Fluorocyclization of norbornenecarboxylic acids with F-TEDA-BF_4

Yurii A. Serguchev,* Lyudmila F. Lourie, Galina V. Polishchuk and Alexander N. Chernega

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02094 Kiev, Ukraine.
Fax: +38 044 573 2043; e-mail: serg@mail.kar.net

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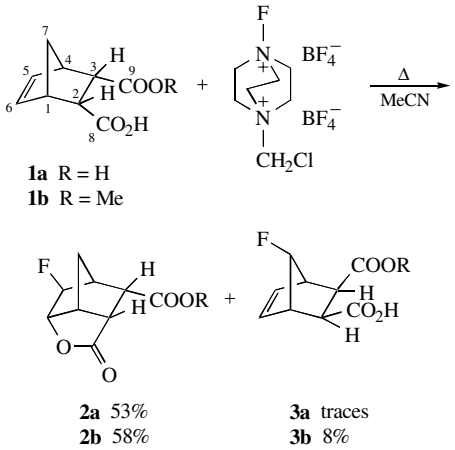
The reactions of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) with *cis*-5-norbornene-*endo*-2,3-dicarboxylic acid, its monomethyl ester and 5-norbornene-*endo*-2-carboxylic acid in acetonitrile lead to the formation of corresponding fluorinated γ-lactones.

Lactones are synthesised by electrophilic heterocyclization of unsaturated carboxylic acids using various agents, such as halogens, metal salts, sulfenyl chlorides, acids and peroxy acids.[1–3] Traditional fluorinating electrophiles (F_2, XeF_2, CF_3OF, RCOOF *etc.*), were never employed in these reactions because of their high reactivity, which considerably hampers the control of addition and cyclization stages. However, the fluorocyclization of unsaturated carboxylic acids seems to be a very alluring direct single-step preparative approach to fluorinated lactones structurally related to biologically important fluorinated carbohydrates.[4–6] The electrophilic fluorocyclization of norbornenecarboxylic acids is of particular interest owing to structural similarity of the compounds to naturally occurring terpenes.

Here, we report the fluorocyclization of *cis*-5-norbornene-*endo*-2,3-dicarboxylic acid **1a**, its monomethyl ester **1b** and 5-norbornene-*endo*-2-carboxylic acid **4** by a soft electrophilic fluorinating agent, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) known as F-TEDA-BF_4.†

On heating with F-TEDA-BF_4 in acetonitrile under reflux, **1a** and **1b** are transformed mainly into corresponding *exo*-fluoro-γ-lactones **2a**,**b** (Scheme 1).



Scheme 1

The *exo*-arrangement of the fluorine atom in compounds **2a**,**b** was inferred from the correlation of their NMR spectra with those previously reported for *exo*-fluoronorbornanes[7–9] and from characteristic values of the coupling constants J_{FH}.

To verify the spectral identification of these products, we performed single-crystal X-ray diffraction analysis of fluoro-γ-lactone **2b** and established unequivocally the *exo*-orientation

† *General procedure.* A mixture of appropriate acid **1a**,**b** or **4** (5 mmol) and F-TEDA-BF_4 (6 mmol) in acetonitrile (20 ml) was heated at reflux and stirred for 37–48 h. The precipitate formed was separated by filtration, and the filtrate was evaporated to leave a solid residue, which was washed with water and extracted with dichloromethane (2×15 ml). The extract was washed with water and 10% aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and separated by column chromatography on silica gel using diethyl ether–hexane (2:1) as an eluent. The ^1H, ^{13}C and ^{19}F NMR spectra were taken on a Varian VXR-300 spectrometer at 299.9, 75.3 and 282.2 MHz, respectively, using TMS and CCl_3F as internal standards. The IR spectra were measured on a Specord IR-75 spectrophotometer in KBr disks. The mass spectra were measured on a MAT 8200 instrument at 70 eV. TLC was carried out on Silufol UV-254 plates (eluent: diethyl ether–hexane 6:1). Single crystals of **2b** were grown from ethyl acetate.

