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Unexpected Ring Transformations on Functionalization of 2-(ω-Alken-1-yl)-3,3,3-trifluoroalanine Derivatives*

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Summary. 2-(ω-Alken-1-yl)-3,3,3-trifluoroalanine derivatives are transformed into trifluoromethyl substituted heterocycles *via* epoxidation reactions.

Keywords. Epoxidation; NBS Bromination; 2-(ω-Alken-1-yl)-3,3,3-trifluoroalanine; 4-Trifluoromethyl-5,6-dihydro-4H-1,3-oxazines; 3a-Methoxy-6a-trifluoromethyl-tetrahydrofurano[2,3d]oxazoline; 3,3-Dimethyl-2-trifluoromethyl-4-hydroxyproline; 3-Trifluoromethyl-tetrahydrofuran-2-ones.

Introduction

Incorporation of α-trifluoromethyl amino acids (α-*Tfm* amino acids) into strategical positions of peptides retards proteolytic degradation, induces secondary structure motifs, and improves lipophilicity [1] enhancing *in vivo* absorption, thus improving permeability through certain body barriers. However, the lipophilic effect of a trifluoromethyl group depends very much on its position in a molecule [2]. Furthermore, ^{19}F NMR spectroscopy represents an efficient tool for conformational studies of fluorine containing peptides as well as for the elucidation of metabolic processes [3]. The spectra can be recorded even in water and under cell-like conditions. Therefore, the synthesis of new members of this special class of $C^{\alpha,\alpha}$-disubstituted amino acids is of current interest as building blocks for

* Dedicated to Prof. Dr. D. Naumann on the occasion of his 60th birthday
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peptide modification and as suicide inhibitors, irreversibly blocking pyridoxal phosphate dependent enzymes [4].

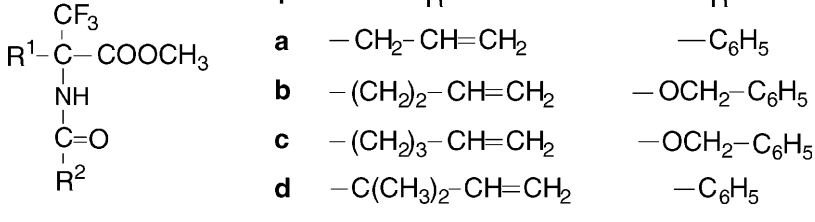
Results and Discussion

The ready access to trifluoromethyl substituted ω-phosphinoyl amino acids from N-protected 2-(ω-Alken-1-yl)-3,3,3-trifluoroalanine methylester (**1**) [5], obtained in excellent yields from the corresponding alkenyl *Grignard* compounds and the highly electrophilic acylimines of methyl trifluoropyruvate [6], and the preparatively simple transformation of compounds of type **1** into α-trifluoromethyl substituted ω-carboxy amino acids on oxidation with potassium permanganate [7], demonstrates that compounds **1** are versatile starting materials for the synthesis of multifunctional *Tfm* amino acids.

In this context, we studied the oxidation reaction of compounds **1** (Scheme 1) with *m*-chloroperbenzoic acid (*MCPBA*). When **1b** und **1c** were treated with *MCPBA* (2 equivalents) in chloroform at room temperature the expected epoxides **2b** und **2c** can be isolated as stabile compounds in high yields as a 1:1 mixture of diastereomers (Scheme 2). The structural assignment is based *i.a.* on the ^{13}C NMR data. The resonance signals of the olefinic C-atoms of compounds **1** in the region of $\delta = 116$–137 ppm have disappeared while two new signals in the region of 46–53 ppm can be found; they are characteristic for an oxirane moiety.

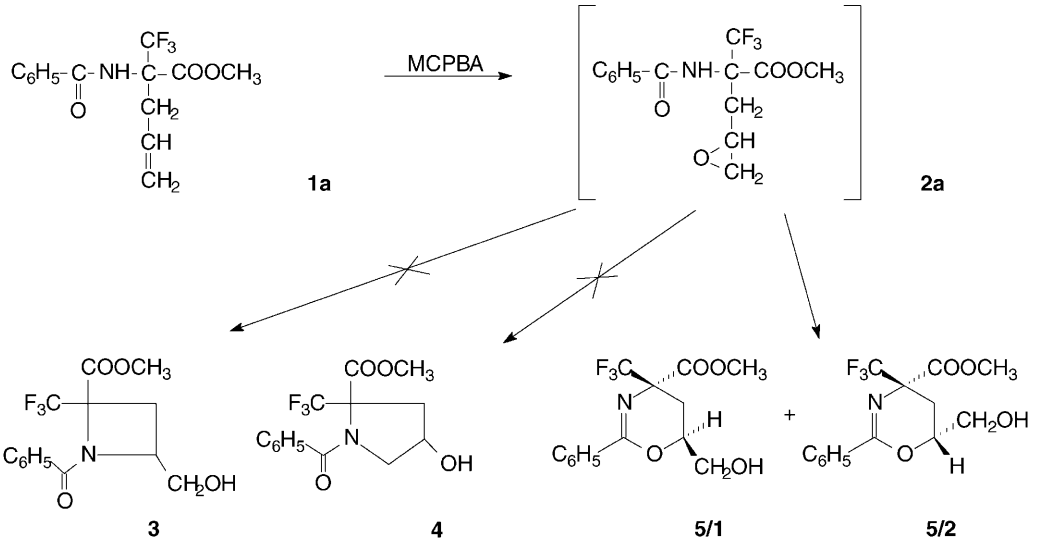
In contrary, when **1a** was treated with *MCPBA* according to the standard protocol the oxirane **2a** formed first immediately undergoes an intramolecular rearrangement with cleavage of the oxirane ring to give a 3:1 mixture of two diastereomers even at room temperature (Scheme 3).

