-hydrogenation of the triple bond was performed using Lindlar catalyst to give the alkenes **5a–h** in good to excellent yields. During these reductions, minor amounts of the corresponding *E*-isomers were obtained in a few cases.



Scheme 3 Synthesis of γ-lactams **7a–h** with the *gem*-difluoroalkylated chains in position 4

On these electrophilic alkenes, the Michael addition of the nitromethane anion was performed in a classical way by using potassium carbonate as the base and DMSO as solvent, affording adducts **6a–h** in good to excellent yields.

Reduction of the nitro group proved to be a little more challenging. After optimization studies we found that the combination of $NiCl_2{\cdot}6H_2O$ and $NaBH_4$,[6] gave the best results, affording the target molecules **7a–h** in excellent yields (Table 2), except for **7d**, for which cleavage of the C–Br bond occurred, affording **7a**. On the other hand, hydrogenation in the presence of $Pd(OH)_2$ gave only the γ-lactam **7a** for compounds **6c** and **6d**, bearing the halogen substituents on the aromatic ring. Under these conditions and for these two molecules, both the reduction of the nitro group and dehalogenation occurred.

Table 2 Synthesis of γ-Lactams **5a–h**, **6a–h**, and **7a–h** with the *gem*-Difluoroalkylated Chains in Position 4

Entry	SM	R	Yield (%)		
			5	**6**	**7**
1	**4a**	Ph	**5a** (86)	**6a** (90)	**7a** (80)
2	**4b**	$PhCH_2CH_2$	**5b** (65)	**6b** (80)	**7b** (77)
3	**4c**	$4\text{-}ClC_6H_4$	**5c** (94)	**6c** (88)	**7c** (84)
4	**4d**	$2\text{-}BrC_6H_4$	**5d** (35)[a]	**6d** (79)	–
5	**4e**	$4\text{-}FC_6H_4$	**5e** (75)	**6e** (87)	**7e** (90)
6	**4f**	$4\text{-}MeOC_6H_4$	**5f** (79)	**6f** (86)	**7f** (92)
7	**4g**	$4\text{-}F_3CC_6H_4$	**5g** (80)	**6g** (85)	**7g** (95)
8	**4h**	$n\text{-}C_8H_{17}$	**5h** (71)	**6h** (70)	**7h** (84)

[a] From 40% conversion.

All compounds **2–7** have spectroscopic (^1H, ^{19}F and ^{13}C NMR) and mass spectrometric data consistent with their structures (see the Supporting Information). In addition, X-ray crystallographic analysis confirmed the structures of γ-lactams **7a** and **7e** (Figure 2).[7]

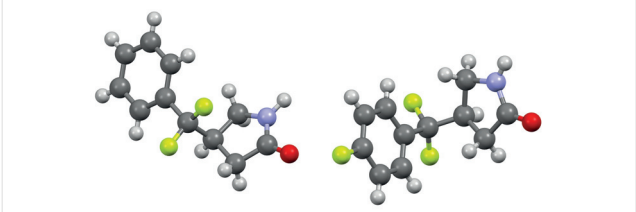
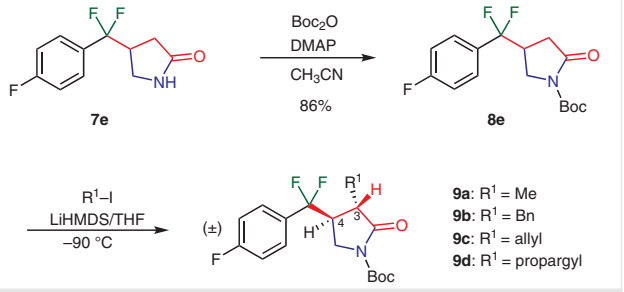


Figure 2 Structures of **7a** and **7e** by X-ray crystallographic analysis

The next step was the extension of molecular diversity around the γ-lactam scaffold. One obvious way was the introduction of R^1 substituents on the carbon vicinal to the

lactam carbonyl. Thus, lactam **7e**, selected as a model, was first protected as its *N*-Boc derivative and then alkylation reactions were performed to introduce various R^1 groups at the desired position (Scheme 4). These reactions (Table 3) proved to be completely stereoselective, affording only the *trans* isomers **9a–d**.



