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Highly selective 1,3-dipolar cycloaddition of a cyclic azomethine ylide to ethyltrifluorocrotonates

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Abstract

The 1,3-dipolar cycloadditions of ethyltrifluorocrotonates to the azomethineylide, generated from 2-(*tert*-butyl)-3-methyl-imidazolin-4-one and formaldehyde, proceeds with a high degree of stereo- and regioselectivity to give precursors of 4-trifluoromethylpyrrolidine-2,3-dicarboxylic acids in good yields. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Among the very important class of proline derivatives, 2,3- and 2,4-dicarboxyl pyrrolidines have retained great attention as conformationally constrained analogues of endogeneous excitatory amino acids like aspartic and glutamic acids [1–3]. Modifications of the carbon backbone have been particularly studied in order to find specific ligands of corresponding receptors [4,5]. This, coupled with the pronounced effect that fluorine can have on biological activity [6,7], makes trifluoromethyl-substituted dicarboxylpyrrolidines **1** and **2** interesting synthetic targets (Fig. 1).

We previously described an access to parent compounds by the interaction between *N*-metallated azomethine ylides and *trans*-ethyl-4,4,4-trifluorocrotonate [8]. The reaction was found to be highly regio- and stereoselective, providing only 2,4-dicarboxylpyrrolidines. As usually observed with β-substituted trifluoromethyl olefins [9], the cycloaddition reaction was governed by the ester group in spite of the presence of the electron withdrawing trifluoromethyl substituent. We then investigated 1,3-dipolar cycloadditions of trifluorocrotonates and a chiral azomethine ylide in order to prepare homochiral fluoro derivatives of dicarboxylpyrrolidines. Results of this study and discussion on the stereochemical outcome of the cycloaddition reaction are presented in this paper.

We chose for this study an azomethine ylide derived from the 2-(*tert*-butyl)-3-methyl-imidazolidine-4-one (**3**). Fitzi and Seebach extensively studied the stereoselective alkylation of **3** in the preparation of chiral amino acids [10,11]. Furthermore, the racemic azomethineylide (**4**) derived from **3** has been shown to undergo cycloaddition reactions with activated alkenes with complete facial selectivity [12]. However, regioselectivity has not been investigated since only 1,3-dipolar cycloadditions with symmetrical alkenes have been reported.

First experiments have been performed with the *trans*-ethyl-4,4,4-trifluorocrotonate (**5**) and the racemic azomethineylide (**4**) generated in situ from the imidazolidinone (**3**) at reflux of toluene. After 18 h, the reaction yielded quantitatively a mixture of three cycloadducts **6**, **7** and **8** (59:22:19). After chromatography on SiO_2, compounds **6** and **7** were recovered as an inseparable mixture (71%) and **8** could be isolated in a 17% yield (Scheme 1).

Structure of these adducts was elucidated by NMR experiments. Complete assignments of protons and carbons by COSY, heteronuclear multiple-quantum coherence (hmqc) and heteronuclear multiple-bond coherence (hmbc) showed that **8** is a regioisomer of **6** and **7**. Then homo- and heteronuclear NOE experiments secured the stereochemistry. For all compounds, there was a correlation (4%) between H-3 and H-5, while none was observed between *t*-Bu and H-5, indicating that the approach of the dipolarophile occurred

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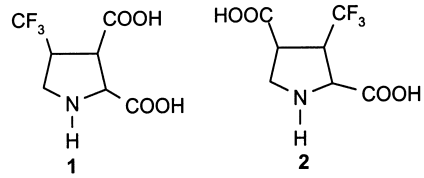


Fig. 1.

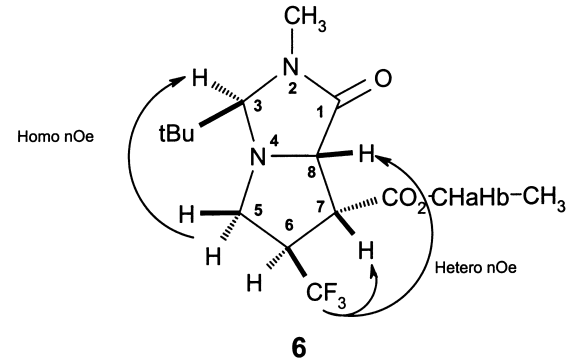


Fig. 2.

