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A Facile Two-Step Synthesis of (ω-1)-Fluoroalkan-ω-olides Influence of a Vicinal Fluorine Substituent in Nucleophilic Substitutions

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Abstract: (ω-1)-Fluoroalkan-ω-olides **3** of medium to large ring size can easily be synthesised in a facile two-step procedure by bromofluorination of terminally unsaturated fatty acids **1** with NBS/Et_3N·3HF and subsequent cyclisation with K_2CO_3 in dimethyl sulfoxide. Electronic and conformational changes induced by the vicinal fluorine substituent in the transition state of S_N2-cyclisation step (calculated by the AM1-method) were found to be responsible for a certainly hindered cyclisation of the monofluorinated compounds **2** in comparison with their non-fluorinated analogues.

Introduction

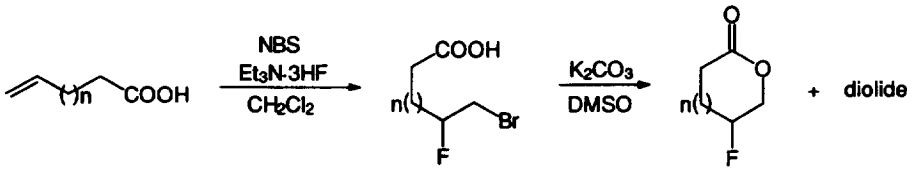
In our ongoing studies into new, potentially bioactive, monofluorinated compounds we intensively looked for the synthesis of monofluorinated lactones with medium to large ring-size.[2] Lactones represent a class of naturally occurring compounds with manifold biological activity,[3] which could possibly be modified or altered by the introduction of one fluorine substituent.[4] Recently we reported the synthesis of the first four representatives of this novel class of monofluorinated fatty acid derivatives starting from terminally unsaturated fatty acids in a five-step sequence.[2a] By regioselective hydrofluorination of an oxirane precursor as the key-step,[5] either unbranched (ω-1)-fluoroalkan-ω-olides or branched ω-fluoroalkan-(ω-1)-olides were obtained. This includes a monofluorinated analogue of the pheromone phoracantholide I (from *Phoracantha synonyma*),[6] namely 10-fluorodecan-9-olide. Both enantiomers of this compound we resynthesised employing a deracemisation of fluorohydrins by enzymatic esterification as the source of optical activity.[2b]

In order to target exclusively the unbranched (ω-1)-fluoroalkan-ω-olides we looked for a shorter sequence. We herein report the synthesis of the 11-13-membered species of such monofluorinated lactones in a facile two-step procedure again starting from terminally unsaturated fatty acids including bromofluorination and subsequent cyclisation via an S_N2-reaction. Furthermore we present some considerations concerning the influence of a vicinal fluorine substituent in the nucleophilic substitution reaction.

Results and discussion

Alk-ω-enoic acids **1**, either commercially available or readily accessible,[7] can easily be converted into ω-bromo-(ω-1)-fluoroalkanoic acids **2** by treatment with N-bromosuccinimide (NBS) and triethylamine-trishydrogen fluoride (Et_3N·3HF) in dichloromethane at room temperature.[8] Cyclisation of **2** with K_2CO_3 in

dimethyl sulfoxide (DMSO) via an intramolecular S_N2-pathway (substitution of bromine with carboxylate)[9] affords the 11-13-membered (ω-1)-fluoroalkan-ω-olides **3** together with about 10-15% of the corresponding diolides. The monofluorinated lactones can be obtained in pure form by bulb-to-bulb distillation.



1a (n = 6) **2a** **3a**
1b (n = 7) **2b** **3b**
1c (n = 8) **2c** **3c**

The bromofluorination reaction proceeds regioselectively (> 92 : 8) towards the Markownikov products, namely the ω-bromo-(ω-1)-fluoroalkanoic acids **2**. All bromofluorinated acids were obtained in good to excellent yields, extending our general bromofluorination method[8] to further substrates. The cyclisation reaction provides the unbranched, fluorinated lactones in moderate to good yields, but in comparison with the cyclisation of the non-fluorinated ω-bromoalkanoic acids[9,10] in lower yields. Nevertheless, for ring strain reasons the tendency of yields to improve with larger ring-size is the same.

