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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 α or β-trifluoromethy-ω-iodoalkanes [5,6], Lewis acid catalysed cyclisation of ω-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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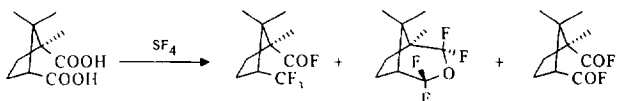
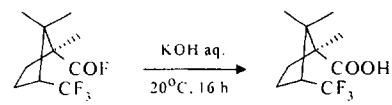
Table 1
Reactions of camphoric acid (**1**) with SF_4

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.



Scheme 1.



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).

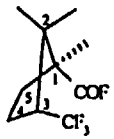
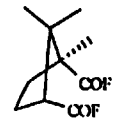
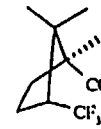
Structures of compounds **2–5** were unambiguously determined by spectral methods (Table 2). The presence of CF_3, CF_2 and COF groups has been clearly demonstrated by the multiplicity of the respective ^{13}C NMR signals and by chemical shift values of the ^{19}F NMR signals. The ^{19}F NMR signals 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 δ (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 δ (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 δ (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, 2xCH_2); 2.26 (dd, $^3J_{HF}$ = 6.5 and 4.3 Hz, CH)	1.07 (s, CH_3); 1.36 (s, 2CH_3); 1.6–2.7 (complex, 2CH_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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