Scheme 4 Introduction of R^1 substituents in position 3

Table 3 Synthesis of γ-Lactams Substituted in Position 3

Entry	R^1	Yield (%)
1	Me	**9a** (90)
2	Bn	**9b** (62)
3	allyl	**9c** (42)
4	propargyl	**9d** (30)

The stereochemistry of compound **9a** was assigned on the basis of extensive NMR experiments. In particular, $^1H–^{19}F$ HOESY experiments revealed strong correlations between the fluorine atoms and the proton at position 3. Furthermore, NOE correlations were observed between the methyl group at position 3 and the proton at position 4. Similar results were obtained for compounds **9b–d** and the structure of **9b** was confirmed by X-ray crystallographic analysis (Figure 3).[7]

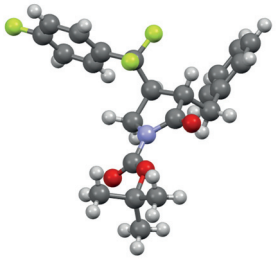
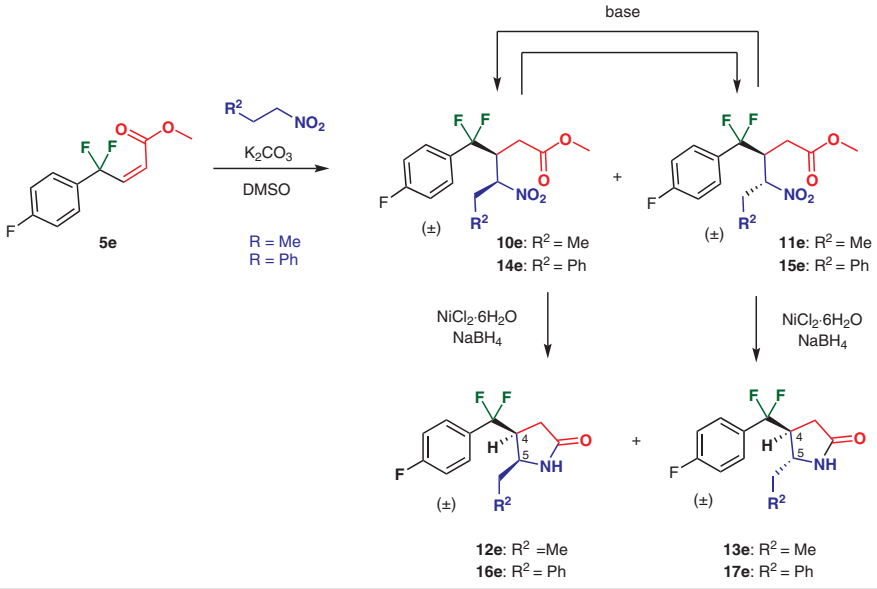


Figure 3 Structure of **9b** by X-ray crystallographic analysis

To expand the scope of this approach, a second option was to introduce a CH_2-R^2 group on the carbon vicinal to the nitrogen atom. By using the α,β-unsaturated ester **5e** as a representative model, this could be achieved by the addition of nitroalkyl groups, instead of nitromethane. First the reaction of 1-nitropropane on **5e** gave a 1:1 mixture of adducts **10e** and **11e**, in 66% overall yield, as shown in Scheme 5. These compounds were separable by chromatography and we could establish that, not surprisingly, there was a slow equilibration between these two stereoisomers under basic conditions. For both compounds, reduction of the nitro group, under the same conditions as before, afforded the γ-lactams **12e** and **13e**, respectively, stereoselectively in good yields. Their stereochemistry was again established by extensive NMR studies. In particular for **13e**, strong NOESY correlations were observed between the protons of the methylene group at position 5 and the neighboring proton



Scheme 5 Synthesis of γ-lactams substituted in position 5

at position 4 of this heterocycle; no such correlations were observed in the case of its diastereoisomer **12e**.

The same reactions were performed starting with 2-nitroethylbenzene, affording a 1:1 inseparable mixture of **14e** and **15e** in 83% overall yield. After reduction of the nitro groups, the desired γ-lactams **16e** and **17e** could be separated by chromatography and their stereochemistries were established by NMR analysis as described for **12e** and **13e**.