For **2a**: white crystals, yield 53%, R_f 0.35, mp 131–132.5 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 1.67 (m, 1H, 7-H$_{anti}$, $^2J_{HH}$ 11.4 Hz), 1.85 (m, 1H, 7-H$_{syn}$, $^2J_{HH}$ 11.4 Hz), 2.77–2.83 (m, 2H, 1-H and 2-H), 3.17 (m, 1H, 3-H, $^3J_{HH}$ 11.1, 5.5 Hz), 3.34 (m, 1H, 4-H, $^3J_{HH}$ 6.0 Hz), 4.72 (dd, 1H, 6-H, $^3J_{HF}$ 20.7 Hz, $^3J_{HH}$ 5.1 Hz), 5.07 (d, 1H, 5-H, $^2J_{HF}$ 50.4 Hz), 11.98 (br. s, 1H, COOH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 33.29 (7-C), 40.81 (1-C), 44.83 (d, 4-C, *J* 24.8 Hz), 47.00 (2-C), 47.30 (d, 3-C, *J* 13.6 Hz), 83.85 (d, 6-C, *J* 26.4 Hz), 94.42 (d, 5-C, *J* 183.1 Hz), 172.99 (8-C), 177.42 (9-C). ^{19}F NMR ([$^2H_6$]DMSO) δ: –183.4 (dd, CHF, $^2J_{FH}$ 51.1 Hz, $^3J_{FH}$ 20.3 Hz). IR (ν/cm^{-1}): 1750 and 1700 (COO). MS, *m*/*z* (%): 200 (3) [M$^+$], 155 (10) [M$^+$ – COOH], 141 (56), 111 (34) [M$^+$ – COOH – CO_2], 97 (83), 79 (100), 59 (81), 39 (70), 27 (42). Found (%): C, 53.72; H, 4.57; F, 8.90. Calc. for $C_9H_9FO_4$ (%): C 54.00; H, 4.53; F, 9.49.

For **2b**: white crystals, yield 58%, R_f 0.39, mp 89–91 °C. ^1H NMR ($CDCl_3$) δ: 1.70 (m, 1H, 7-H$_{anti}$, $^2J_{HH}$ 11.4 Hz), 2.14 (m, 1H, 7-H$_{syn}$, $^2J_{HH}$ 11.4 Hz), 2.85 (dd, 1H, 2-H, $^3J_{HH}$ 10.6, 4.5 Hz), 2.88–2.92 (m, 1H, 1-H), 3.12 (m, 1H, 3-H, $^3J_{HH}$ 10.6, 5.1 Hz), 3.34–3.38 (m, 1H, 4-H), 3.73 (s, 3H, Me), 4.71 (dd, 1H, 6-H, $^3J_{HF}$ 20.4 Hz, $^3J_{HH}$ 5.1 Hz), 5.19 (d, 1H, 5-H, $^2J_{HF}$ 49.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 33.58 (7-C), 41.30 (1-C), 44.73 (d, 4-C, *J* 22.8 Hz), 46.80 (2-C), 47.52 (d, 3-C, *J* 9.1 Hz), 52.91 (Me), 84.08 (d, 6-C, *J* 28.1 Hz), 93.38 (d, 5-C, *J* 186.9 Hz), 170.95 (9-C), 179.91 (8-C). ^{19}F NMR ($CDCl_3$) δ: –184.7 (dd, CHF, $^2J_{FH}$ 49.9 Hz, $^3J_{FH}$ 21.2 Hz). IR (ν/cm^{-1}): 1790 and 1730 (COO). MS, *m*/*z* (%): 214 (4) [M$^+$], 183 (13) [M$^+$ – MeO], 155 (83) [M$^+$ – COOMe], 127 (21) [M$^+$ – – COOMe – CO], 111 (59) [M$^+$ – COOMe – CO_2], 98 (94), 79 (69), 66 (35), 59 (100), 39 (62), 27 (35). Found (%): C, 55.83; H, 5.11; F, 9.05. Calc for. $C_{10}H_{11}FO_4$ (%): C, 56.07; H, 5.18; F, 8.87.

For **3a** (not isolated): ^{19}F NMR ([$^2H_6$]DMSO) δ: –211.8 (dd, CHF, $^2J_{FH}$ 54.7 Hz, $^3J_{FH}$ 7.3 Hz).