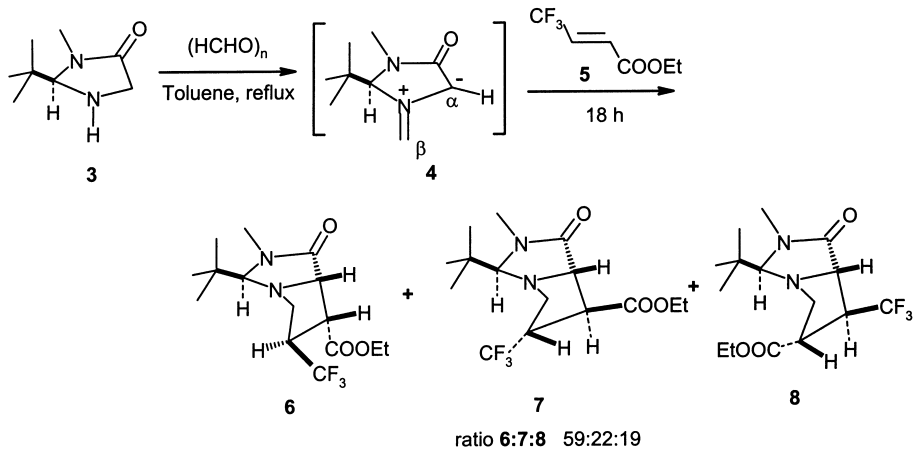
from the opposite face to the sterically demanding *t*-butyl group. Heteronuclear NOE difference experiments allowed the determination of other relative carbon configurations: for example the irradiation of fluorine nuclei of CF_3 in the major isomer **6** resulted in a signal enhancement for the protons H-5 (9%), H-6 (15%), H-7 (5%), and H-8 (8%) identifying their spatial proximity, while there was no enhancement of the H-8 signal in **7** (Fig. 2). The presence of a $\{^{19}F\}$, ^1H NOE on H-5 (which was not observed for **8**) confirms the regiochemistry. In **8**, a $\{^{19}F\}$, ^1H NOE on H-8 identifies the *cis* relationship between these nuclei.

In all adducts, conservation of the configuration of starting alkene strongly suggests a concerted process despite the severe conditions of the cycloaddition reaction. The regio orientation leading to the minor product **8** is the one predicted by orbital coefficients to be the most favourable [9,13,14]. However, this transition state is disfavoured by the steric requirements of the bulky CF_3 at the more hindered site α of **4** (Scheme 1). When this orientation does occur, only the less sterically demanding *exo*/CF_3 transition state is formed giving rise to **8**. The major regioisomers **6** and **7** arise from the transition state in which the CF_3 group is orientated towards the less hindered site β of **4**. The major stereoisomer **6** results from the *endo*/ester transition state. It has been previously reported that secondary orbital overlaps between a dipole and an ester group greatly predominates over those with a CF_3 group, when these two substituents are in competition [8,9,13,14]. However, secondary orbital interactions between an unsaturated system and a CF_3 group can also be stabilising [14]. This, along with the repulsive steric interactions at the site α of **4**, opposes the stabilising interactions of the *endo*/ester, resulting in significant amounts of the stereoisomer **7**.

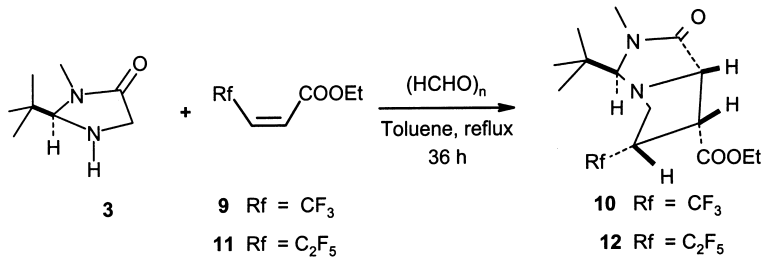
If the outcome of this dipolar cycloaddition is actually governed by steric and electronic factors as explained above, the reaction with the *cis*-ethyltrifluorocrotonate (**9**) should be highly regio- and stereoselective.