Three different reaction pathways have to be considered. According to „*Baldwin*'s Rules" [8], azetidine formation **2a** → **3** should be more favorable than the formation of the pyrrolidine system **2a** → **4**, since the latter is an endocyclic process to give a five-membered ring system. However, a ring transformation **2a** → **5**



Scheme 1

Scheme 2

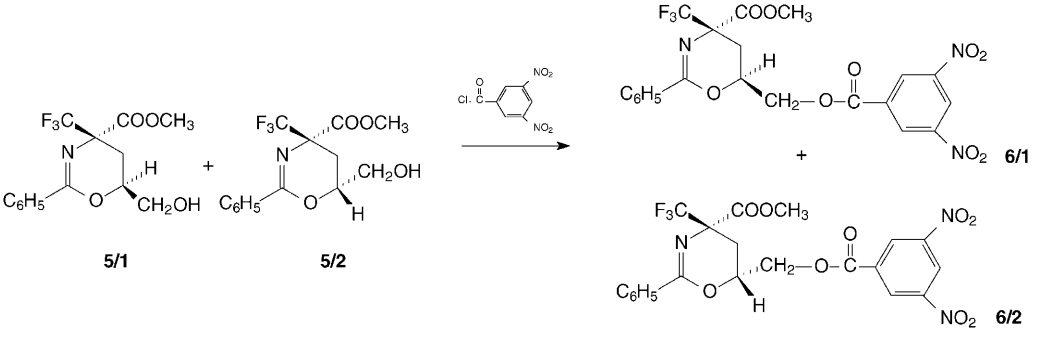


Scheme 3

with attack of the amide oxygen on the oxirane ring represents an exocyclic ring closure and therefore is a plausible alternative route.

After separation by flash chromatography (eluent: ether/hexanes 4:1) both diastereomers exhibit absorptions in the ^{13}C NMR spectra at $\delta = 158.81$, 168.45 and 159.29, 168.64 ppm, respectively. These data are not in agreement with structures represented by formulae **3** and **4** where an ester and an amide group are directly bonded to an azetidine and a pyrrolidine ring system, respectively. Both carbonyl groups should resonate in the region of 165 ppm. On the other hand, a resonance signal at 158 ppm is well in agreement with a –N=C(R)–O-substructure in a six-membered ring, *e.g.* in a 5,6-dihydro-4*H*-1,3-oxazine system [9].

To confirm the 5,6-dihydro-4*H*-1,3-oxazine structure **5** for the oxidation products we decided to perform an X-ray structure analysis [10]. Since both diastereomers are oils we acylated the –OH function with 3,5-dinitrobenzoyl chloride to get crystalline compounds **5** → **6** [11] (Scheme 4). The X-ray structure analysis was performed with crystals of the minor diastereomer after acylation. This compound was eluted first on flash chromatography (eluent: ether/hexanes 1:1).



Scheme 4

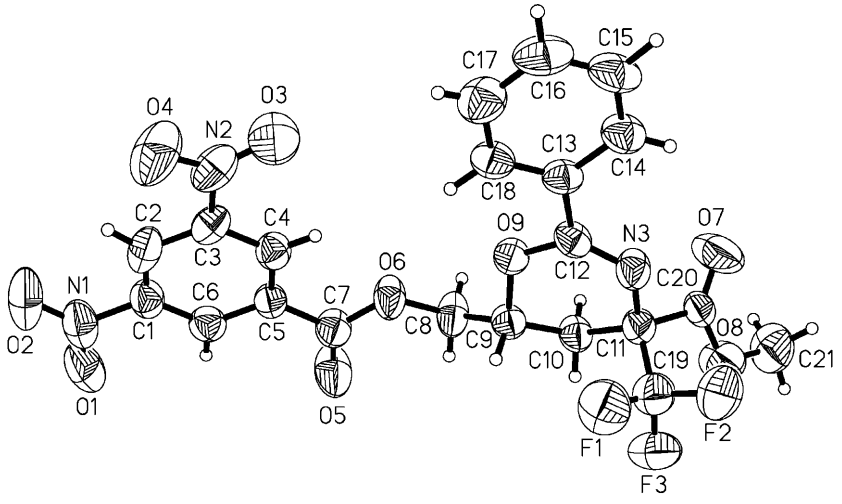
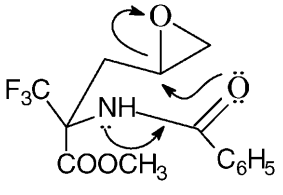


Fig. 1. Structure of **6**/**2** in the crystal

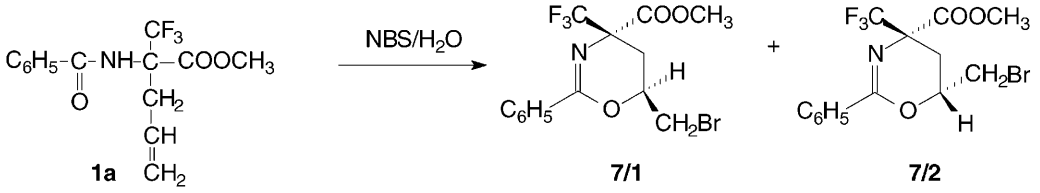
On recrystallisation from chloroform/hexanes suitable crystals for X-ray structure analysis were obtained.

The X-ray data revealed that compound **6**/**2** is indeed a six-membered heterocycle, namely methyl 4-(*RS*)/6-(*SR*)-6-(3,5-dinitrobenzoyloxymethyl)-2-phenyl-4-trifluoromethyl-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate with the trifluoromethyl group and the methine proton in *cis*-position with respect to the plane of the ring system; consequently **6**/**1** is 4-(*RS*)/6-(*RS*)-configurated (Fig. 1). Therefore, we can assign the major component of the epoxidation reaction the structure of methyl 4-(*RS*)/6-(*RS*)-6-hydroxymethyl-2-phenyl-4-trifluoromethyl-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate (**5**/**1**), while the minor compound **5**/**2** is 4-(*RS*)/6-(*SR*)-configurated. The asymmetric induction can be explained by adopting preferentially a chair-like six-membered transition state with both substituents, the CF_3-group and the newly formed CH_2OH-group, ending up in energetically favorable equatorial positions (Scheme 5).