For **3b**: white crystals, yield 8%, R_f 0.72, mp 134–135 °C. ^1H NMR ($CDCl_3$) δ: 2.61–2.71 (m, 2H, 2-H, 3-H), 3.20–3.28 (m, 2H, 1-H, 4-H), 3.70 (s, 3H, Me), 5.42 (d, 1H, 7-H, $^2J_{FH}$ 58.2 Hz), 6.24 (m, 2H, 5-H, 6-H), 7.5 (br. s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 43.90 (d, 2-C, *J* 5.2 Hz), 44.12 (d, 3-C, *J* 5.3 Hz), 47.8 (d, 1-C, 4-C, *J* 17.8 Hz), 52.19 (Me), 101.47 (d, 7-C, *J* 199.7 Hz), 133.08 (5-C), 133.28 (6-C), 172.51 (9-C), 178.33 (8-C). ^{19}F NMR ($CDCl_3$) δ: –211.3 (dd, CHF, $^2J_{FH}$ 58.1 Hz, $^3J_{FH}$ 6.5 Hz). IR (ν/cm^{-1}): 1740 and 1700 (COO). MS, *m*/*z* (%): 214 (18) [M$^+$], 183 (45) [M$^+$ – MeO], 155 (28) [M$^+$ – COOMe], 111 (16) [M$^+$ – – COOMe – CO_2], 98 (20), 79 (11), 66 (100), 59 (13), 39 (21). Found (%): F, 8.78. Calc. for $C_{10}H_{11}FO_4$ (%): F, 8.87.

For **5**: white crystals, yield 27%, R_f 0.60, mp 166–167 °C. ^1H NMR ($CDCl_3$) δ: 1.59–1.70 (m, 2H, 3-H$_{endo}$, 7-H$_{anti}$), 1.99–2.10 (m, 2H, 3-H$_{exo}$, 7-H$_{syn}$), 2.55 (m, 1H, 2-H, $^3J_{HH}$ 11.1, 4.5 Hz), 2.66 (m, 1H, 4-H), 3.22 (m, 1H, 1-H), 4.50 (d, 1H, 5-H, $^2J_{HF}$ 49.8 Hz), 4.64 (dd, 1H, 6-H, $^3J_{HF}$ 20.4 Hz, $^3J_{HH}$ 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 30.13 (d, 3-C, *J* 9.8 Hz), 33.33 (7-C), 37.72 (2-C), 41.58 (d, 4-C, *J* 21.2 Hz), 44.28 (1-C), 83.77 (d, 6-C, *J* 28.1 Hz), 95.79 (d, 5-C, *J* 189.4 Hz), 179.28 (8-C). ^{19}F NMR ($CDCl_3$) δ: –179.2 (dd, CHF, $^2J_{FH}$ 50.5 Hz, $^3J_{FH}$ 20.6 Hz). MS, *m*/*z* (%): 156 (49) [M$^+$], 128 (12) [M$^+$ – CO], 112 (20) [M$^+$ – CO_2], 97 (64), 79 (73), 66 (100) [M$^+$ – CO_2 – CHF=CH_2], 59 (53), 39 (31), 27 (19). Found (%): C, 60.76; H, 5.92. Calc. for $C_8H_9FO_2$ (%): C, 61.53; H, 5.81.

For **6**: oil, yield 37%, R_f 0.58. ^1H NMR ($CDCl_3$) δ: 1.64–1.79 (m, 2H, 3-H$_{endo}$, 5-H$_{endo}$), 1.97–2.07 (m, 1H, 3-H$_{exo}$), 2.28–2.39 (m, 1H, 5-H$_{exo}$), 2.46–2.52 (m, 1H, 4-H), 2.54–2.62 (m, 1H, 2-H), 3.18–3.24 (m, 1H, 1-H), 5.03 (dd, 1H, 6-H, $^3J_{HH}$ 6.8, 4.5 Hz), 5.07 (m, 1H, 7-H, $^2J_{HF}$ 56.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.84 (d, 3-C, *J* 6.7 Hz), 34.08 (d, 5-C, *J* 2.9 Hz), 36.02 (d, 2-C, *J* 7.3 Hz), 38.87 (d, 4-C, *J* 16.1 Hz), 48.36 (d, 1-C, *J* 19.2 Hz), 80.09 (6-C), 98.55 (d, 7-C, *J* 193.1 Hz), 179.28 (8-C). ^{19}F NMR ($CDCl_3$) δ: –204.1 (d, CHF, $^2J_{FH}$ 56.7 Hz). MS, *m*/*z* (%): 156 (38) [M$^+$], 128 (61) [M$^+$ – CO], 112 (13) [M$^+$ – CO_2], 97 (31), 79 (91), 66 (100) [M$^+$ – CO_2 – CFH=CH_2], 59 (29), 39 (31), 27 (20).

