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# Selective fluorination of (1R,3S)-(+)-camphoric acid with sulphur tetrafluoride. Preparation of fluorinated optically active derivatives of 1,2,2-trimethylcyclopentane [1]

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**Abstract**

Treatment of (1R,3S)-(+)-camphoric acid (**1**) with sulphur tetrafluoride at ambient temperature gives, in general, three products: 1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanoyl fluoride (**2**), 2,2,4,4-tetrafluoro-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octane (**3**) and camphoroyl difluoride (**4**). The ratio of products strongly depends on the reaction time. Alkaline hydrolysis of (**2**) gives 1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanecarboxylic acid (**5**), quantitatively. All products exhibit optical activity.

*Keywords:* Camphoric acid; Fluorination; Sulphur tetrafluoride; 1,2,2-Trimethyl-3-trifluoromethyl-1-cyclopentanoyl fluoride; 2,2,4,4-Tetrafluoro-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octane; 1,2,2-Trimethyl-3-trifluoromethyl-1-cyclopentanecarboxylic acid

## 1. Introduction

The introduction of fluorine or fluorinated substituents, particularly trifluoromethyl groups, into biologically important molecules has attracted much attention [1–3]. For this reason, a search for synthetic methods leading to suitable trifluoromethylated molecules is of considerable importance [4]. Cyclopentane and cyclohexane rings are common structural fragments of numerous naturally occurring compounds such as steroids, vitamins D, prostaglandins and terpenes. The access to alicyclic compounds bearing a $CF_3$ group remains a difficult synthetic problem but a number of such compounds have already been synthesised. There are four general routes to functionalised five and six membered trifluoromethyl alicyclics: radical cyclisation of $\alpha$ or $\beta$-trifluoromethy-$\omega$-iodoalkanes [5,6], Lewis acid catalysed cyclisation of $\omega$-ethylenic trifluoromethylketones and ketoesters [7,8], functionalisation of readily available 2-trifluorome-thyl-1,3-cyclopentanedione [9,10] and recently, trifluoromethylation of cyclic ketones with trialkyl-(trifluoromethyl)silanes [11,12]. Trifluoromethylated cyclopentane carboaldehydes, carbinols and esters, intended to serve as ring D precursors of steroids, were obtained by the three first methods and trifluoromethylated terpenoids by the fourth. 1,2-Diphenyl-4-trifluoromethylcyclopentenes, prepared by a multistep synthesis were found to be effective cycloxygenase inhibitors [13]. From among other routes to $CF_3$ bearing alicyclics, it is worth mentioning electrochemical trifluoromethylation of 1,4-diene-1,5-dicarboxylates leading to 3,5-bis(trifluoromethyl)-cyclopentane-1,2-dicarboxylates [14].

In the present paper we report a sulphur tetrafluoride fluorination of commercially available and inexpensive (1R,3S)-(+)-camphoric acid (**1**) leading to optically active fluorinated derivatives of 1,2,2-trimethyl-3-trifluoromethyl-cyclopentane, **2–4**. We believe that the fluoride **2** and a product of its hydrolysis, acid **5**, could be applied as intermediates to some trifluoromethylated terpenoids.

## 2. Results and discussion

The different steric environments of carboxylic groups in positions 1 and 3 of camphoric acid (**1**) has been reflected by their different reactivities towards sulphur tetrafluoride (Scheme 1 and Table 1). In general, three compounds were formed, (1R,3S)-(+)-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanoyl fluoride (**2**), (1R,5S)-(+)-2,2,4,4-tetrafluoro-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octane **3** and (1R,3S)-(+)-camphoroyl difluoride **4**, but the 1,3-

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[1] Dedicated to Professor Alois Haas on his 65th birthday.