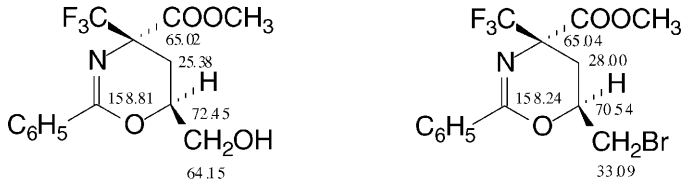
The reaction of *N*-bromosuccinimide (*NBS*) with olefins in aqueous medium represents a well established standard procedure for the synthesis of bromohydrins [12]. When **1a** was treated with *NBS* in a dioxane/water mixture at room temperature a diastereomeric mixture (ratio 4:1, ^{19}F NMR analysis) can be isolated (Scheme 6). The NMR data of the two diastereomers which can be separated by flash chromatography are very similar to those recorded for compounds **5**/**1** and



Scheme 5



Scheme 6



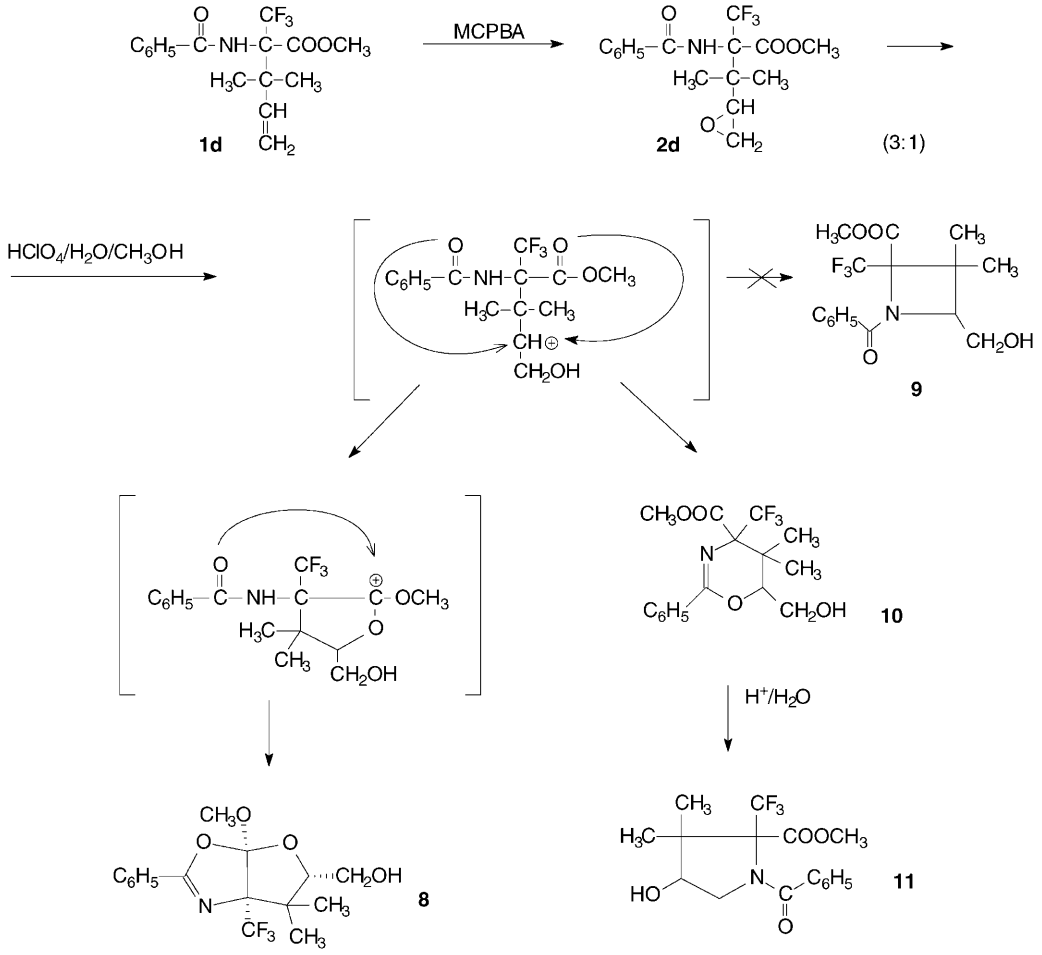
Scheme 7

5/**2**. An absorption in the region of $\delta = 158$ ppm in the ^{13}C NMR spectra undoubtedly indicates the presence of a 5,6-dihydro-4*H*-1,3-oxazine substructure.

Two dimensional heteronuclear N*O*E-experiments (^{19}F–^{1}H-HOESY) with compound **7**/**1** (major isomer) elucidates the relative stereochemistry at the chiral centers at C-4 and C-6. In the N*O*E spectrum a correlation between the $-CF_3$ and the $-CH_2Br$ group can be found, while no correlation could be detected between the CF_3 group and the C(6)–H proton (Scheme 7). Therefore, in the major isomer **7**/**1** the $-CF_3$ and the $-CH_2Br$ group are placed *cis* with respect to the plain of the six-membered ring system. Consequently, the reactions of **1a** with *MCPBA* in chloroform and with *NBS* in dioxane/water belong to the same mechanistic type.

Addition of bromine at 0°C to **1b** gives nearly quantitatively the expected dibromo adduct. Unfortunately, the bromine is lost during the hydrogenolytical cleavage of the *N*-benzyloxycarbonyl group [13].