In conclusion, we have developed a flexible synthesis of novel γ-lactams with *gem*-fluorinated side-chains at position 4 of the heterocyclic ring.[8] Furthermore, molecular diversity was increased by adding other substituents in positions 3 and 5 of the γ-lactam. Molecules of this type are of interest in various areas of bioorganic or medicinal chemistry and further studies will be performed in the near future.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690715.

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(7) CCDC 1941252 (for compound **7a**), CCDC 1941251 (for compound **7e**) and CCDC 1941250 (for compound **9b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(8) **Typical Procedures: Synthesis of Methyl 4,4-Difluoro-4-phenylbut-2-ynoate (4a)**

To propargylic ketone **3a** (1 g, 5.31 mmol), one drop of 95% ethanol and DAST (4.2 mL, 31.8 mmol, 6 equiv) were added. The reaction mixture was stirred at 60 °C for 6 h. After returning to room temperature and aqueous work-up, the reaction mixture was extracted with DCM (3 × 40 mL). The organic layers were separated, washed with H_2O (3 × 20 mL), dried over Na_2SO_4, and filtrated through silica. After purification by chromatography on silica gel, the fluorinated compound **4a** (0.73 g, 65%) was obtained as a yellow oil; R_f = 0.4 (cyclohexane/EtOAc, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71–7.59 (m, 2 H), 7.56–7.41 (m, 3 H), 3.84 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 134.4 (t, $^2J_{C-F}$ = 26.8 Hz), 131.4 (t, $^5J_{C-F}$ = 1.7 Hz), 128.8 (2C), 125.3 (t, $^3J_{C-F}$ = 4.9 Hz, 2C), 111.5 (t, $^1J_{C-F}$ = 235.1 Hz), 78.0 (t, $^3J_{C-F}$ = 5.9 Hz), 77.4 (t, $^2J_{C-F}$ = 44.3 Hz), 53.4. ^{19}F {H} NMR (471 MHz, $CDCl_3$): δ = –79.61 (s). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8O_2F_2Na$: 233.03846; found: 233.0383 (1 ppm).

Synthesis of Methyl (*Z*)-4,4-Difluoro-4-phenylbut-2-enoate (5a)

Methyl 4,4-difluoro-4-phenylbut-2-ynoate (**4a**; 0.5 g, 2.38 mmol) was stirred with Lindlar catalyst (10%) in MeOH (15 mL) under hydrogen. The reaction was monitored by TLC and, on completion, the reaction mixture was filtrated through Celite® and the product was purified by chromatography to obtain the methyl (*Z*)-4,4-difluoro-4-phenylbut-2-enoate (**5a**; 434 mg, 86%) as a colorless oil. R_f = 0.4 (cyclohexane/EtOAc, 8:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 2 H), 7.46–7.41 (m, 3 H), 6.22 (dd, $^3J_{H-F}$ = 25.0, $^3J_{H-H}$ = 12.5 Hz, 1 H), 6.13 (dt, $^3J_{H-H}$ = 12.6,

$^4J_{H-F}$ = 1.3 Hz, 1 H), 3.69 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.5, 135.9 (t, $^2J_{C-F}$ = 27.1 Hz), 134.7 (t, $^2J_{C-F}$ = 32.3 Hz), 130.4 (t, $^5J_{C-F}$ = 1.7 Hz), 128.6 (s, 2C), 125.5 (t, $^3J_{C-F}$ = 5.6 Hz, 2C), 124.9 (t, $^3J_{C-F}$ = 7.1 Hz), 118.6 (t, $^1J_{C-F}$ = 240.5 Hz), 52.1. ^{19}F {H} NMR (471 MHz, $CDCl_3$): δ = –88.90 (s). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{10}O_2F_2Na$: 235.05411; found: 235.0540 (0 ppm).