Under the same conditions as preceeding, the 1,3-dipolar cycloaddition of **4** with *cis*-ethyl-4,4,4-trifluorocrotonate [15] provided, after 36 h at reflux, the regio- and stereoisomer **10** (90%), accompanied with traces of three other unidentified cycloadducts (10%). Compound **10** could be isolated in a 70% yield (Scheme 2). Structure of **10** was elucidated as described above. This high selectivity is the result of a preferred *endo* orientation of both ester and CF_3 groups in the transition state and of an impeded *endo* approach of the CF_3 substituted terminus of the alkene to the sterically hindered α site of **4**.

This cycloaddition has been generalised to the (Z)-ethyl-5,5,5,4,4-pentafluoropentenoate (**11**), and similar selectivity was observed with the isolation of the single isomer **12** (40%), and recovering of starting material.



Scheme 1.



Scheme 2.

We then investigated reactivity of **4** in its chiral form, towards the *cis*-ethyltrifluorocrotonate (**9**). The imidazolidinone (**3**) has been resolved according to the described procedure through mandelate salts [10]. However, in our hands, only the isomer (S)(+) **3** could be easily isolated pure ($[\alpha]_D = +21$). The cycloaddition was conducted under the same conditions as before and provided the cycloadduct **10** ($[\alpha]_D = -1.3$). This $[\alpha]_D$ low value suggested that a racemisation could occur in the course of the reaction. Effectively, when the reaction was stopped before completion, the recovered imidazolidinone **3** had an $[\alpha]_D$ of only 2.5 instead of 21.

In conclusion, the 1,3-dipolar cycloaddition reaction between ethyltrifluorocrotonates and the cyclic azomethineylide **4** derived from **3** is highly selective. With the *cis*-ethyltrifluorocrotonate, the combination of repulsive steric interactions and attractive p-orbital overlaps between the dipole and both the perfluoroalkyl and ester groups resulted in a completely regio- and stereoselective reaction, providing masked fluoroalkyl-2,3-dicarboxyl pyrrolidines which cannot be obtained in reactions with non bulky azomethineylides. However, in spite of the excellent facial diastereoselectivity due to the presence of *t*-butyl substituent, the imidazolidinone (**3**) is not an efficient precursor of chiral azomethineylide under these conditions of cycloaddition reactions.

2. Experimental

trans-Ethyl-4,4,4-trifluorocrotonate (**5**) was obtained from Aldrich Chemical Company. 2-(*t*-Butyl)-3-methyl-4-imidazolidinone (**3**) [10,11], *cis*-ethyl-4,4,4-trifluorocrotonate (**9**) [15], ethyl-5,5,5,4,4-pentafluoropentynoate [16], were prepared according to the literature procedures. ^{1}H NMR spectra were recorded on Bruker ARX400 and AC200 instruments at 400, 200 MHz in $CDCl_3$ or benzene-d_6. ^{19}F NMR was recorded in 50 and 100 MHz in $CDCl_3$. ^{19}F NMR was recorded in 188.3 MHz in $CDCl_3$. TLC were performed on 0.25 mm Merck pre-coated silica plates (60F-254).

2.1. (Z)-Ethyl-4,4,5,5,5-pentafluoro-pent-2-enoate (**11**)

A Parr reactor was charged with ethyl-5,5,5,4,4-pentafluoropentynoate [16] (3.98 g, 0.02 mol), Lindlar catalyst (0.4 g of 5% Pd/$BaSO_4$), quinoline (five drops) and anhydrous ethylether (30 ml). The reactor was evacuated and hydrogen was admitted. Hydrogen pressure was maintained between 1.4 and 3.4 atm. The reaction was monitored by ^{19}F NMR. After complete disappearance of starting alkyne, the reaction mixture was filtered through a short celite column. The filtrate was distilled under reduced pressure to give **11** as a colourless liquid (3.65 g, 91%); IR (neat): *v*, 1735 and 1660 cm^{-1}; ^{19}F NMR: −85.3 (CF_3), −113.9 (dd, $^2J_{FH} = 280$ Hz, $^3J_{FH} = 6.3$ Hz, F), −114.2 (dd, $^2J_{FF} = 280$ Hz, $^3J_{FH} = 6.3$ Hz, F). ^{1}H NMR: δ, 1.19 (t, $J = 7$ Hz, 3H, CH_3), 4.25 (q, $J = 7$ Hz, 2H, CH_2), 6.05 (dd, $^3J_{FH} = 6.3$ Hz, $^3J_{HH} = 12.0$ Hz, $CHCF_2$), 6.3 (d, $J = 12.0$ Hz, $CHCO_2Et$).