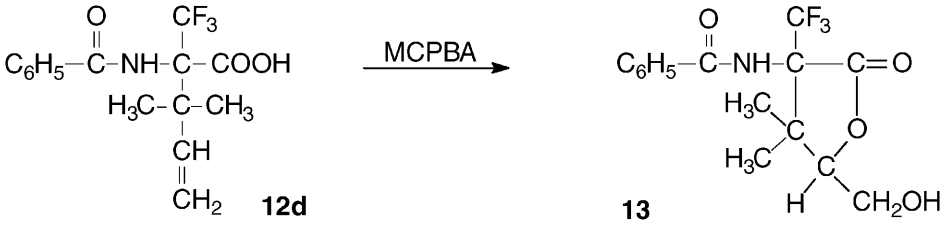
The *N*-benzoyl 2-(1,1-dimethylallyl)-3,3,3-trifluoroalanine methylester **1d** gives a stable oxirane **2d** on reaction with *MCPBA* at room temperature. When **2d** is subjected to a proton-catalyzed hydrolytic ring opening (30% $HClO_4$) in a two-phase system ether/water at room temperature two isomers are formed (Scheme 8). They can be separated by flash chromatography, with the minor compound exhibiting some spectroscopical peculiarities. The signal of the carbonyl C-atom of the methyl ester has disappeared, but the methoxy group still being present [^{13}C NMR: $\delta = 52.99$ ppm; ^{1}H NMR: $\delta = 3.73$ ppm (s, 3H)]. A new signal can be found for a quarterny C-atom at $\delta = 126.34$ ppm. We assign it to an orthoester function [14]. The quartet of the quarternary C-atom adjacent to the trifluoromethyl group is shifted downfield by more than 14 ppm to resonate at $\delta = 84.09$ ppm ($^{2}J_{FC} = 27.0$ Hz). Likewise, the signal of the methylene group is shifted downfield from $\delta = 44.04$ to 61.0 ppm indicating the presence of a $-CH_2OH$ function. The proton-catalyzed ring opening of the oxirane should proceed *via* a secondary carbenium ion, which can be attacked by the oxygen atom of the ester moiety,



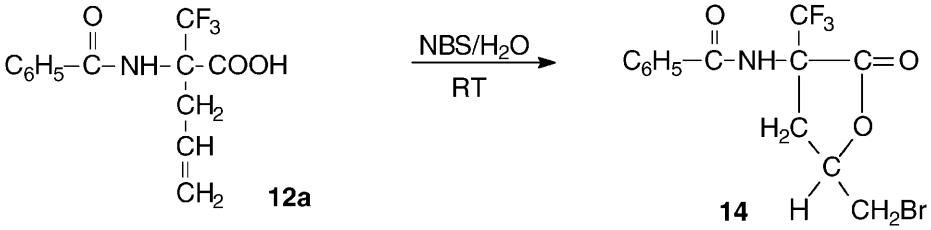
Scheme 8

generating a new carbenium ion which immediately is attacked by the oxygen atom of the amide function resulting in the formation of a bicyclic system **8**.

Likewise, the main product should be formed *via* the secondary carbenium ion intermediate, which alternatively can be directly attacked by the nitrogen or the oxygen atom of the amide group providing a four- and/or a six-membered ring. However, an azetidine (**2d** → **9**) as well as a 5,6-dihydro-4*H*-oxazine formation (**2d** → **10**) can be ruled out for the diastereomeric mixture isolated by flash chromatography, because in the ^{13}C NMR spectrum the characteristic absorptions of a $-CH_2OH$ (60–65 ppm) and of a $-N{=}C(R)–O$-moiety (158 ppm) are missing. The spectroscopic data are in agreement with a proline derivative **11**. However, a direct ring closure **2d** → **11** is an unfavorable process according to *Baldwin*'s rules [8]. *S.N. Osipov et al.* describe that methyl 6-chloromethyl-5,6-dihydro-2,4-bis(trifluoromethyl)-4*H*-1,3-oxazine is acid labile, being transformed into a pyrrolidine on treatment with catalytic amounts of HCl/H_2O in methanol already at room temperature [9c]. Therefore, we postulate a reaction sequence **2d** → **10** → **11** for the formation of the 3,3-dimethyl-2-trifluoromethyl-4-hydroxyproline methylester, a new sterically highly crowded proline derivative.



Scheme 9



Scheme 10

When the unprotected acid **12d** instead of the ester **1d** is used as a substrate for the epoxidation process a highly diastereoselective reaction (de 95%) with formation of a lactone is observed (Scheme 9). The characteristic IR absorption of the carboxylic group ($\nu = 1750–1760\,cm^{-1}$) is shifted to shorter wave lengths, giving rise to two absorption bands at 1785 and 1795 cm^{-1}. A low field shift of the two C-atoms of the oxirane carbon skeleton from $\delta = 44.0$ (CH_2), 56.3 (CH) to 63.0 (CH_2OH), 79.3 (CH) ppm indicates that a ring opening of the oxirane system is involved in the ring transformation. Based on the spectroscopic data we assign the compound structure **13**.

Analoguously, 2-benzoylamino-2-trifluoromethyl-4-pentenoic acid (**12a**) reacts with *NBS* in a dioxane/water mixture (5:1) at room temperature to give a typical halolactonization product **14** (Scheme 10). On application of compounds **5**, **7**, **13**, and **14** for the synthesis of multifunctional α-*Tfm* amino acids and their incorporation into peptide surrogates we will report elsewhere.

Experimental

General

Solvents were purified and dried prior to use. Reagents were used as purchased. Melting points (uncorrected) were determined on a Boetius heating table. Mass spectra were recorded on a VG 12-250 and a MAT 212 (Masslab) electron ionization spectrometer (EI-MS, EI = 70 eV). IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam) and a Specord M 80 (Fa. Carl Zeiss, Jena). ^1H (200 MHz, 300 MHz), ^{13}C (50 MHz, 75 MHz), and ^{19}F (188 MHz) NMR spectra were recorded on a Varian Gemini 2000 spectrometer. *TMS* was used as reference for ^1H and ^{13}C NMR spectra (internal), and CF_3COOH for ^{19}F NMR spectra (external). Flash chromatography was performed using silica gel (32–63 μm) with solvent systems given in the text. Elemental analyses were performed with a CHNO–S Rapid apparatus (Fa. Heraeus).