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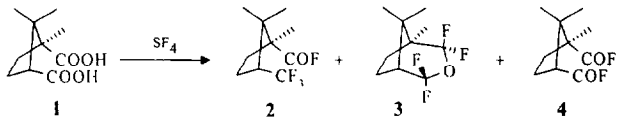
Table 1
Reactions of camphoric acid (**1**) with $SF_4$

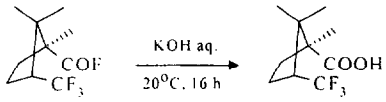
| Entry | Reaction temperature (°C) | Reaction time (h) | Products distribution (GLC%) [a] | | | Appearance of row mixture of products |
|---|---|---|---|---|---|---|
| | | | **2** | **3** | **4** | |
| 1 [b] | 60 | 20 | 31 | 18 | 37 | black viscous tar |
| 2 | 25 | 24 | 12 | 3 | 73 | yellow solid |
| 3 | 25 | 5 | 7 | 1 | 85 | yellow solid |
| 4 | 25 | 0.5 | 0.8 | trace | 92 | yellow solid |
| 5 | 25 | 113 | 62 | 10 | 18 | yellow oil |
| 6 [c] | 25 | 90 | 61 | 15 | 3 | brown oil |
| 7 | 15 | 235 | 68 | 12 | 10 | dark brown oil |
| 8 | 15 | 300 | 52 | 12 | <1 | black oil |

[a] Determined in crude mixture of products. Not calibrated.
[b] Products distribution determined after steam distillation.
[c] HF was generated in situ by addition of equimolar amount of water.



1 2 3 4

Scheme 1.



2 5 (100%)

Scheme 2.

bis(trifluoromethyl) derivative was not found among the reaction products.

The reaction, carried out at 60 °C, gave all three products but the yield was low because of considerable tar formation. At ambient temperature (15–18 °C) little or no tar was formed and the total yields were generally good. The camphoroyl difluoride (**4**) is formed almost immediately just by allowing the reaction mixture to warm up from −76 °C to ambient temperature (Entry 4). This compound is sufficiently resistant to hydrolysis to be washed (in a $CH_2Cl_2$ solution) with aqueous $K_2CO_3$ or steam distilled, however, it slowly hydrolyses with evolution of hydrogen fluoride when stored in a glass vial. Interestingly, hydrolysis of **4** by atmospheric moisture or even, in organic solvents, by dilute alkaline solutions does not give the acid **1** but camphoric anhydride.

Further fluorination of **4** proceeds slowly but after prolonged reaction time (4–12 days) bicyclic tetrafluoroether (**3**) and the trifluoromethyl acid fluoride (**2**) were formed as the minor and major product, respectively. Formation of **3** is a rare case when 1,3-dicarboxylic groups in an alicyclic ring react with $SF_4$ with ring closure to give a cyclic tetrafluoroether. The only example reported prior to this work was the reaction of *trans,cis,trans*-1,2,3,4-cyclopentanetetracarboxylic acid in which 2-3 and 1-4 carboxylic groups cyclised to give a 15% yield of tricyclic octafluoroether as a minor product [15].

The major, and the most interesting compound **2**, similarly to **4**, slowly hydrolyses when stored in a glass vial but in an organic solvent it practically does not react with aqueous bases. Quantitative conversion of **2** into (1R,3S)-(+)-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanecarboxylic acid (**5**) was achieved by agitating neat **2** with 10% aqueous KOH at ambient temperature, overnight (Scheme 2).

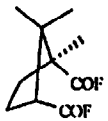
Structures of compounds **2–5** were unambiguously determined by spectral methods (Table 2). The presence of $CF_3$, $CF_2$ and COF groups has been clearly demonstrated by the multiplicity of the respective $^{13}C$ NMR signals and by chemical shift values of the $^{19}F$ NMR signals. The $^{19}F$ NMR signals of the $CF_2$ groups in **3** appear as AB spin systems with large geminal coupling constants thus showing high magnetic nonequivalence of *endo* and *exo* fluorine atoms. All compounds **2–5** are optically active though their optical rotations vary in a wide range, depending on the polarity (Table 2).

Compounds **2**, **3** and **4**, due to their considerably different polarities, are easily separable by column chromatography on silica gel using *n*-hexane as eluent. However, their volatility causes severe losses during evaporation of large volumes of the solvent. A method for the preparation of acid **5** directly from the crude reaction mixture, avoiding separation of acid fluoride **2**, is under development and will soon be published. Some chemical transformations of **2** and **5** and their synthetic utilities are also being investigated.