2.2. (S)-2-(t-Butyl)-3-methyl-4-imidazolidinone-(S)-mandelic acid [10]

A mixture of racemic imidazolidinone (**3**) (8.28 g, 52.6 mmol) and (S)-(+)-mandelic acid (8.2 g, 53.9 mmol) was dissolved in boiling acetone (20 ml) which was then allowed to cool slowly to room temperature. After 24 h in a refrigerator (5°C), the crystal cake was pressed and filtered, washed with cold acetone and dried under vacuum affording crystals (4.45 g, 27%); mp: 120°C (lit. mp, 115.5–116.5°C); $[\alpha]_D$: +87.3 (*c*: 1.1, EtOH; lit. $[\alpha]_D$, +89 (*c*: 1.0, EtOH); ^{1}H NMR (200 MHz, DMSO-d_6): δ, 0.9 (s, 9H, ^{t}Bu), 2.8 (s, 3H, N–CH_3), 3.2 (s, 2H), 4.0 (s, 1H), 5.0 (s, 1H), 6.4–6.8 (br, 3H), 7.20–7.60 (m, 5H, Ph).

2.3. Preparation of (S)-2-t-butyl-3-methyl-4-imidazolidinone

A suspension of the (S)-(+)-mandelate (1 g, 3.3 mmol) in CH_2Cl_2 (20 ml) was shaken with 2 M aqueous NaOH (2.5 ml). The organic layer was separated, washed with water (20 ml), dried (anhydrous $MgSO_4$) and filtered. After evaporation of the solvent, imidazolidinone was obtained as a colourless oil. $[\alpha]_D$: +21.0 (*c*: 2, EtOH).

2.4. Typical procedure for 1,3-dipolar cycloadditions

Paraformaldehyde (0.5 g, 16.7 mmol) was added to a solution of *trans*-ethyltrifluorocrotonate (4 mmol) and 2-(*t*-butyl)-3-methyl-4-imidazolidinone (**3**) (0.312 g,

2 mmol) in dry toluene. The flask was fitted with a Dean–Stark apparatus and the mixture heated for 18 h with stirring to reflux. After cooling to room temperature and evaporation of solvent under vacuum, the residue was purified by silica gel column chromatography.

2.5. Reaction of **3** with paraformaldehyde and trans-ethyltrifluorocrotonate (**5**)

Mixture of three isomers obtained are **6**, **7** and **8** (59:22:19). Column chromatography (15% ether/pentane) yielded a colourless liquid **8** (0.18 g, 17%); IR (CH_2Cl_2): ν, 1741 and 1709 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ, 72.9 (d, $J = 9$ Hz); ^1H NMR (C_6D_6): δ, 0.92 (s, 9H, ^{t}Bu), 1.21 (t, $J_{CH_3/CH_2} = 7.1$ Hz, 3H, CH_3), 2.8 (dd, $J_{H\text{-}5'/H\text{-}6} = 8.6$ Hz, $J_{H\text{-}5'/H\text{-}5} = 9.8$ Hz, 1H, H-5′), 2.91 (s, 3H, NCH_3), 3.15 (dt, $J_{H\text{-}6/H\text{-}7} = 7.1$ Hz, $J_{H\text{-}6/H\text{-}5} = 6.8$ Hz, $J_{H\text{-}6/H\text{-}5'} = 8.6$ Hz, 1H, H-6), 3.4 (dd, $J_{H\text{-}7/H\text{-}8} = 4.5$ Hz, $J_{H\text{-}7/H\text{-}6} = 7.1$ Hz, 1H, H-7), 3.5 (dd, $J_{H\text{-}5/H\text{-}6} = 6.8$ Hz, $J_{H\text{-}5/H\text{-}5'} = 9.8$ Hz, 1H, H-5), 3.6 (d, $J_{H\text{-}3/H\text{-}8} = 1.1$ Hz, 1H, H-3), 3.78 (dd, $J_{H\text{-}8/H\text{-}7} = 4.5$ Hz, $J_{H\text{-}8/H\text{-}3} = 1.1$ Hz, 1H, H-8), 4.14 (q, $J_{H\text{-}b/H\text{-}a} = 7.1$ Hz, 2H, CH_2); ^{13}C NMR (C_6D_6): δ, 13.9 (CH_3), 25.7 (^{t}Bu), 32.0 (N–CH_3), 38.4 (CMe_3), 44.5 (q, $^3J = 1.9$ Hz, C-6), 48.4 (q, $^2J = 28.6$ Hz, C-7), 59.5 (C-5), 61.4 (OCH_2), 64.5 (q, $^3J = 2.4$ Hz, C-8), 91.9 (C-3), 125.6 (q, $^1J = 262$ Hz, CF_3), 170.9 (COOEt), 172.8 (CO).