Oxidation of the CC double bond with MCPBA; general procedure

To a solution of the corresponding *N*-protected 2-(ω-Alken-1-yl)-3,3,3-trifluoroalanine methylester **1** (10 mmol) in dry chloroform (30 cm^3) *MCPBA* (3.35 g, 20 mmol) was added with stirring at 0°C. The reaction mixture was stirred at room temperature until ^{19}F NMR analysis indicated complete consumption of the starting material. The organic phase was extracted with an aqueous solution of $NaHSO_3$ and then with an ice-cold aqueous solution of $NaHCO_3$ (3X). After drying the organic phase with $MgSO_4$, the solvent was evaporated *in vacuo*. The crude product was purified by recrystallization from chloroform/hexanes (1:1) or by flash chromatography (eluent: ether/hexanes 4:1).

Methyl 2-(N-benzyloxycarbonylamino)-5,6-epoxy-2-trifluoromethylhexanoate
(**2b**, $C_{16}H_{18}F_3NO_5$)

Yield 82%, diastereomeric mixture (1:1); colorless oil; ^1H NMR ($CDCl_3$): $\delta = 1.22–1.31$ (m, 1H)/1.38–1.43 (m, 1H), 1.53–1.63 (m, 2H), 2.19–2.45 (m, 4H), 2.70–2.72 (m, 2H), 2.89 (m, 4H), 3.84 (s, 6H), 5.09 (s, 2H)/5.10 (s, 2H), 5.60 (s, 1H)/6.02 (s, 1H), 7.28–7.43 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.94/25.33$, 26.11/26.71, 46.62/46.85, 50.95/51.28, 53.85/53.98, 65.45 (q, $J = 28.7$ Hz)/65.62 (q, $J = 28.7$ Hz), 67.08, 123.80 (q, $J = 288.0$ Hz), 128.02/128.22, 128.44, 129.65/129.96, 133.28/135.70, 153.72, 166.82 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 3.11$ (s, 3F)/3.24 (s, 3F) ppm; IR (film): $\nu = 3400–3260$, 1765–1710, 1540–1500 cm^{-1}; MS (EI): $m/z = 361$ $[M]^+$, 237 $[M–C_7H_8O_2]^+$, 150 $[C_7H_7OCONH]^+$, 108 $[C_7H_8O]^+$, 107 $[C_7H_7O]^+$, 91 $[C_7H_7]^+$.

Methyl 2-(N-benzyloxycarbonylamino)-6,7-epoxy-2-trifluoromethylheptanoate
(**2c**, $C_{17}H_{20}F_3NO_5$)

Yield 90%, mixture of diastereomers (1:1); mp 94–95°C; ^1H NMR ($CDCl_3$) $\delta = 1.22–1.29$ (m, 2H), 1.44–1.45 (m, 4H), 1.60 (m, 2H), 2.10–2.19 (m, 2H), 2.41–2.43 (m, 2H), 2.70–2.73 (m, 2H), 2.83 (m, 4H), 3.84 (s, 6H), 5.07 (d, $J = 12.4$ Hz, 2H)/5.13 (d, $J = 12.4$ Hz, 2H), 5.94 (s, 1H)/5.98 (s, 1H), 7.30–7.41 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.73/20.21$, 28.28, 31.56/31.90, 46.69/46.84, 51.43/51.74, 53.97, 66.00 (q, $J = 28.7$ Hz), 67.02, 123.85 (q, $J = 287.80$ Hz), 128.06, 128.23, 128.48, 135.86, 153.70, 167.07 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 3.17$ (s, 3F), 3.22 (s, 3F) ppm; IR (KBr): $\nu = 3325$, 1755, 1725 cm^{-1}; MS (EI): $m/z = 375$ $[M]^+$, 316 $[M–CO_2CH_3]^+$, 108 $[C_7H_8O]^+$, 107 $[C_7H_7O]^+$, 91 $[C_7H_7]^+$.

4-(RS)/6-(RS)- and 4-(RS)/6-(SR)-methyl (6-hydroxymethyl-2-phenyl-4-trifluoromethyl-5,6-dihydro-4H-1,3-oxazine)-4-carboxylate (**5**/**1**, **5**/**2**, $C_{14}H_{14}F_3NO_4$)

Yield 72%, diastereomeric mixture (3:1); colorless oil; IR (film): $\nu = 3660–3150$, 1750, 1655 cm^{-1}; MS (EI): $m/z = 317$ $[M]^+$, 258 $[M–CO_2CH_3]^+$, 240 $[M–C_6H_5]^+$, 212 $[M–C_6H_5, -CO]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

5/**1**: Yield 45%, oil; $R_f = 0.29$ (ether/hexanes, 4:1); ^1H NMR ($CDCl_3$): $\delta = 2.05$ (dd, $J = 13.6$, $J = 12.5$ Hz, 1H), 2.47 (dd, $J = 13.6$, $J = 2.7$ Hz, 1H), 2.71 (s, 1H), 3.76 (dd, $J = 12.3$, $J = 4.7$ Hz, 1H), 3.82 (s, 3H), 3.94 (dd, $J = 12.3$, $J = 3.4$ Hz, 1H), 4.27–4.34 (m, 1H), 7.35–7.40 (m, 2H), 7.43–7.48 (m, 1H), 7.98–8.03 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.39$, 53.72, 64.15, 65.02 (q, $J = 28.3$ Hz), 72.45, 123.98 (q, $J = 283.2$ Hz), 127.93, 128.18, 131.67, 132.27, 158.81, 168.45 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 0.6$ (s, 3F) ppm.

