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Synthesis of Partially Modified Retro and Retroinverso ψ[NHCH(CF_3)]-Peptides

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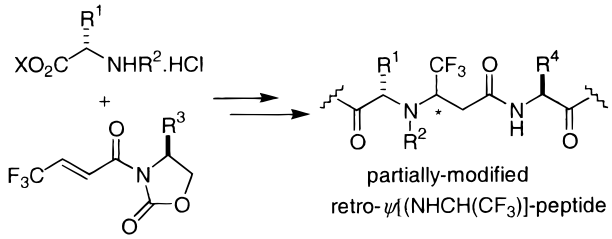
ABSTRACT



Asymmetric conjugate additions of chiral α-amino esters to chiral 4-CF_3 Michael-acceptors were exploited to prepare a small library of enantiomerically pure partially modified retropeptides having a ψ[NHCH(CF_3)] unit as a possible mimic of the classical ψ(NHCO) retropeptide unit. Yields were nearly quantitative, and the stereoselectivity, which is controlled mainly by the nitrogen nucleophile, was progressively higher with increasing the steric bulk of the α-amino ester side-chain R^1.

The pharmacological properties of most peptides preclude their use as drugs. The main problems are connected with their poor bioavailability, bioselectivity, and biostability, and also to the fact that very often a single conformation of a peptide is responsible for its biological activity and hence function. The aim of peptide modification is to discover and produce analogues that can overcome the barriers and drawbacks described above, while retaining selected activity, i.e., as specific receptor antagonists or agonists. Two of the most popular strategies to modify peptides are (a) to replace a peptide bond with a surrogate unit X, which is usually symbolized as ψ(X);[1] (b) to reverse all or some of the peptide bonds (NH−CO instead of CO−NH), giving rise to the so-called retro- or partially modified retropeptides, respectively.[2] When the stereochemistry of one or more amino acids of the reversed segment is inverted, the resulting pseudopeptide is termed as retroinverso. A malonic unit is classically incorporated to provide partially modified retropeptides, while the direction can be restored incorporating an additional *gem*-diaminoalkyl unit.[3]

Our idea is to combine these strategies in a novel class of pseudopeptides having a novel ψ[NHCH(CF_3)] as a possible mimic of the classical ψ(NHCO) unit featured by retropeptides (Figure 1).[4] This surrogate is expected to be stable toward proteolytic degradation, isopolar with the NH−CO unit, and eventually the stereoelectronically demanding CF_3 might introduce some conformational constraint, thus limiting

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(3) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1−7. (b) Chorev, M.; Willson, C. G.; Goodman, M. *J. Am. Chem. Soc.* **1977**, *99*, 8075−8076.

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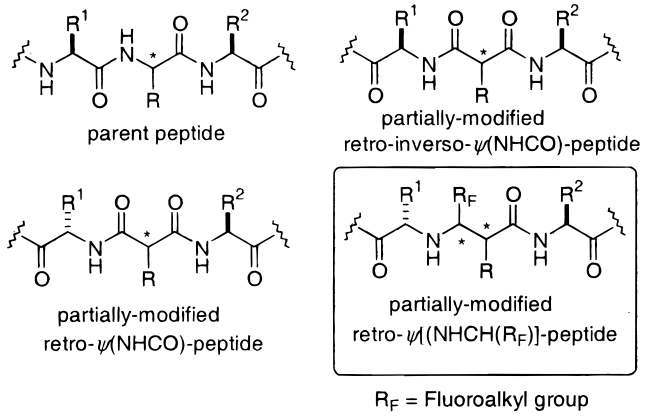


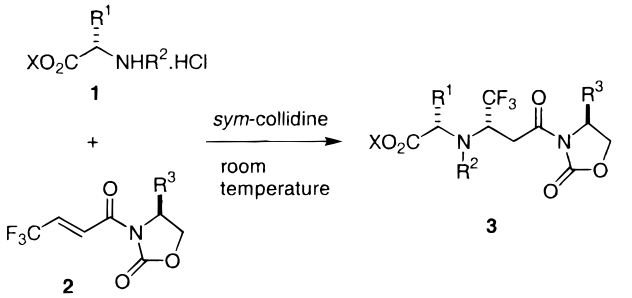
Figure 1.

the number of stable conformational isomers, as well as modify the binding properties acting as a hydrogen bond acceptor or coordinative site with enzymes or receptor subsites.[5]

In this communication we report the synthesis of the first, and simplest, series of partially modified retro- and retro-inverso ψ[NHCH(CF_3)]-tripeptides, where the central unit is a mimic of glycine (R = H).