Further elution with 20% ether/pentane gave compound **6** and compound **7** as a 73/27 mixture (0.77 g, 71%).

- Compound **6**: ^{19}F NMR ($CDCl_3$): δ, −72.6 (d, $J_{FH} = 8.9$ Hz); ^1H NMR ($CDCl_3$): δ, 0.91 (s, 9H, ^{t}Bu), 1.26 (t, $J_{CH_3/CH_2} = 7.1$ Hz, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.07 (dtq, $J_{H\text{-}6/H\text{-}5'} = 7.7$ Hz, $J_{H\text{-}6/H\text{-}5} = 5.7$ Hz, $J_{H\text{-}6/F} = 8.9$ Hz, 1H, H-6), 3.18 (dd, $J_{H\text{-}5'/H\text{-}6} = 7.7$ Hz, $J_{H\text{-}5'/H\text{-}5} = 10.5$, 1H, H-5′), 3.39 (dd, $J_{H\text{-}7/H\text{-}8} = 9$ Hz, $J_{H\text{-}7/H\text{-}6} = 5.7$ Hz, 1H, H-7), 3.4 (dd, $J_{H\text{-}5/H\text{-}6} = 5.7$ Hz, $J_{H\text{-}5/H\text{-}5'} = 10.5$ Hz, 1H, H-5), 3.67 (d, $J_{H\text{-}8/H\text{-}3} = 1.8$ Hz, 1H, H-3), 4.13 (dd, $J_{H\text{-}8/H\text{-}7} = 9$ Hz, $J_{H\text{-}8/H\text{-}3} = 1.8$ Hz, 1H, H-8), 4.14 (dq, $J_{H\text{-}b/H\text{-}a} = 10.8$ Hz, $J_{CH_3/CH_2} = 7.1$ Hz, 1H, H_b), 4.18 (qd, $J_{H\text{-}a/H\text{-}b} = 10.8$ Hz, $J_{CH_3/CH_2} = 7.1$ Hz, 1H, H_a); ^{13}C NMR (100 MHz, $CDCl_3$): δ, 13.9 (CH_3), 25.6 (^{t}Bu), 31.3 (N–CH_3), 38.2 (CMe_3), 46.2 (q, $^2J = 28.2$ Hz, C-6), 46.6 (q, $^3J = 1.9$ Hz, C-7), 56.5 (q, $^3J = 2.3$ Hz, C-5), 61.6 (OCH_2), 66.8 (C-8), 92.4 (C-3), 126.3 (q, $^1J = 278$ Hz, CF_3), 170.8 (COOEt), 171.5 (CO). Analysis for **6** and **7**: found: C, 53.59; H, 6.90; N, 8.27%. Calc. for $C_{15}H_{23}N_2F_3O_3$: C, 53.56; H, 6.89; N, 8.33%.
- Compound **7**: ^{19}F NMR($CDCl_3$): δ, −72.00 (d, $J_{F/H\text{-}6} = 8.4$ Hz); ^1H NMR (400 MHz, $CDCl_3$): δ, 0.9 (s, 9H, ^{t}Bu), 1.27 (t, $J = 7.15$ Hz, 3H, CH_3), 2.7 (dd, $J_{H\text{-}5'/H\text{-}5} = 9.7$ Hz, $J_{H\text{-}5'/H\text{-}6} = 9.7$ Hz, 1H, H-5′), 2.9 (s, 3H, NCH_3), 3.2 (dd, $J_{H\text{-}7/H\text{-}8} = 5.2$ Hz, $J_{H\text{-}7/H\text{-}6} = 8.3$ Hz, 1H, H-7), 3.3 (dtq, $J_{H\text{-}6/H\text{-}5} = 6.9$ Hz, $J_{H\text{-}6/H\text{-}5'} = 9.7$ Hz, $J_{H\text{-}6/H\text{-}7} = 8.3$ Hz, $J_{H\text{-}6/F} = 8.4$ Hz, 1H, H-6), 3.48 (dd, $J_{H\text{-}5/H\text{-}5'} = 9.7$ Hz, $J_{H\text{-}5/H\text{-}6} = 6.97$, 1H, H-5), 3.6 (s, 1H, H-3), 3.97 (d, $J_{H\text{-}8/H\text{-}7} = 5.2$ Hz, 1H, H-8), 4.19 (qd, $J_{H\text{-}b/H\text{-}a} = 10.7$ Hz, $J_{H\text{-}b/Me} = 7.15$ Hz, 1H, H_b), 4.24 (qd, $J_{H\text{-}a/H\text{-}b} = 10.7$ Hz, $J_{H\text{-}a/Me} = 7.15$ Hz, 1H, H_a); ^{13}C NMR ($CDCl_3$): δ, 13.9 (CH_3), 25.6 (^{t}Bu), 31.8 N–CH_3), 38.4 (CMe_3), 46.2 (q, $^3J = 2.1$ Hz, C-7), 46.6 (q, $^2J = 29.9$ Hz, C-6), 56.4 (q, $^3J = 2.3$ Hz, C-5), 61.8 (OCH_2), 67.9 (C-8), 91.9 (C-3), 125.9 (q, $^1J = 277.3$ Hz, CF_3), 171.4, 173.1.