## 3. Experimental details

Melting points were determined in capillaries and boiling points were measured during distillation; both are uncorrected. $^1H$, $^{19}F$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 spectrometer at 200, 188 and 50 MHz, respectively. Chemical shifts are quoted in p.p.m. from internal TMS for $^1H$ and carbon $^{13}C$ (positive downfield) and from internal $CFCl_3$ for $^{19}F$ (positive upfield). Crude mixture of products were analysed with a Shimadzu GC-14A Chromatograph using a 5 m × 2 mm column packed with 5% silicone oil SE-52 on Chromosorb G. GC–MS anal-

Table 2
Physical and spectral data for compounds 2–5

| Compound |  **2** b.p. 106-108°C/60 Torr $[\alpha]_D^{22}$ +23.5 (n-hexane) |  **3** m.p. 161-163°C $[\alpha]_D^{22}$ +5.7 (n-hexane) |  **4** m.p. 104-105°C $[\alpha]_D^{22}$ +55.5 ($CH_2Cl_2$) |  **5** m.p. 101-103°C $[\alpha]_D^{22}$ +37.8 (EtOH) |
|---|---|---|---|---|
| $^{19}$F NMR $\delta$ (p.p.m.) | −36.6 (s, COF); 65.4 (d, $^3J_{FH}$ = 9.9 Hz, $CF_3$) | Two overlapping AB systems: 58.9 and 66.4 (AB); 66.4 and 73.9 (A'B'), $J_{AB} = J_{A'B'} = 158$ Hz | −36.4 (s, COF); −47.7 (s, COF) | 65.3 (d, $^3J_{FH}$ = 10.0 Hz, $CF_3$) |
| $^{13}$C NMR $\delta$ (p.p.m.) | 20.3(s, $CH_3$); 20.68(s, $CH_3$); 20.72(q, J < 1, $CH_2$); 23.3(s, $CH_3$); 31.85(d, $^3J$ = 2.5 Hz, $CH_2$); 45.2(q, $^3J$ = 2.2 Hz); 50.5 (qd, $^2J$ = 26.8 Hz, $^4J$ = 4.1 Hz, C-3); 56.5 (dq, $^2J$ = 40.9 Hz, $^4J$ = 1.6 Hz, C-1); 127.9 (q, $^1J$ = 277.6 Hz, $CF_3$); 165.1 (d, $^1J$ = 369.4 Hz, COF) | 11.9 (s, $CH_3$); 20.1 (t, $^4J$ = 7.9 Hz, $CH_3$); 21.8 (dd, $^4J$ = 5.6 and 3 Hz, $CH_3$); 24.3 (s, $CH_2$); 29.8 (t, $^3J$ = 3.3 Hz, $CH_2$); 42.5 (t, $^3J$ = ca.6 Hz, C-2); 49.3 (t, $^2J$ = 21.2 Hz, C-1); 49.5 (dd, $^2J$ = ca.22.6 Hz, C-3); 125.7 (ddd, $^1J$ = 268 and 269.5 Hz, $^3J$ = ca.7.5 Hz, $CF_2$); 127.3 (ddd, 272.5 and 253.5 Hz, $^3J$ = ca. 7.5 Hz, $CF_2$) | 20.5 (s, $CH_3$); 21.5 (s, $CH_3$); 22.5 (2xs, $CH_3$ and $CH_2$); 32.3 (s, $CH_2$); 47.0 (t, $^3J$ = 2.2 Hz, C-2); 51.6 (dd, $^2J$ = 46.0 Hz, $^4J$ = 4.3 Hz, C-3); 56.0 (dd, $^2J$ = 42.0, $^4J$ = 4.5 Hz, C-1); 163.6 (d, $^1J$ = 360.4 Hz, COF); 164.7 (d, $^1J$ = 388.0 Hz, COF) | 20.4 (q, $^4J$ = ca. 2 Hz, $CH_3$); 20.6 (q, $^3J$ = 2.7 Hz, $CH_2$); 21.2 (s, $CH_3$); 23.2 (s, $CH_3$); 31.5 (s, $CH_2$); 45.0 (s, C-2); 50.6 (q, $^2J$ = 25.3 Hz, C-3); 56.3 (q, $^4J$ = 1.75 Hz, C-1); 128.2 (q, $^1J$ = 277.7 Hz. $CF_3$); 182.0 (s, COOH) |