5/**2**: Yield 17%, oil; $R_f = 0.31$ (ether/hexanes, 4:1); ^1H NMR ($CDCl_3$): $\delta = 2.15$ (s, 1H), 2.32–2.43 (m, 2H), 3.72–3.77 (m, 1H), 3.84 (s, 3H), 3.92 (dd, $J = 12.3$, $J = 3.8$ Hz, 1H), 4.44–4.48 (m, 1H), 7.37–7.48 (m, 3H), 8.00–8.03 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.50$, 53.57, 63.60 (q, $J = 27.5$ Hz), 64.07, 71.93, 123.98 (q, $J = 283.2$ Hz), 128.01, 128.18, 131.78, 132.50, 159.29, 168.64 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 4.28$ (s, 3F) ppm.

4-(RS)/6-(RS)- and 4-(RS)/5-(SR)-methyl [6-(3,5-dinitrobenzoyloxymethyl)-2-phenyl-4-trifluoromethyl-5,6-dihydro-4H-1,3-oxazine]-4-carboxylate (**6**/**1**, **6**/**2**, $C_{21}H_{16}F_3N_3O_9$)

To a solution of the diastereomeric mixture **5** (0.8 g, 2.5 mmol) and dry triethylamine (0.26 g, 2.5 mmol) in dry ether (20 cm^3) at 0°C a solution of 3,5-dinitrobenzoylchloride (0.6 g, 2.6 mmol) in ether/methylene chloride (1:1, 5 cm^3) was added with stirring. Stirring was continued for 12 h. Then the solvent was evaporated *in vacuo*. The remaining crude product was dissolved in methylene chloride, washed carefully with 1*N* HCl, $NaHCO_3$ solution and water and dried with $MgSO_4$. After evaporation of the solvent *in vacuo* the two diastereomers were separated by flash chromatography (eluent: ether/hexanes, 1:1). Yield 78%, diastereomeric mixture; IR (KBr): $\nu = 1760$, 1745, 1655, 1555–1545 cm^{-1}; MS (EI): $m/z = 511$ $[M]^+$, 452 $[M–CO_2CH_3]^+$, 136 $[M–C_6H_5CO, -CO_2C_6H_3(NO_2)_2]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

6/**1**: Yield 41%; mp 172°C; $R_f = 0.30$ (ether/hexanes, 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 2.00$–2.08 (m, 1H), 2.68 (dd, $J = 13.9$, $J = 2.6$ Hz, 1H), 3.89 (s, 3H), 4.58–4.85 (m, 3H), 7.37–7.49 (m, 3H), 7.99–8.03 (m, 2H), 9.19 (m, 2H), 9.24–9.25 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.65$, 53.93, 64.73 (q, $J = 28.7$ Hz), 67.05, 69.75, 123.83 (q, $J = 285.1$ Hz), 122.83, 127.88, 128.29, 128.67, 129.56, 131.89, 133.07, 148.81, 158.04, 162.20, 168.02 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 0.62$ (s, 3F) ppm.

6/**2**: Yield 11%; mp 138–140°C; $R_f = 0.35$ (ether/hexanes, 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 2.35$–2.43 (m, 1H), 2.62 (dd, $J = 14.7$, $J = 3.5$ Hz, 1H), 3.89 (s, 3H), 4.57–4.63 (m, 1H), 4.77–4.83 (m, 2H), 7.38–7.51 (m, 3H), 8.01–8.03 (m, 2H), 9.19–9.20 (m, 2H), 9.24–9.25 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.92$, 53.78, 63.41 (q, $J = 27.6$ Hz), 66.89, 69.24, 122.83, 123.83 (q, $J = 285.1$ Hz), 127.94, 128.29, 129.57, 129.70, 131.97, 133.05, 148.79, 158.51, 162.19, 168.01 ppm; ^{19}F NMR ($CDCl_3$) $\delta = 4.06$ (s, 3F) ppm.

4-(RS),6-(RS)-methyl [6-bromomethyl-2-phenyl-4-trifluoromethyl-5,6-dihydro-4H-1,3-oxazine]carboxylate (**7**/**1**, **7**/**2**, $C_{14}H_{13}BrF_3NO_3$)

1a (2.2 g, 7.3 mmol) and *N*-bromosuccinimide (2.6 g, 14.6 mmol) were stirred in a dioxane/water mixture (50 cm^3) at room temperature for 24 h. Then the solvent mixture was evaporated *in vacuo*. The residue was dissolved in ether (50 cm^3) and washed with water (2X). The organic phase was dried with $MgSO_4$. After evaporation to dryness, the diastereomeric mixture was separated by flash chromatography (eluent: chloroform).

7/**1**: Yield 40%; mp 80–82°C; $R_f = 0.30$ (chloroform); ^{1}H NMR ($CDCl_3$): $\delta = 1.97$ (dd, $J = 13.5$, $J = 12.1$ Hz, 1H), 2.67 (dd, $J = 13.5$, $J = 2.9$ Hz, 1H), 3.58 (dd, $J = 11.1$, $J = 5.5$ Hz, 1H), 3.63 (dd, $J = 11.1$, $J = 4.8$ Hz, 1H), 3.84 (s, 3H), 4.41–4.48 (m, 1H), 7.38–7.42 (m, 2H), 7.46–7.51 (m, 1H), 8.03–8.05 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.00$, 33.09, 53.72, 65.04 (q, $J = 28.6$ Hz), 70.54, 123.71 (q, $J = 283.3$ Hz), 127.90, 128.13, 131.69, 131.80, 158.24, 168.02 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 0.67$ (s, 3F) ppm; IR (KBr): $\nu = 1740$, 1640 cm^{-1}.

7/**2**: Yield 8%; mp 162°C; $R_f = 0.26$ (chloroform); ^{1}H NMR ($CDCl_3$): $\delta = 2.28$ (ddq, $J = 15.0$, $J = 13.0$, $J = 1$ Hz, 1H), 2.63 (dd, $J = 15.0$, $J = 4$ Hz, 1H), 3.57 (m, 2H), 3.86 (s, 3H), 4.54 (m, 1H), 7.44 (m, 3H), 8.06 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.22$, 33.00, 53.57, 63.75 (q, $J = 28.0$ Hz), 70.16, 123.77 (q, $J = 285.0$ Hz), 128.01, 128.14, 131.77, 132.05, 158.69, 168.01 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 4.31$ (s, 3F) ppm; IR (KBr): $\nu = 1735$, 1650 cm^{-1}.