2.6. Reaction of **3** with paraformaldehyde and cis-ethyltrifluorocrotonate (**9**)

Purification through column chromatography (30% ether/pentane) yielded **10** as an oil (0.47 g, 70%); IR (neat): ν, 1740 and 1705 cm^{-1}; ^{19}F NMR (C_6D_6): δ, −65.6 (d, $^3J = 8.8$ Hz); ^1H NMR (C_6D_6): δ, 0.76 (s, 9H, ^{t}Bu), 1.02 (t, $J_{CH_3/CH_2} = 7.2$ Hz, 3H, CH_3), 2.37 (td, $J_{H\text{-}6/H\text{-}5} = 11.9$ Hz, $J_{H\text{-}6/H\text{-}5'} = 6.6$ Hz, $J_{H\text{-}6/H\text{-}7} = 6.6$ Hz, 1H, H-6), 2.77 (d, $J_{CH_3/H\text{-}8} = 0.6$ Hz, 3H, CH_3), 3.06 (dt, $J_{H\text{-}5'/H\text{-}5} = 8.1$ Hz, $J_{H\text{-}5'/H\text{-}6} = 6.7$ Hz, $J_{H\text{-}5'/H\text{-}8} = 0.6$ Hz, 1H, H-5′), 3.15 (dd, $J_{H\text{-}7/H\text{-}6} = J_{H\text{-}7/H\text{-}8} = 6.6$ Hz, 1 H, H-7), 3.19 (dd, $J_{H\text{-}5/H\text{-}5'} = 8.1$ Hz, $J_{H\text{-}5/H\text{-}6} = 11.9$ Hz, 1H, H-5), 3.46 (d, $J_{H\text{-}3/H\text{-}8} = 2.4$ Hz, 1H, H-3), 3.8 (dtq, $J_{H\text{-}8/H\text{-}7} = 6.6$ Hz, $J_{H\text{-}8/H\text{-}3} = 2.4$ Hz, $J_{H\text{-}8/H\text{-}5'} = 0.6$ Hz, $J_{H\text{-}8/NCH_3} = 0.6$ Hz, 1H, H-8), 4.01 (qd, $J_{H\text{-}b/H\text{-}a} = 10.6$ Hz, $J_{H\text{-}b/Me} = 7.2$ Hz, 1H, H_b), 4.04 (qd, $J_{H\text{-}a/H\text{-}b} = 10.6$ Hz, $J_{H\text{-}a/Me} = 7.2$ Hz, 1H, H_a); ^{13}C NMR (C_6D_6): δ, 13.9 (CH_3), 25.5 (^{t}Bu), 31.2 (N–CH_3), 37.8 (C–Me_3), 45.1 (q, $^3J = 1.8$ Hz, C-7), 48.0 (q, $^2J = 28.9$ Hz, C-6), 55.0 (q, $^2J = 2.2$ Hz, C-5), 61.3 (OCH_3), 67.8 (C-8), 92.6 (C-3), 125.7 (q, $^1J = 278$ Hz, CF_3), 170.3 (COOEt), 171.8 (CO); analysis: found: C, 53.60; H 6.87; N 8.30. Calc. for $C_{15}H_{23}N_2F_3O_3$: C, 53.56; H, 6.89; N, 8.33%.