| $^1$H NMR $\delta$ (p.p.m.) | 1.09 (q, $^5J_{HF}$ = 1.5 Hz, $CH_3$); 1.28 (s, $CH_3$); 1.31 (s, $CH_3$); 1.68 (1H), 1.9–2.104 (2H) and 2.48–2.65 (1H); 2.60 (q, $^3J_{HF}$ = 9.85 Hz, CH) | 1.00 (s, $CH_3$); 1.12 (s, $CH_3$); 1.21 (t, $^5J_{HF}$ = 3.4 Hz, $CH_3$); 1.5–2.2 (complex, 2x$CH_2$); 2.26 (dd, $^3J_{HF}$ = 6.5 and 4.3 Hz, CH) | 1.07 (s, $CH_3$); 1.36 (s, 2$CH_3$); 1.6–2.7 (complex, 2$CH_2$); 2.99 (dd, $^3J$ = 9.4 and 9.5 Hz, CH) | 1.03 (q, $J_{HF}$ = 1.7 Hz, $CH_3$); 1.25 (s, $CH_3$); 1.28 (s, $CH_3$); 1.57 (1H), 1.8–2.1 (2H) and 2.4–2.73 (1H); 2.60 (q, $^3J_{HF}$ = 10.0 Hz, CH)10.68 (br, OH) |
| MS $m/z$ (%) assignement | 226 (<1) $M^+$; 211 (2) $(M-Me)^+$; 206 (1) $(M-HF)^+$; 186 (18) $(M-2HF)^+$; 163 (43) $C_8H_{10}F_3^+$; 158 (60) $C_9H_{12}F_2^+$; 138 (90) $C_6H_9F_3^+$; 124 (20); 118 (35); 116 (45); 102 (35); 89 (82) $C_4H_6FO^+$; 69 (75) $C_4H_5O^+$; 55 (75) $C_4H_7^+$; 41 (100) $C_3H_5^+$ | 226 (14) $M^+$; 211 (25) $(M-Me)^+$; 206 (10) $(M-HF)^+$; 191 (10) $(M-HF-Me)^+$; 186 (25) $(M-2HF)^+$; 163 (55) $C_8H_{10}F_3^+$; 158 (85) $C_9H_{12}F_2^+$; 138 (85) $C_9H_{11}F^+$; 104 (50) $C_5H_9FO^+$; 91 (50) $C_4H_8FO^+$; 89 (55) $C_4H_6FO^+$; 69 (70) $C_4H_5O^+$; 61 (100) $C_2H_2FO^+$; 55 (26) $C_4H_7^+$; 41 (38) $C_3H_5^+$ | 204 (<1) $M^+$; 189 (<1) $(M-Me)^+$; 176 (<1) $(M-CO)^+$; 164 (xx) $(M-2HF)^+$; 156 (16) $(M-CO-HF)^+$; 141 (18) $(M-CO_2F)^+$; 136 (100) $C_9H_{12}O^+$; 87 (40) $C_5H_8F^+$; 69 (70) $C_5H_9^+$ or $C_4H_5O^+$; 68 (65) $C_5H_8^+$ or $C_4H_4O^+$; 67 (30) $C_5H_7^+$; 55 (40) $C_4H_7^+$; 53 (25) $C_4H_5^+$; 41 (45) $C_3H_5^+$; 39 (30) $C_3H_3^+$ | 225 (0.3) $(M+1)^+$; 224 (0.5) $M^+$; 209 (3) $(M-Me)^+$; 204 (4) $(M-HF)^+$; 184 (17) $(M-2HF)^+$; 164 (8) $(M-Me-CO_2H)^+$; 163 (8) $C_8H_{10}F_3^+$; 139 (10) $(M-CO_2H-2HF)^+$; 87 (100) $C_5H_8F^+$; 55 (13) $C_4H_7^+$; 41 (10) $C_3H_5^+$ |
| HRMS | calc. for $C_{10}H_{14}F_4O$: 226.09808 found: 226.09806 | calc. for $C_{10}H_{14}F_4O$: 226.09808 found: 226.09894 | calc. for $C_{10}H_{14}F_2O_2$: 204.09619 found: 204.09592 | calc. for $C_{10}H_{15}F_3O_2$: 224.10241 found: 224.10179 |
| IR ($cm^{-1}$) | film: 1831 (vs, COF) | | in $CCl_4$: 1835.6 (vs, COF) | in $CCl_4$: 1699.3 (vs, CO) |