Additionally, we looked more detailed into the cyclisation reaction. If a 1:1-mixture of 11-bromo-undecanoic acid and 11-bromo-10-fluoroundecanoic acid (**2b**) is submitted to cyclisation under standard conditions,[9] but using only 10 mol % of base, the resulting product ratio of undecan-11-olide vs. 10-fluoroundecan-11-olide (**3b**) is about 10:1. To gain an understanding for the cause of these remarkable differences in reactivity, and therefore of the influence of a vicinal fluorine substituent in nucleophilic substitution of a bromine substituent, we calculated the cyclisation reaction and its transition state for 11-bromoundecanoate and 11-bromo-10-fluoroundecanoate on a semiempirical basis (AM1[11]) using the program MOPAC 7.[12] Calculations utilising the SADDLE routine revealed an about 3 kcal/mol higher activation barrier for the 11-bromo-10-fluoro-undecanoate. This is consistent with the hindered cyclisation observed for the fluorinated compound. Both transition states (Fig. 1: 11-bromoundecanoate; Fig. 2: 11-bromo-10-fluoro-undecanoate) were calculated by TS routine and proved by FORCE analysis.

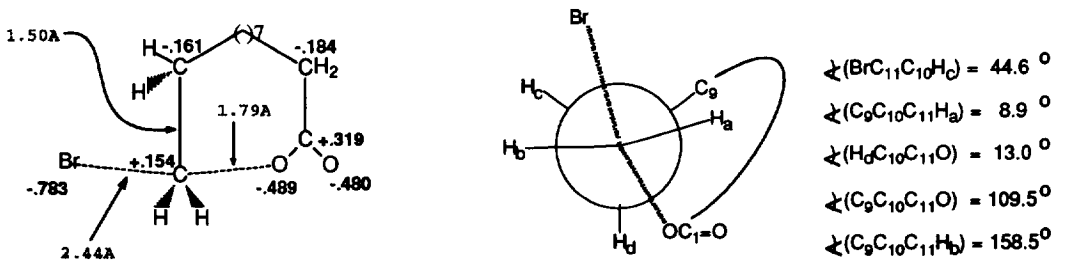


Fig. 1: Transition state structure (AM1[11]) of the cyclisation of 11-bromoundecanoate, including bond lengths, electron densities and dihedral angles.

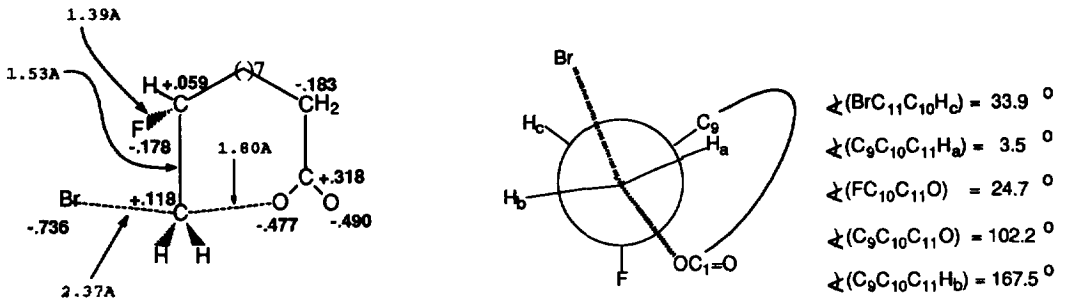


Fig. 2: Transition state structure (AM1[11]) of the cyclisation of 11-bromo-10-fluoroundecanoate (**2b**), including bond lengths, electron densities and dihedral angles.

Comparing the transition states of **2b** and its unfluorinated parent compound (Fig. 1 and 2), the fluorine substituent causes a bad polarization of the bromine-carbon bond (shortened), which is to be cleaved. The electron density at the terminal C-11 is increased by the fluorine and the bromine is about 0.07 Å closer to this carbon. However, the most significant differences caused by the introduction of fluorine seem to be conformational not electronic changes. In both cases the reaction centre is not perfectly plane, due to the fact that the relative position of all substituents is determined by the conformation of the 12-membered ring to be formed. The oxygen of the carboxylate is in a gauche orientation with C-9. This results in an ecliptic orientation between H_c and the bromine atom as well as H_a and C-9 (dihedral angles in the non-fluorinated compound 44.6° and 8.9°, respectively). Especially these interactions are increased by the vicinal fluorine substituent (dihedral angles in the 11-bromo-10-fluoro compound 33.9° and 3.5°, respectively). The reason for this increase should be mainly due to lone pair repulsion between the carboxylate-oxygen and the fluorine substituent. In summary, concerning the results of semiempirical calculations, additional conformational interactions seem to be the main reason for the more difficult nucleophilic cyclisation reaction of the monofluorinated compounds compared to the non-fluorinated ones.