Synthesis of Methyl 4,4-Difluoro-3-(nitromethyl)-4-phenylbutanoate (6a)

To methyl (*Z*)-4,4-difluoro-4-phenylbut-2-enoate (**5a**; 150 mg, 0.7 mmol) were added nitromethane (75 µL, 1.4 mmol) and potassium carbonate (289 mg, 2.1 mmol) in DMSO (3 mL). The reaction mixture was stirred at room temperature and analyzed by TLC. On completion, saturated NH_4Cl (10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were separated, washed with H_2O (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. After purification by chromatography on silica gel, methyl 4,4-difluoro-3-(nitromethyl)-4-phenylbutanoate (**6a**; 174 mg, 90%) was obtained as a yellow oil; R_f =0.4 (cyclohexane/EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.45 (m, 5 H), 4.73 (dd, $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ = 5.8 Hz, 1 H), 4.53 (dd, $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ = 6.2 Hz, 1 H), 3.77–3.57 (m, 1 H), 3.62 (s, 3 H), 2.66 (dd, $^2J_{H-H}$ = 16.9 Hz, $^3J_{H-H}$ = 5.2 Hz, 1 H), 2.50 (dd, $^2J_{H-H}$ = 16.9 Hz, $^3J_{H-H}$ = 8.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 133.9 (t, $^2J_{C-F}$ = 25.8 Hz), 131.0, 129.0 (2C), 125.5 (t, $^3J_{C-F}$ = 6.4 Hz, 2C), 123.7 (dd, $^1J_{C-F}$ = 247.4 Hz), 73.4 (t, $^3J_{C-F}$ = 3.4 Hz), 52.3, 42.6 (t, $^2J_{C-F}$ = 27.1 Hz), 31.4 (dd, $^3J_{C-F}$ = 4.2, 3.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$): δ = –98.05 (AB system, *J* = 250.8 Hz), –104.55 (AB system, *J* = 250.8 Hz). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{12}H_{13}NO_4F_2Na$: 296.07048; found: 296.0706 (0 ppm).

Synthesis of 4-(Difluoro(phenyl)methyl)pyrrolidin-2-one (7a)

To a stirred solution of methyl 4,4-difluoro-3-(nitromethyl)-4-phenylbutanoate (**6a**; 50 mg, 0.18 mmol) in MeOH (2 mL), $NiCl_2{\cdot}6H_2O$ (85 mg, 0.36 mmol) was added at room temperature. After stirring for 5 min, $NaBH_4$ (75 mg, 1.98 mmol) was added in four portions. The reaction mixture was stirred for 30 min at room temperature, then a saturated solution of NH_4Cl was added and the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were separated, washed with H_2O (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. 4-(Difluoro(phenyl)methyl)pyrrolidin-2-one **7a** was precipitated and washed with Et_2O to give a white solid. Yield: 31 mg (80%); R_f = 0.2 (DCM/MeOH, 95:5); mp 95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 5 H), 6.55 (s, 1 H, *N*H), 3.2 (dd, $^2J_{H-H}$ = 9.9 Hz, $^3J_{H-H}$ = 7.0 Hz, 1 H), 3.40 (dd, $^2J_{H-H}$ = 9.9 Hz, $^3J_{H-H}$ = 8.8 Hz, 1 H), 3.35–3.13 (m, 1 H), 2.51 (dd, $^2J_{H-H}$ = 17.3 Hz, $^3J_{H-H}$ = 8.1 Hz, 1 H), 2.35 (dd, $^2J_{H-H}$ = 17.3 Hz, $^3J_{H-H}$ = 9.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 135.4 (t, $^2J_{C-F}$ = 26.4 Hz), 130.5 (t, $^5J_{C-F}$ = 1.7 Hz), 128.9 (2C), 125.2 (t, $^3J_{C-F}$ = 6.3 Hz, 2C), 121.9 (t, $^1J_{C-F}$ = 244.7 Hz), 42.5 (t, $^2J_{C-F}$ = 28.4 Hz), 42.0 (t, $^3J_{C-F}$ = 4.8 Hz), 30.8 (t, $^3J_{C-F}$ = 3.7 Hz). ^{19}F NMR {H} (282 MHz, $CDCl_3$): δ = –103.04 (AB system, F_A, $^2J_{F-F}$ = 248.2 Hz), –104.48 (AB system, F_B, $^2J_{F-F}$ = 248.2 Hz). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}NOF_2Na$: 234.07009; found: 234.0699 (1 ppm).