Methyl 2-(N-benzoylamino)-4,5-epoxy-3,3-dimethyl-2-trifluoromethlypentanoate (**2d**, $C_{16}H_{18}F_3NO_4$)

To a cooled solution (0°C) of **1d** (3.29 g, 10 mmol) in dry chloroform (30 cm^3) *MCPBA* (3.45 g, 20 mmol) was added. Stirring at room temperature was continued for 48 h. The organic phase was extracted with ice-cold $NaHCO_3$ solution (3×10 cm^3). After drying with $MgSO_4$, the solvent was

evaporated to dryness the diastereomeric mixture (ratio 3:1) was recrystallized from chloroform/hexanes to give the major diastereomer as pure compound. Yield 61%; mp 155°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.15$ (s, 3H), 1.27 (s, 3H), 2.81 (t, $J = 4.0$ Hz, 1H), 2.87 (m, 1H), 3.32 (m, 1H), 3.90 (s, 3H), 7.31 (s, br., 1H), 7.54 (m, 3H), 7.80 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.41$, 21.55, 40.43, 44.04, 52.84, 56.84, 69.78 (q, $J = 27.0$ Hz), 125.14 (q, $J = 290.0$ Hz), 127.17, 128.78, 132.10, 133.40, 164.72, 165.47 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 14.74$ (s, 3F) ppm; IR (KBr): $\nu = 3420$, 1750, 1525, 1490 cm^{-1}; MS (EI): $m/z = 345$ $[M]^+$, 327 $[M–H_2O]^+$, 314 $[M–OCH_3]^+$, 286 $[M–CO_2CH_3]^+$, 261 $[M–CF_3, -CH_3]^+$, 105 $[C_7H_5O]^+$, 85 $[C_5H_9O]^+$, 77 $[C_6H_5]^+$.

6,6-Dimethyl-5-hydroxymethyl-3a-methoxy-2-phenyl-6a-trifluoromethyl-tetrahydrofurano-[2,3-d]oxazoline and N-benzoyl-3,3-dimethyl-2-trifluoromethyl-4-hydroxyproline methylester (**8**, $C_{16}H_{18}F_3NO_4$/**11**, $C_{16}H_{18}F_3NO_4$)

To a solution of oxirane **2d** (0.35 g, 1 mmol) in ether (10 cm^3), an aqueous solution of perchloric acid (30%, 2 cm^3) was added with stirring. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. When the reaction was complete (24 h), the organic phase was separated and washed carefully (2X) with $NaHCO_3$ solution and water. After drying with $MgSO_4$, the solvent was evaporated *in vacuo*, and the two isomers were separated by flash chromatography.

8: Yield 10%; mp 118–120°C; $R_f = 0.09$ (ether/hexanes, 1:3); ^{1}H NMR ($CDCl_3$): $\delta = 1.16$ (q, $J = 2.3$ Hz, 3H), 1.23 (s, 3H), 2.14 (s, 1H), 3.67–3.83 (m, 3H), 3.73 (s, 3H), 7.41–7.45 (m, 2H), 7.51–7.55 (m, 1H), 8.00–8.02 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.06$ (q, $J = 3.0$ Hz), 20.76, 45.73, 52.99, 61.00, 84.09 (q, $J = 27.0$ Hz), 85.69, 124.01 (q, $J = 283.1$ Hz), 126.34, 128.33, 128.47, 128.67, 132.51, 164.72 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 10.61$ (s, 3F) ppm; IR (KBr): $\nu = 3520–3380$, 1640 cm^{-1}; MS (EI) $m/z = 345$ $[M]^+$, 330 $[M–CH_3]^+$, 314 $[M–OCH_3]^+$, 286 $[M–CO_2CH_3]^+$, 269 $[M–CO_2CH_3, -OH]^+$, $[M–C_7H_5NO]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$.

11: Yield 60%, mixture of two diastereomers.

Diastereomer 1 (**11**/**1**): Oil; $R_f = 0.24$ (ether/hexanes, 1:3); ^{1}H NMR ($CDCl_3$): $\delta = 1.18$ (s, 3H), 1.38 (q, $J = 1.8$ Hz, 3H), 3.09 (s, 1H), 3.19 (dd, $J = 11.0$, $J = 5.0$ Hz, 1H), 3.59 (dd, $J = 11.0$, $J = 5.8$ Hz, 1H), 3.88 (s, 3H), 5.29–5.31 (m, 1H), 7.44–7.48 (m, 2H), 7.56–7.58 (m, 1H), 7.99–8.02 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.04$, 22.68 (q, $J = 2.8$ Hz), 48.00, 48.85, 53.40, 75.88 (q, $J = 26.6$ Hz), 80.86 (q, $J = 1.8$ Hz), 125.13 (q, $J = 285.5$ Hz), 128.53, 129.68, 129.73, 133.35, 165.70, 169.61 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 8.74$ (s, 3F) ppm.

Diastereomer 2 (**11**/**2**): Mp 49–50°C; $R_f = 0.21$ (ether/hexanes, 1:3); ^{1}H NMR ($CDCl_3$): $\delta = 1.12$ (s, 3H), 1.38 (q, $J = 1.9$ Hz, 3H), 3.06 (s, 1H), 3.18 (dd, $J = 11.8$, $J = 2.7$ Hz, 1H), 3.77 (dd, $J = 11.8$, $J = 6.2$ Hz, 1H), 3.87 (s, 3H), 5.23 (dd, $J = 6.2$, $J = 2.7$ Hz, 1H), 7.43–7.47 (m, 2H), 7.55–7.59 (m, 1H), 8.05–8.07 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.47$ (q, $J = 2.7$ Hz), 25.95, 48.34, 50.32, 53.37, 76.89 (q, $J = 27.1$ Hz), 81.36, 125.05 (q, $J = 285.8$), 128.51, 129.73, 129.86, 133.28, 166.05, 169.57 (q, $J = 1.9$ Hz) ppm; ^{19}F NMR ($CDCl_3$): $\delta = 8.83$ (s, 3F) ppm.