2.7. Reaction of **3** with paraformaldehyde and cis-4,4,5,5,5-pentafluoro-pent-2-enoate (**11**)

Colourless liquid **12**; yield: 0.31 g, 40%; ^{19}F NMR (C_6D_6): δ, −85.4 (CF_3), −117.2 (dq, $J_{FF} = 9.5$ Hz, $J_{FH} = 12.3$ Hz, F_A), −120.2 (dq, $J_{FF} = 9.5$ Hz, $J_{FH} = 19$ Hz, F_B); ^1H NMR (400 MHz, C_6D_6): δ, 0.76 (s, 9H, ^{t}Bu), 1.03 (t, $J_{CH_3/CH_2} = 7.1$ Hz, 3H, CH_3), 2.55 (ddddd, $J_{H\text{-}6/H\text{-}5'} = 8.3$ Hz, $J_{H\text{-}6/H\text{-}5} = 6.8$ Hz, $J_{H\text{-}6/H\text{-}7} = 6.2$ Hz, $J_{H\text{-}6/H\text{-}A} = 12.3$ Hz, $J_{H\text{-}6/H\text{-}B} = 19$ Hz, 1H, H-6), 2.76 (d, $J_{Me/H\text{-}8} = 0.6$ Hz, 3H, CH_3), 3.16 (dd, $J_{H\text{-}5'/H\text{-}5} = 11.9$ Hz, $J_{H\text{-}5/H\text{-}6} = 6.8$ Hz, 1H, H-5), 3.18 (dd, $J_{H\text{-}7/H\text{-}8} = 6.6$ Hz, $J_{H\text{-}7/H\text{-}6} = 6.2$ Hz, 1H, H-7), 3.32 (dd, $J_{H\text{-}5/H\text{-}5'} = 11.9$ Hz, $J_{H\text{-}5'/H\text{-}6} = 8.3$ Hz, 1H, H-5′), 3.47 (d, $J_{H\text{-}4/H\text{-}8} = 2.4$ Hz, 1H, H-3), 3.75 (dd, $J_{H\text{-}8/H\text{-}7} = 6.6$ Hz, $J_{H\text{-}8/H\text{-}3} = 2.4$ Hz, 1H, H-8), 4.01 (dq, $J_{H\text{-}b/H\text{-}a} = 10.8$ Hz, $J_{H\text{-}b/Me} = 7.1$ Hz, 1H, H_b), 4.06 (dq, $J_{H\text{-}a/H\text{-}b} = 10.8$ Hz, $J_{H\text{-}a/Me} = 7.1$ Hz, 1H, H_a); ^{13}C NMR (C_6D_6): δ, 13.5 (CH_3), 25.3 (^{t}Bu), 31.1 (N–CH_3), 37.5 (CMe_3), 44.6 (C-7), 45.4 (t, $^2J_{CF} = 21.5$ Hz, C-6), 54.5 (C-5), 61.4 (OCH_2), 67.5 (C-8), 92.2 (C-4), 170.2

(COOEt), 171.3 (CO) (CF_2, CF_3 non obs.); analysis: found: C, 50.00; H, 6.12; N, 6.95%. Calc. for $C_{16}H_{23}N_2F_5O_3$: C, 49.74; H, 6.00; N, 7.25%.

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