Despite the more difficult cyclisation of ω-bromo-(ω–1)-fluoroalkanoic acids the reported two-step synthesis of (ω–1)-fluoroalkan-ω-olides by bromofluorination of ω-unsaturated carboxylic acids and subsequent cyclisation is a convenient and the shortest method to prepare such monofluorinated lactones of medium to large ring-size.

We are continuing to look more detailed into general neighbouring group effects of vicinal fluorine substitution in different reactions of fluorinated organic compounds.

Experimental

Melting/boiling points: uncorrected value. - Refraction indices: C. Zeiss, Jena, Abbé refractometer. – ^{1}H (300 MHz), ^{13}C NMR (75.5 MHz): Bruker WM 300, TMS for ^{1}H and $CDCl_3$ for ^{13}C NMR as internal standard. – ^{19}F NMR: Bruker WM 300 (282.3 MHz) and Bruker AC 200 (188.0 MHz), α,α,α-trifluorotoluene (δ = - 63.0 ppm from $CFCl_3$) as internal standard. – Mass spectra (70 eV): GLC/MS coupling: Varian GC 3400/Varian Saturn IT (ion trapping) and data system NIST. – GLC: Hewlett-Packard 5890 II gas chromatograph, quartz capillary column 0.33 mm x 25 m, 0.52 µm HP-1 (Hewlett-Packard) and quartz capillary column 0.2 mm x 25 m, 0.11 µm HP-5 (Hewlett-Packard), nitrogen as carrier gas, FID-detector. – Elementary analyses: Mikroanalytisches Laboratorium, OC, Universität Münster. – Bulb-to-bulb distillation: Büchi GRK-50. – Dec-9-en-1-ol was kindly donated by *Hüls AG/Marl*. Triethylamine-trishydrofluoride ($Et_3N{\cdot}3HF$) is a gift from *Hoechst AG/Frankfurt*. All other starting materials and applied reagents were obtained from Fluka or Janssen chemicals; dichloromethane was purified by distillation and dried by storage over molecular sieves 0.4 nm.

Preparation of ω-alkenoic acids: Dec-9-enoic acid was prepared by Jones oxidation of dec-9-en-1-ol,[7a] undec-10-enoic acid is commercially available and dodec-11-enoic acid was prepared from undec-10-en-1-ol by conversion into 1-bromoundec-10-ene (using PPh_3 and bromine) and subsequent Grignard reaction with CO_2.[7b]

Bromofluorination of ω-alkenoic acids:[8] A magnetically stirred mixture of the terminally unsaturated fatty acid **1a**, **1b** or **1c** (40 mmol) and 16 g (10 ml, 0.1 mol) of triethylamine-trishydrofluoride ($Et_3N{\cdot}3HF$) in 40 ml of dry dichloromethane at 0 °C is treated with 7.8 g (44 mmol) N-bromosuccinimide (NBS). After 15 min at 0 °C, stirring is continued at room temperature for 5 h. Subsequently the mixture is poured into ice water (1000 ml), concentrated ammonia is added until the pH-value reaches 7-8 and the mixture is extracted with dichloromethane (5 x 80 ml). The combined organic extracts are washed with 150 ml of aqueous hydrochloric acid (0.1 N) and 150 ml of water and dried over magnesium sulfate. Evaporation of the solvent yields the ω-bromo-(ω-1)-fluorocarboxylic acids **2a**, **2b** or **2c** as a mixture with their regioisomeric (ω-1)-bromo-ω-fluorocarboxylic acids (ratio: >92 : 8). The acids can be recrystallysed from petroleum ether/ether = 1 : 1.

10-Bromo-9-fluorodecanoic acid (2a): yield: 9.80 g (36.5 mmol, 91%); m.p. = 49 °C (decomp.); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.28-1.38 (br s, 8H, 4-H_2 to 7-H_2), 1.42 (m, 2H, 8-H_2), 1.61 (m, 2H, 3-H_2), 2.35 (t, $^3J_{HH}$ = 7.55 Hz, 2H, 2-H_2), 3.4-3.5 (2 ddd, $^3J_{HF}$ = 19.6 Hz, 2H, 10-H_2), 4.6 (m, $^2J_{HF}$ = 48.05 Hz, 1H, 9-H), 9.5 (br s, 1H, -COOH); ^{13}C NMR ($CDCl_3$): δ [ppm] = 24.62 (dt, $^3J_{CF}$ = 3.85 Hz, C-7), 24.8 (t, C-4), 28.9-29.2 (3 t, C-3 and C-5, C-6), 33.3 (dt, $^2J_{CF}$ = 20.35 Hz, C-8), 33.7 (dt, $^2J_{CF}$ = 25.4 Hz, C-10), 34.0 (t, C-2), 92.0 (dd, $^1J_{CF}$ = 174.2 Hz, C-9), 180.1 (s, COOH, C-1); ^{19}F NMR ($CDCl_3$): δ [ppm] = -178.5 (m, 9-F); MS of the corresponding methyl alkanoate (GLC/MS, 70 eV, Ion Trap): m/z (%) = 282/284 (0) [M^+], 263/265 (28/25) [M^+-F], 231/233 (15/15) [263-CH_3OH], 219/221 (10/9) [263-CO_2], 183 (81) [263-HBr], 151 (92) [183-CH_3OH], 133 (75) [151-H_2O], 93/95 (12/12) [CH_2Br^+], 74 (100) [$C_3H_6O_2^+$], 59 (55) [$COOCH_3^+$], 43 (98) [$C_2H_3O^+$], 41 (88), 39 (90); Elemental analysis: cal. C 44.63 H 6.74, found C 44.45 H 6.69.