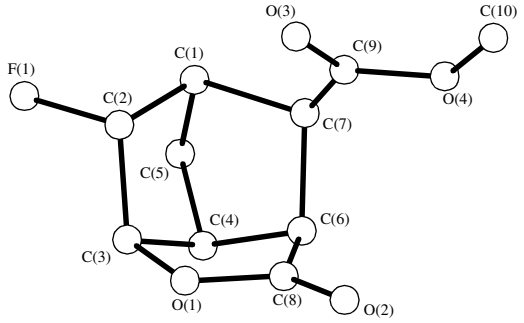


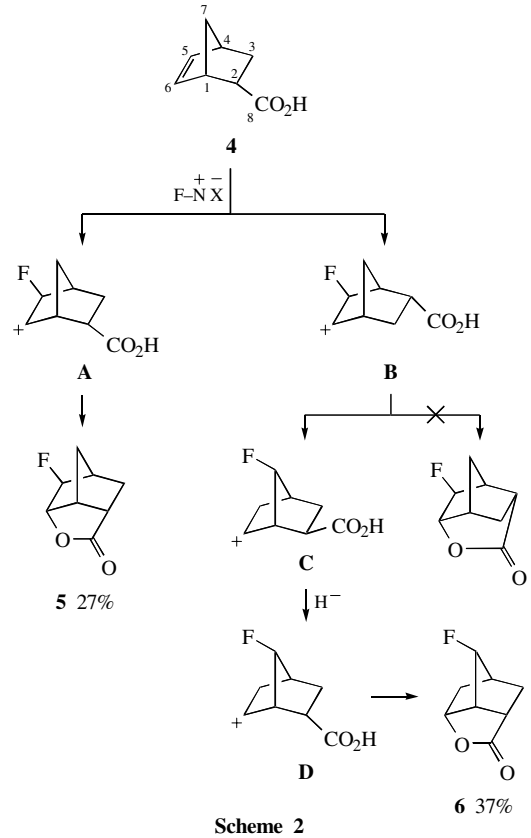
Figure 1 Molecular structure of **2b**. Selected bond lengths (Å): O(1)–C(3) 1.458(7), O(1)–C(8) 1.358(7), O(2)–C(8) 1.190(7), C(1)–C(2) 1.524(5), C(1)–C(5) 1.537(4), C(1)–C(7) 1.547(11), C(2)–C(3) 1.534(5), C(3)–C(4) 1.533(5), C(4)–C(5) 1.523(5), C(4)–C(6) 1.533(9), C(6)–C(7) 1.568(4), C(6)–C(8) 1.510(5).

of its fluorine substituent (Figure 1).‡ All geometric parameters of **2b** are unexceptional.[12] In particular, the bond lengths and angles in the lactone chain C(3)O(1)C(8)O(2)C(6), in contrast to dilactone bridged systems,[13] are virtually the same as the statistical X-ray data for γ-lactones.[14] As expected, the lactone group C–O–C(=O)–C in **2b** is almost planar, and the torsion angle C(3)–O(1)–C(8)–C(6) is as small as –1.7°.

The by-product, isolated in 8% yield in the reaction of monoester **1b** with F-TEDA-BF_4, was identified as methyl hydrogen *cis*-7-fluoro-5-norbornene-*exo*-2,3-dicarboxylate **3b**. The position of the fluorine atom in the bridge of **3b** is evidenced from close similarity between the ^{19}F NMR spectra of this compound and related fluorine-substituted norbornans.[15] The presence of a double bond in **3b** is confirmed by ^{13}C NMR spectra containing signals at 133.08 and 133.28 ppm characteristic of sp^2-hybridised carbon atoms.