Assembling of ψ[NHCH(CF_3)]-containing dipeptide units was achieved by conjugate *N*-addition of a series of L-α-amino esters **1** (Scheme 1) to the enantiomerically and geometrically pure Michael acceptors (*S*)-(*E*)-**2**, prepared according to literature methods.[6] Pseudodipeptides **3** were formed in excellent yields by mixing the hydrochlorides or PTSA salts of **1** (2 equiv) with (*S*)-(*E*)-**2** and *sym*-collidine (4 equiv) in the appropriate solvent and stirring at room temperature (rt) for 16−88 h (Table 1).[7] Diastereomerically pure **3** were smoothly isolated by flash chromatography on silica gel. The solvent has a strong influence on the stereoselectivity, as shown by experiments carried out on the sample reaction between L-**1a** and **2a**. The best results were obtained in DCM (entry 1), while a remarkable drop of de was observed with more polar solvents such as ethanol, acetonitrile, THF, DMF, or mixtures of them (entries 2−5). In light of these results, DCM was used as the solvent of choice for the preparation of pseudodipeptides **3a**−**j**. The facial diastereoselectivity of these reactions is mainly controlled by α-amino esters **1**. In fact, in all cases L-configured **1** (Scheme 1 and Table 1) attacks preferentially

Scheme 1



the *Si*-face of (*S*)-**2a** producing (*S*)-configured centers, whereas enantiomeric D-Ala-OMe **1a** (Scheme 2) attacks the *Re*-face producing the other diasteromer **4**, although with lower diastereocontrol (mismatch).[8] Moreover, compound **3f** was produced with good diastereocontrol when L-Val-OBn **1c** was reacted with the achiral Michael-acceptor **2c** (entry 10), while achiral Gly-OEt **1f** added to (*S*)-**2a** (entry 14) without stereocontrol, affording an equimolar mixture of **3j**.

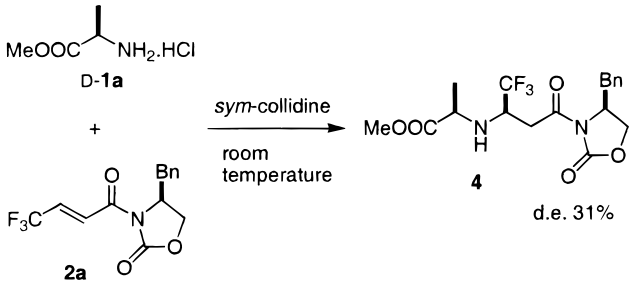
In this context, it is not surprising that the stereoelectronic features of the R^1 side-chain have a remarkable impact on the degree of diastereoselectivity, which follows the trend iso-Pr > iso-Bu > Me > Bn > H (de up to 78% in the case of **3e**, entry 9). Modest de was obtained with the cyclic α-amino ester L-Pro-OBn **1e**, but the reaction occurred also in this case with very good yield. The R^3 substituent on the

Table 1.

entry	prod.	amino acid	oxaz	R^1	R^2	R^3	X	solvent	*T* (h)	yield (%)[c]	de (%)[d]
1	**3a**	**1a**	**2a**	Me	H	Bn	Me	DCM	16	90	50
2	**3a**	**1a**	**2a**	Me	H	Bn	Me	EtOH	16	80	20
3	**3a**	**1a**	**2a**	Me	H	Bn	Me	MeCN	40	80	31
4	**3a**	**1a**	**2a**	Me	H	Bn	Me	THF/DMF 4:1	40	nd[b]	26
5	**3a**	**1a**	**2a**	Me	H	Bn	Me	PhH/DMF 4:1	40	>98	29
6	**3b**	**1a**	**2b**	Me	H	iso-Pr	Me	DCM	64	91	60
7[a]	**3c**	**1b**	**2a**	Bn	H	Bn	Bn	DCM	24	78	43
8	**3d**	**1c**	**2a**	iso-Pr	H	Bn	Bn	DCM	64	92	72
9	**3e**	**1c**	**2b**	iso-Pr	H	iso-Pr	Bn	DCM	68	>98	78
10	**3f**	**1c**	**2c**	iso-Pr	H	H	Bn	DCM	68	90	65
11[a]	**3g**	**1d**	**2a**	iso-Bu	H	Bn	Bn	DCM	88	>98	50
12	**3h**	**1d**	**2b**	iso-Bu	H	iso-Pr	Bn	DCM	68	>98	60
13	**3i**	**1e**	**2a**	-(CH_2)$_3$-		Bn	Bn	DCM	40	>98	29
14	**3j**	**1f**	**2a**	H	H	Bn	Et	DCM	40	>98	ca. 0

[a] PTSA salt of the amino acid was used. [b] Not determined. [c] Overall isolated yield of both diastereomeric products. [d] Determined by 500 MHz ^{1}H and ^{19}F NMR.