11-Bromo-10-fluoroundecanoic acid (2b): yield: 10.80 g (38 mmol, 95%); m.p. = 59 °C (decomp.); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.25-1.4 (br s, 10H, 4-H_2 to 8-H_2), 1.42 (m, 2H, 9-H_2), 1.61 (m, 2H, 3-H_2), 2.34 (t, $^3J_{HH}$ = 7.5 Hz, 2H, 2-H_2), 3.37-3.5 (2 ddd, $^3J_{HF}$ = 18 Hz, 2H, 11-H_2), 4.62 (m, $^2J_{HF}$ = 48.6 Hz, 1H, 10-H), 10.2 (br s, 1H, -COOH); ^{13}C NMR ($CDCl_3$): δ [ppm] = 24.66 (dt, $^3J_{CF}$ = 5.3 Hz, C-8), 25.1 (t, C-4), 28.8-29.4 (4 t, C-3 and C-5 to C-7), 33.4 (dt, $^2J_{CF}$ = 20.3 Hz, C-9), 33.7 (dt, $^2J_{CF}$ = 25.4 Hz, C-11), 34.1 (t, C-2), 92.1 (dd, $^1J_{CF}$ = 175.5 Hz, C-10), 180.3 (s, COOH, C-1); ^{19}F NMR ($CDCl_3$): δ [ppm] = -181.0 (m, 10-F); MS of the corresponding methyl alkanoate (GLC/MS, 70 eV, Ion Trap): m/z (%) = 296/298 (0) [M^+], 277/279 (70/67) [M^+-F], 245/247 (35/32) [277-CH_3OH], 227/229 (10/8) [245-H_2O], 197 (65) [277-HBr], 165 (100) [197-CH_3OH], 147 (70) [165-H_2O], 93/95 (30/27) [CH_2Br^+], 74 (85) [$C_3H_6O_2^+$], 59 (50) [$COOCH_3^+$], 39 (95); Elemental analysis: cal. C 46.66 H 7.12, found C 46.89 H 7.29.

12-Bromo-11-fluorododecanoic acid (2c): yield: 9.03 g (30.4 mmol, 76%); m.p. = 65 °C (decomp.); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.2-1.4 (br s, 12H, 4-H2 to 9-H2), 1.62 (m, 2H, 10-H2), 1.71 (m, 2H, 3-H2), 2.34 (t, $^3J_{HH}$ = 7.5 Hz, 2H, 2-H_2), 3.39-3.5 (2 ddd, $^3J_{HF}$ = 19.8 Hz, 2H, 12-H_2), 4.6 (m, $^2J_{HF}$ = 47.7 Hz, 1H, 11-H), ≅ 10 (1H, COOH); ^{13}C NMR ($CDCl_3$): δ [ppm] = 24.63 (t, C-9), 29.0-29.4 (6 t, C-3 to C-8), 33.3 (dt, $^2J_{CF}$ = 20.4 Hz, C-10), 33.7 (dt, $^2J_{CF}$ ≅ 25.6 Hz, C-12), 33.97 (t, C-2), 92.05 (dd, $^1J_{CF}$ = 175.5 Hz, C-11), 179.48 (s, C-1); ^{19}F NMR ($CDCl_3$): δ[ppm] = -177.8 (m, 11-F); Elemental analysis: cal. C 48.50 H 7.46, found C 49.76 H 7.26 (solvent inclusion).