The fluorocyclization of 5-norbornene-*endo*-2-carboxylic acid **4** by F-TEDA-BF_4 leads to the formation of two isomeric products, *exo*-fluoro-γ-lactone **5** and rearranged lactone **6** (Scheme 2). Compound **5** is very similar to *exo*-fluoro-γ-lactones **2a** and **2b** in spectral properties. The ^{19}F NMR signal of **6** is downfield as compared to that of **5**, and the geminal spin–spin coupling constants J_{FH} in the ^1H and ^{19}F NMR spectra (56.1 and 56.7 Hz) are characteristic of the fluorine substituent at the bridge carbon atom in norbornane structures.[15] The ^{13}C NMR spectrum of **6** is consistent with the structure proposed. The signals of the bridgehead atoms 1-C and 4-C are split into doublets with similar coupling constants ($^2J_{CF}$ 19.2 and 16.1 Hz). For the remote atoms 2-C, 3-C and 5-C, the coupling with fluorine is markedly weaker ($^3J_{CF}$ 7.3, 6.7 and 2.9 Hz). The 6-C atom appears as a singlet, in contrast to compound **5** where its signal is split into a doublet with $^2J_{CF}$ 28.1 Hz on the fluorine at 5-C.

It is remarkable that *exo*- rather than *endo*-γ-fluorolactones are formed in the fluorocyclization. Because norbornene systems are considered to be sterically much more accessible to electrophilic agents from the *exo*- than from the *endo*-side,[1,16] the bulkiness of F-TEDA-BF_4 can explain the highly selective *exo*-addition of fluorine to the norbornenecarboxylic acids.



Scheme 2

The formation of skeletal-rearrangement products **3b** and **6** in the fluorocyclization suggests the carbocationic reaction mechanism, which is generally accepted in the reactions of norbornene with electrophilic fluorinating agents such as [fluoro(organylsulfonyloxy)iodo]benzenes,[3] methoxyxenon fluoride,[7] xenon difluoride[9,17–19] and F-TEDA-BF_4.[15] Taking into account the inability of a fluorine atom to form three-membered cyclic cations,[20] we may presume the intermediacy of open (or nonclassical) fluorocarbocations in the reaction. With such an assumption, the mechanism of the fluorocyclization of acid **4** can be represented as shown in Scheme 2. The quantum-chemical calculations performed for **4** at the semiempirical PM3 level also count in favour of the proposed mechanism.

In the interaction of F-TEDA-BF_4 with the double bond in **4**, carbocations **A** and **B** are formed. Cation **A** is cyclised into five-membered *exo*-fluoro-γ-lactone **5** with an activation energy of 0.3 kcal mol^{-1}. The cyclization of cation **B** into the six-membered lactone is unfavourable because of a high activation barrier (29 kcal mol^{-1}) of the process, and it is isomerised to carbocation **C** (E_a = 25 kcal mol^{-1}). Next, cation **C** is transformed, *via* a series of hydride 1,2-shifts ($E_a \leq$ 14.5 kcal mol^{-1}), into cation **D**, which easily undergoes lactonization into **6** (E_a = = 3 kcal mol^{-1}).

Compound **3b** is evidently formed in the reaction of **1b** with F-TEDA-BF_4 through the deprotonation of a **C**-type intermediate carbocation.

‡ *Crystallographic data for* **2b**: $C_{10}H_{11}FO_4$, M = 214.19, orthorhombic, space group $P2_12_12_1$, a = 7.160(4), b = 9.656(12) and c = 13.739(9) Å, V = 1456.1 Å^3, Z = 4, d_{calc} = 1.498 g cm^{-3}, μ = 10.63 cm^{-1}, F(000) = 449.7, crystal size 0.16×0.28×0.33 mm. All data were collected using CuKα radiation (λ = 1.54178 Å) on an Enraf-Nonius CAD4 diffractometer, θ_{max} = 70°, 293 K, 1497 reflections were collected (845 independent, R_{int} = 0.017). An empirical absorption correction based on azimuthal scan data was applied. The structure was solved by direct methods and refined by a full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package.[10] All hydrogen atoms were located in the difference Fourier maps and included in the final refinement with fixed positional and thermal parameters. Convergence was obtained at R = 0.043 and R_w = 0.044, GOF = 1.189 [820 reflections with $I > 3\sigma(I)$, 136 refined parameters; obs/variabl. 6.0, difference electronic density 0.20 and –0.26 e Å^{-3}]. The Chebyshev weighting scheme[11] with parameters of 9.74, 3.02, 10.40, 0.65, and 3.09 was used in the refinement. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/107.

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