3-(N-benzoylamino)-4,4-dimethyl-5-hydroxymethyl-3-trifluoromethyltetrahydrofuran-2-one (**13**, $C_{15}H_{16}F_3NO_4$)

Yield 68%; mp 70–71°C; de 95%; ^{1}H NMR ($CDCl_3$): $\delta = 1.09$ (s, 3H), 1.78 (q, $J = 1.2$ Hz, 3H), 2.46 (s, 1H), 3.87–3.89 (m, 2H), 4.67–4.70 (m, 1H), 6.84 (s, 1H), 7.46–7.51 (m, 2H), 7.55–7.60 (m, 1H), 7.79–7.82 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.88$, 20.19, 45.42, 60.85, 69.46 (q, $J = 28.3$ Hz), 88.20, 123.58 (q, $J = 290.4$ Hz), 127.13, 128.88, 132.54, 133.12, 166.59, 169.96 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 9.45$ (s, 3F) ppm; IR (KBr): $\nu = 3480–3380$, 3410, 1795, 1785, 1675, 1530 cm^{-1}; MS (EI): $m/z = 314$ $[M–OH]^+$, 313 $[M–H_2O]^+$, 301 $[M–2x\ CH_3]^+$, 300 $[M–CH_2OH]^+$, 247 $[M–CH_3, -CF_3]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

3-(N-benzoylamino)-5-bromomethyl-3-trifluoromethyl-tetrahydrofuran-2-one
(**14**, $C_{13}H_{11}F_3NO_3Br$)

2-Benzoylamino-2-trifluoromethyl-4-pentenoic acid (**12a**) (0.29 g, 1 mmol) and *NBS* (0.40 g, 2 mmol) were stirred at room temperature in a dioxane/water mixture (5:1) for 19 h. After evaporation of the solvent *in vacuo* the residue was dissolved in ether (20 cm^3). The organic phase was washed with water, dried with $MgSO_4$ and evaporated to dryness *in vacuo*. The diastereomeric mixture was separated by preparative DC (eluent: ether/hexanes, 2:1).

Diastereomer 1 (**14**/**1**): Yield 22%; mp 104°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.79$ (dd, $J = 15.0$ Hz, $J = 9.0$ Hz, 1H), 3.22 (dd, $J = 15.0$ Hz, $J = 7.0$ Hz, 1H), 3.72 (m, 2H), 4.84 (m, 1H), 6.86 (s, br., 1H), 7.51 (m, 3H), 7.79 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 32.19$, 34.52, 63.79 (q, $J = 29$ Hz), 76.06, 123.58 (q, $J = 286.0$ Hz), 127.30, 128.93, 132.04, 132.95, 167.02, 167.59 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 2.52$ (s, 3F) ppm; IR (KBr): $\nu = 3385$, 1790, 1665 cm^{-1}; MS (EI): $m/z = 367/365$ $[M]^+$, 298/296 $[M–CF_3]^+$, 286 $[M–Br]^+$, 242 $[M–Br, -CO_2]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

Diastereomer 2 (**14**/**2**): Yield 44%; mp 106°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.79$ (dd, $J = 15.0$ Hz, $J = 7.0$ Hz, 1H), 3.22 (dd, $J = 15.0$ Hz, $J = 8$ Hz, 1H), 3.50 (m, 1H), 3.68 (m, 1H), 5.25 (m, 1H), 6.85 (s, br., 1H), 7.49 (m, 3H), 7.82 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 32.18$, 34.73, 63.98 (q, $J = 29.0$ Hz), 75.84, 123.76 (q, $J = 286.0$ Hz), 127.36, 128.97, 131.56, 133.11, 167.64, 171.49 ppm; ^{19}F NMR ($CDCl_3$): $\delta = 2.39$ (s, 3F) ppm; IR (KBr): $\nu = 3360$, 1795, 1770, 1665 cm^{-1}; MS (EI): $m/z = 367/365$ $[M]^+$, 298/296 $[M–CF_3]^+$, 286 $[M–Br]^+$, $[M–Br, -CO_2]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

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[10] Crystal structure analysis of compound **6**/**2**. The data were collected on an Enraf Nonius CAD4 diffractometer, using graphite-monochromated Mo K_α radiation. The structure was solved by a combination of direct methods and difference-Fourier syntheses and refined by full matrix least-squares calculations on F^2. The thermal motion was treated anisotropically for all non-hydrogen atoms. All hydrogen atoms except for those of the methyl group were located and refined with isotropic contributions. The methyl hydrogen atoms were calculated and allowed to ride on their corresponding C atoms with fixed isotropic contributions. *Crystal data for* $C_{21}H_{16}F_3N_3O_9$. $M_r = 511.37$, colorless crystal, monoclinic, $a = 6.351(1)$, $b = 43.188(9)$, $c = 8.116(2)$ Å, $\beta = 95.54(3)^\circ$, space group $P2_1/c$, $Z = 4$, $V = 2215.7(8)$ Å^3, $\rho_{calc} = 1.533\,g\,cm^{-3}$, $F(000) = 1048$; $T = 22^\circ C$. 11148 measured and 3479 unique reflections [$R_{int} = 0.0433$]; 377 refined parameters, w$R2 = 0.1162$, $R1 = 0.0706$. Residual electron densities: $+0.239/-0.164\,e/Å^3$. The function minimized was: w$R2 = \{[\Sigma w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (ap)^2 + bp]$; $p = (F_o^2 + 2F_c^2)/3$; $a = 0.0561$, $b = 0.33$. Anisotropic thermal parameters and complete lists of interatomic distances and angles have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. The data are available on request on quoting CCDC-186573

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