Synthesis of (ω-1)-fluoroalkan-ω-olides: In a 500 ml-flask with thermometer, cooler and dropping funnel a suspension of 7.5 g (55 mmol) potassium carbonate in 250 ml of dry dimethyl sulfoxide (DMSO) is heated to 100 °C. Within 1.5 h a solution of 19 mmol of the ω-bromo-(ω-1)-fluorocarboxylic acid **2a**, **2b** or **2c** and 100 ml dry DMSO is added at this temperature under vigorous stirring. After cooling solid compounds are filtered off and washed with 30 ml of DMSO. The filtrate is diluted with 125 ml of water and extracted with petroleum ether (5 x 75 ml). To reach an optimal separation of the organic layer from the aqueous one, it could become necessary to filter off solid precipitates once or twice again. The combined organic extracts are washed with water (2 x 50 ml) and dried over magnesium sulfate. Removal of the solvent gives the crude mixture of the lactone and its corresponding diolide, which can be separated by bulb-to-bulb distillation to supply the lactones as colourless liquids.

9-Fluorodecan-10-olide (3a): yield: 1.13 g (6 mmol, 32%); All other data found for **3a** are identical with those described earlier.[2a]

10-Fluoroundecan-11-olide (3b): yield: 1.43 g (7 mmol, 37%); All data found for **3b** are identical with those described earlier.[2a]

11-Fluorododecan-12-olide (3c): yield: 2.60 g (12 mmol, 64%); b.p. = 144 °C / 15 Torr; ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.3-1.5 (br s, 12H, 4-H_2 to 9-H_2), 1.65-2.0 (2 m, 4H, 3-H_2 and 10-H_2), 2.4 (t, $^3J_{HH}$ = 6 Hz, 2H, 2-H_2), 4.2-4.45 (2 ddd, $^3J_{HF}$ ≅ 25.9 Hz, 2H, 12-H_2), 4.65 (dm, $^2J_{HF}$ = 45.8 Hz, 1H, 11-H); ^{13}C NMR ($CDCl_3$): δ [ppm] = 21.8 (t, C-9), 24.3-26.7 (6 t, C-3 to C-8), 29.85 (dt, $^2J_{CF}$ = 20.3 Hz, C-10), 34.0 (t, C-2), 63.7 (dt, $^2J_{CF}$ = 27.9 Hz, C-12), 90.05 (dd, $^1J_{CF}$ = 170.8 Hz, C-11), 173.5 (s, C-1); ^{19}F NMR ($CDCl_3$): δ [ppm] = -181.2 (m, 11-F); MS (GLC/MS, 70 eV, Ion Trap): m/z (%) = 216 (10) [M^+], 197 (100) [M^+-F], 186 (5) [M^+-CH_2O], 179 (28) [197-H_2O], 161 (26) [179-H_2O], 149 (7) [179-CH_2O], 136 (14), 121 (14), 112 (18), 98 (40) [$C_6H_{10}O^+$], 95 (42), 81 (47), 67 (14), 55 (20), 41 (25), 39 (49); Elemental analysis: cal. C 66.64 H 9.79, found C 66.60 H 9.88.

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References and Notes

1. New address: Bayer AG, Organic Chemicals Business Group, R&D / Product Development - New Products, D-51368 Leverkusen, Germany.
2. a) A. Sattler, G. Haufe, *Liebigs Ann. Chem.* **1994**, 921-925.
   b) A. Sattler, G. Haufe, *Tetrahedron Asymm.* **1995**, *6* , 2841-2848.
3. G. Boyd in *The Chemistry of Acid Derivatives* (Ed.: S. Patai), Suppl. B, Wiley Interscience, Chicester, **1992**, 547-614.
4. J.T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley & Sons, New York, **1991**.
5. A.Sattler, G. Haufe, *J. Fluorine Chem.* **1994**, *69*, 185-190.
6. a) B.P. Moore, W.V. Brown, *Aust. J. Chem.* **1976**, *29*, 1365-1374.
   b) T. Kitahara, K. Koseki, K. Mori, *Agric. Biol. Chem.* **1987**, *51*, 3417-3421.
7. a) P. Yates, J. Wong, S. McLean, *Tetrahedron* **1981**, *37*, 3357-3363.
   b) M. Bartra, J. Vilarrasa, *J. Org. Chem.* **1991**, *56*, 5132-5138 and K.B. Chai, P. Sampson, *Tetrahedron Lett.* **1992**, *33*, 585-588.
8. G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562-564.
9. C. Galli, L. Mandolini, *Org. Synth.* **1978**, *58*, 98-101.
10. H. Hunsdiecker, H. Erlbach, *Chem. Ber.* **1947**, *80*, 129-137.
11. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stuart, *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
12. MOPAC 7, QCPE Program #455.

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