yses were performed with a Hewlett-Packard 5890 apparatus (70 eV) using a 30 m capillary column coated with a HP5 oil. High resolution mass spectra of pure compounds were obtained with an AMD-604 spectrometer and IR spectra with a Perkin-Elmer 1640 instrument. Optical rotations were measured at ambient temperature (ca. 22 °C) as 10% solutions with a JASCO DIP-360 digital polarimeter using a 100 mm cell.

(1R,3S)-(+)-Camphoric acid (Fluka, $[\alpha]_D^{22}$ +48.9, $c=10$, $C_2H_5OH$]; lit. $[\alpha]_D^{20}$ +46.5±2 [16]) and sulphur tetrafluoride (Air Products) were commercial reagent grade products.

### 3.1. Reactions of camphoric acid (1) with $SF_4$ and isolation of compounds 2–4

Acid **1** (2 g, 0.01 mmol or 6 g, 0.03 mol) was placed in a 30 ml capacity stainless steel autoclave fitted with a needle valve, the autoclave was cooled in an acetone–dry ice bath, evacuated, then sulphur tetrafluoride (7 g, 0.065 mol or 21 g, 0.2 mol, respectively to the amount of **1**) was condensed in. The autoclave was agitated in a rocking furnace under conditions given in Table 1. After completion of the reaction, gaseous products were let off ($SF_4$, $SOF_2$, HF) and the residue was dissolved in $CH_2Cl_2$ (50 ml), washed with 5% aqueous $K_2CO_3$ and dried over $MgSO_4$. Removal of the solvent gave a crude mixture of products (2.1–2.4 g or ca. 6.5 g, depending on the amount of **1** used) which was subjected to GC–MS and/or GLC investigations; the results are given in Table 1. A mixture obtained from Entry 1, prior to GLC analysis, was steam distilled to give colourless oil (0.9 g from 2 g of **1**.

Compound **2** and **3** were isolated from a crude mixture of products obtained in Entry 7 (6.5 g) by column chromatography on silica gel (50 g) using *n*-hexane as eluent. Evaporation of the eluent under atmospheric pressure (both compound are volatile) gave **2** as an almost colourless oil (yield 2.85 g, 42%, GLC purity >99%) and **3** as yellowish crystals (0.9 g, 13%, GLC purity >99%). Analytical, colourless samples were obtained by vacuum distillation or sublimation, respectively.

Pure compound **4** (isolated yield 1.8 g, 88%, GLC purity 98%) was obtained as a white amorphous solid by vacuum sublimation of crude product formed in Entry 4 (2.1 g).

Compounds **2**, **3** and **4** possess a weak characteristic smell resembling that of camphor; HRMS, NMR data and physical properties are given in Table 2.

### 3.2. (1R,3S)-(+)-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanecarboxylic acid (5)

A suspension of acid fluoride **2** (1.37 g, 6 mmol) in a 10% aqueous KOH (20 ml) was vigorously agitated overnight at ambient temperature. A clear homogenous solution was formed. A white solid obtained after acidification with concentrated hydrochloric acid was filtered off, washed with cold water and dried over $P_4O_{10}$. This product, containing considerable amount of non-melting inorganic material, was dissolved in *n*-pentane (ca. 10 ml) and inorganic salts were removed by filtration. Evaporation of the solvent gave pure **5** as a white odourless crystalline solid (1.37 g, 100%). HRMS, NMR data and physical properties are given in Table 2.

### 3.3. Atmospheric hydrolysis of difluoride 4

A sample of **4** stored in a closed glass vial slowly eliminated hydrogen fluoride. After ten days the sample was found by comparative GLC to contain 95% of camphoric anhydride: m.p. ca. 220 °C (lit. 223.5 °C [17]; IR ($CCl_4$) ($cm^{-1}$): 1762 (vs, CO) and 1810 (vs, CO) (lit. 1770 and 1820 $cm^{-1}$ [17]).

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