Scheme 2

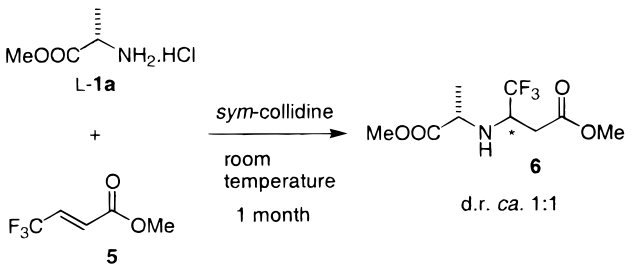


oxazolidinone residue has lower effect on the stereoselectivity. In fact, (*S*)-configured products **3e** (R^3 = iso-Pr, entry 9), **3d** (R^3 = Bn, entry 8), and **3f** (R^3 = H, entry 10) were obtained from L-Val-OBn **1c** in 78%, 72%, and 65% de respectively, with little variation and the same sense of facial selectivity.

The results above can be rationalized if one considers that in the absence of chelating agents *N*-(*E*)-enoyl-oxazolidin-2-ones **2** are known to exist in *s-trans* conformation,[9] with the R^3 substituent being pointed away from the C=C bond, thus exerting little control of the facial selectivity.[10] In contrast, the R^1 side-chain of α-amino esters **1** should be spatially close to the forming stereogenic center in the transition state; therefore, its influence is much more important. Reaction time has no effect on the diastereoselectivity; in fact **3g** was formed with the identical 50% de after 16 h (ca. 50% conversion) or after 88 h as well (entry 11), as shown by 500 MHz NMR of the crude reaction mixture. This strongly supports the conclusion that adducts **3** are formed irreversibly, and the stereochemical outcome is under kinetic control.

It is worth noting that stereocontrol is totally absent in the 1,4-addition of L-Ala-OMe **1a** to methyl 4,4,4-trifluorocrotonate **5**, which was chosen initially as the Michael acceptor (Scheme 3), and the reaction is much slower (1

Scheme 3



month, rt). This is likely to be a consequence of the lower conformational rigidity and electrophilicity of **5** with respect to the oxazolidinone acceptors **2**.

With a number of pseudo-dipeptides **3** in hand we addressed the next issue, namely the chemoselective cleavage of the oxazolidinone auxiliary. This result was achieved in 55−82% yields upon treatment of **3** with $LiOH/H_2O_2$ (30 min, 0 °C) (Scheme 4).[11] The resulting pseudodipeptides having a terminal CO_2H group were purified by FC and then coupled with another α-amino ester (HATU/HOAt, *sym*-

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(7) This reaction is extraordinarily simple and efficient, if one considers that examples of 1,4-additions by chiral α-amino esters to 4-substituted Michael-acceptors are very scarce in the literature: (a) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143−1146. (b) Eckert, H. G.; Badian, M. J.; Gantz, D.; Kellner, H.-M-; Volz, M. *Arzneim. Forsch.* **1984**, *34*, 1435−1447. For Michael-type reactions of amines with 4-substituted acceptors: (c) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1996**, 621−622. (d) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112−8114. (e) Cardillo, G.; Di Martino, E.; Gentilucci, L.; Tomasini, C.; Tomasoni, L. *Tetrahedron: Asymmetry* **1995**, *6*, 1957−1963. (f) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615−5619. (g) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179−182. (h) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797−1798. (i) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Walters, I. A. S. *Tetrahedron: Asymmetry* **1994**, *5*, 35−36. (j) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129−1139. (k) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141−1147. (l) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1994**, *59*, 649−652. (m) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274−6282. (n) Rudolf, K.; Hawkins, J. M.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3879−3882. (o) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820−2822. (p) Liebeskind, L. S.; Welker, M. E. *Tetrahedron Lett.* **1985**, *26*, 3079−3082. (q) De, A.; Basak, P.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 8383−8386. (r) Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427−5429. (s) Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293−2304. (t) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112−8114. (u) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500−503. (v) Cardillo, G.; Casolari, S.; Gentilucci, L.; Tomasini, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1848−1849.

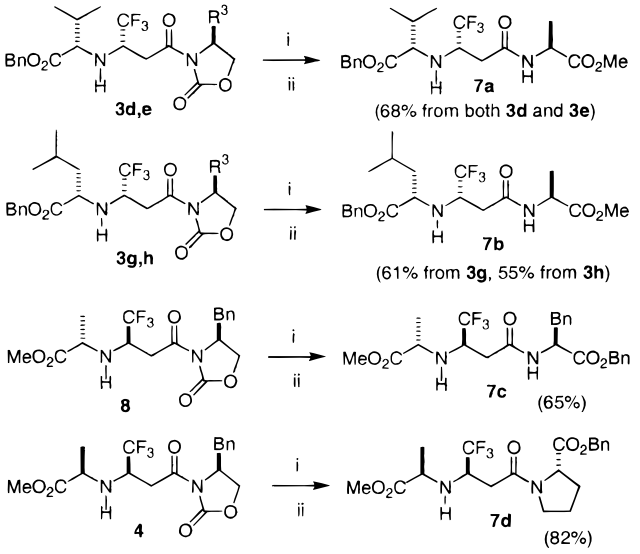
(8) The stereochemistry of **3a** was assigned by X-ray diffraction (X-ray data will be published in a full-paper), while the stereochemistry of the other major diastereomers **3b**−**j** was assigned on the basis of their spectral and chemical−physical similarities with **3a**. The stereochemistry of **6**, derived from D-Ala-OMe **1a** was determined by chemical correlation with **3a**, after cleavage of the oxazolidinone auxiliary.

(9) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030. See also: (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747−750.

(10) The use of Lewis acids for achieving higher stereocontrol via prechelation of oxazolidin-2-ones **2** was tried with little success. For example, treatment of **2a** with $Sc(OTf)_3$ in CH_2Cl_2 at rt for 30 min., followed by addition of L-**1c** and *sym*-collidine, produced **3d** in 58% de and ca. 85% yield (determined by ^{19}F NMR of the crude reaction mixture) after 30 h at rt. For a very recent successful example of use of $Sc(OTf)_3$ in related reactions: Mero, C. L.; Porter, N. A. *J. Org. Chem.* **2000**, *65*, 775−781.

(11) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030. Oxazolidin-2-one auxiliaries were usually recovered in nearly quantitative yields after cleavage.

Scheme 4



collidine, DMF). The final retro- and retroinverso tripeptides **7a**−**d**, orthogonally protected at the carboxy end-groups and therefore suitable for further selective elongation, were obtained in quantitative yields as solid materials.[12]

In conclusion, we have described the synthesis of a novel class of retropeptides incorporating a ψ[NHCH(CF_3)] unit as a surrogate of the ψ[NH−CO] retropeptide bond. This result has been achieved by exploiting uncommon conjugate additions of chiral α-amino esters to 4-substituted Michael-acceptors, which take place in excellent yields and moderate to good stereocontrol. Both this novel class of retropeptides and the synthetic approach appear to be particularly suitable for solid-phase/combinatorial chemistry. Indeed, the central R group (in this paper R = H), as well as the R^1, R^2, ..., R^n amino acidic side-chains, and even the fluorinated R_F residue can be modified in order to prepare a wide library of structures for biological screening. Solid-phase/combinatorial synthesis and biological activity evaluation of the new retro ψ[NHCH(CF_3)]-peptides are currently in progress.

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(12) Only proline derived pseudo-tripeptide **7d**, obtained as a ca. 3:1 mixture of isomers at the peptide bond, was isolated as a foam.

(13) **Experimental Section**. **Michael Addition**. Typical procedure. To a stirred solution of **2a** (80 mg, 0.27 mmol) and **1c** (131 mg, 0.54 mmol) in dry CH_2Cl_2 (3.4 mL) was added neat *sym*-collidine (0.14 mL, 1.08 mmol). After 64 h at rt the solvent was removed in vacuo, the crude dissolved in AcOEt and washed once with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4 and filtered, the solvent removed in vacuo, and the crude purified by FC (hexane/diethyl ether 65:35) affording 136 mg (92%) of diastereomerically pure **3d** and its minor diastereomer in 6:1 ratio. **3d** (major diastereoisomer): $[\alpha]^{23}_D = +28.3°$ ($c = 1.0$, $CHCl_3$); FT IR (film): ν_{max} = 3449, 1794, 1700, 1385 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.38-7.20$ (m, 10H), 5.13 (d, $J = 12.1$ Hz, 1H), 5.06 (d, $J = 12.1$ Hz, 1H), 4.70 (m, 1H), 4.24 (m, 1H), 4.16 (dd, $J = 8.8$, 2.8 Hz, 1H), 3.62 (m, 1H), 3.42 (dd, $J = 15.3$, 3.6 Hz, 1H), 3.36 (m, 2H), 3.15 (dd, $J = 15.3$, 9.6 Hz, 1H), 2.77 (dd, $J = 13.7$, 10.1 Hz, 1H), 2.01 (m, 1H), 1.88 (br s, 1H), 0.96 (d, $J = 6$, 7 Hz, 3H), 0.85 (d, $J = 6$, 7 Hz, 3H); ^{19}F NMR (250 MHz, $CDCl_3$): $\delta = -77.5$ (d, $J = 6.7$ Hz, 3F); ^{13}C (250 MHz, $CDCl_3$): δ = 174.8, 169.3, 153.6, 135.6, 135.4, 129.4, 129.0, 128.6, 128.4, 128.2, 127.4, 126.0 (q, $J = 282.3$ Hz), 66.8, 66.6, 66.5, 55.7 (q, $J = 29.3$ Hz), 55.5, 37.9, 36.3, 31.8, 19.3, 17.5; MS (70 eV): *e*/*z* (%): 507 (8) [$M^+ + 1$], 371 (90), 91 (100). **Cleavage of the Oxazolidinone from 3**. Typical procedure. To a cooled solution of **3d** (97 mg, 0.21 mmol) in THF/H_2O 4:1 (1.5 mL) at 0 °C under nitrogen atmosphere was added a 30% aqueous H_2O_2 solution (0.86 mL, 0.85 mmol), followed by solid LiOH (5 mg, 0.21 mmol). After 60 min the reaction was quenched with saturated aqueous Na_2SO_3, warmed to room temperature, and extracted three times with AcOEt, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (1:1 hexane/AcOEt until complete recovery of the oxazolidin-2-one and then MeOH) afforded 50 mg of the acid (68%). **Synthesis of Retropeptides 7**. Typical procedure. To a stirred solution of the acid above (30 mg, 0.08 mmol) and **1a** (12 mg, 0.08 mmol) in dry DMF (1 mL) was added, at 0 °C under nitrogen atmosphere, neat *sym*-collidine (0.032 mL, 0.24 mmol), followed by solid HOAt (11 mg, 0.08 mmol) and solid HATU (31 mg, 0.08 mmol). After 40 min the solution was quenched with 1 N HCl, warmed to room temperature, and extracted with AcOEt, and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (75:25 hexane/AcOEt) afforded 35 mg of **7b** (quantit). **7b**: $R_f = 0.35$ (hexane/AcOEt 70:30); $[\alpha]^{23}_D = -15.1°$ ($c = 0.7$, $CHCl_3$); FTIR (film): ν_{max} = 3335, 1742, 1657, 1536, 1384 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.35$ (m, 5H), 7.23 (br d, $J = 6.4$ Hz, 1H), 5.15 (s, 2H), 4.60 (q, $J = 7.2$ Hz, 1H), 3.74 (s, 3H), 3.67 (q, $J = 7.2$ Hz, 1H), 3.54 (m, 1H), 2.64 (dd, $J = 15.4$, 3.4 Hz, 1H), 2.40 (dd, $J = 15.4$, 9.4 Hz, 1H), 2.02 (br s, 1H), 1.78 (m, 1H), 1.5 (m, 2H), 1.44 (d, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 4.1$ Hz, 3H), 0.88 (d, $J = 4.1$ Hz, 3H); ^{19}F NMR (250 MHz, $CDCl_3$): $\delta = -76.4$ (d, $J = 7.6$ Hz, 3F); ^{13}C (250 MHz, $CDCl_3$): δ = 175.4, 173.5, 168.2, 135.5, 128.6, 128.4, 128.2, 126.0 (q, $J = 282.2$ Hz), 66.8, 58.4, 55.3 (q, $J = 27.7$ Hz), 52.4, 48.2, 42.9, 35.9, 24.6, 22.9, 21.6, 17.9; MS (70 eV): *e*/*z* (%): 447 (7) [$M^+ + 1$], 311 (93), 208 (30), 166 (30), 91 (100).