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Selective fluorination of (1*S*,4*R*)-(−)-camphanic acid with sulphur tetrafluoride: preparation of new fluorinated optically active derivatives of camphor and 1,2,2-trimethylcyclopentane

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Dedicated to Prof. Yoshiro Kobayashi on his 75th birthday

Abstract

Treatment of (1*S*,4*R*)-(−)-camphanic acid (**1**) with sulphur tetrafluoride affords (1*R*,4*S*)-(−)-3-oxa-4-(trifluoromethyl)camphor (**2**) as a main product together with small amounts of (1*S*,4*R*)-camphanoyl fluoride (**3**), (1*R*)-3-(trifluoromethyl)camphonenoyl fluoride (**4**) and (1*R*)-3,4-dehydrocamphoroyl difluoride (**5**). Reduction of **2** with $LiAlH_4$ gives the diol, (1*R*,3*S*)-(+)-3-hydroxy-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanemethanol (**6**), which when heated with $KHSO_4$ readily dehydrates to (1*R*,4*S*)-(−)-3-oxa-4-(trifluoromethyl)bornane (**7**). Acylation of the diol **6** proceeds regioselectively at the primary hydroxyl group to give exclusively monoacylated derivative **8**.

Keywords: Camphanic acid; Fluorination; Sulphur tetrafluoride; (1*R*,4*S*)-(−)-3-Oxa-4-(trifluoromethyl)camphor; 3-Hydroxy-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanemethanol; (1*R*,4*S*)-(−)-3-Oxa-4-(trifluoromethyl)-bornane

1. Introduction

In the preceding paper [1] it has been reported that a sulphur tetrafluoride fluorination of commercially available (1*R*,3*S*)-(+)-camphoric acid proceeds selectively to give, besides two minor compounds, (1*R*,3*S*)-(+)-3-(trifluoromethyl)camphonanoyl fluoride as a main product. The expedient isolation of the latter as (1*R*,3*S*)-(+)-3-(trifluoromethyl)camphonanic acid has also been later described [2]. This result showed that in camphoric acid only the less sterically hindered carboxylic group at the position 3 can be converted into the CF_3 group while the reaction with the second, sterically more crowded carboxylic group at the position 1, stops at the stage of an acyl fluoride. This rather rare case of selective fluorination of carbonyl functions with SF_4 stimulated further studies on fluorination of polyfunctional substrates, particularly derivatives of terpenes, aiming in the preparation of new trifluoromethyl derivatives with the definite configuration. The present paper reports a sulphur tetrafluoride fluorination of the lactone, (1*S*,4*R*)-(−)-camphanic acid (**1**) readily available from camphoric acid [3], and related chemistry.

2. Results and discussion

A prolonged treatment of camphanic acid (**1**) with sulphur tetrafluoride at ambient temperature (ca. 20°C) resulted in a mixture consisting mostly (84 GLC%) of a bicyclic lactone, (1*R*,4*S*)-(−)-3-oxa-4-(trifluoromethyl)camphor (**2**), together with small amounts of the intermediate bicyclic acyl fluoride **3** and the lactone opening products **4** and **5**, although the structures of these side products were tentatively assigned based on GC–MS analyses.

It is known that esters and lactones are much less reactive towards sulphur tetrafluoride than free carboxylic acids [4], and in compound **1** the reactivity of lactone moiety should be lowered by steric crowdness due to the neighbouring methyl groups in positions 4 and 7; this explains high selectivity of the fluorination.

Treatment of the crude reaction mixture with aqueous potassium hydroxide effectively removed acyl fluorides **3–5** leaving compound **2** unchanged and thus enabling its efficient isolation. Reduction of **2** with $LiAlH_4$ gave the diol **6** in

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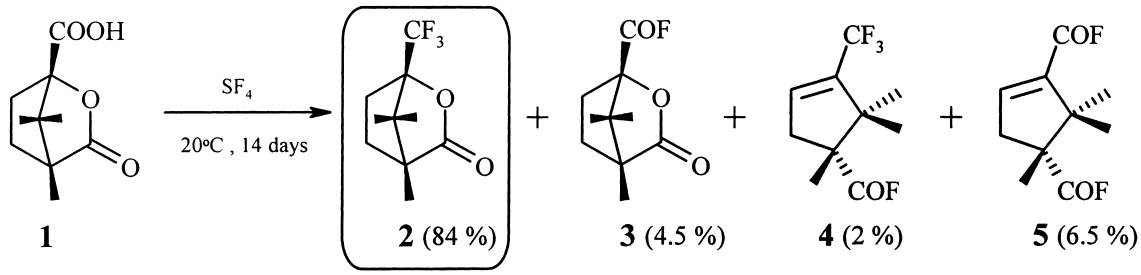
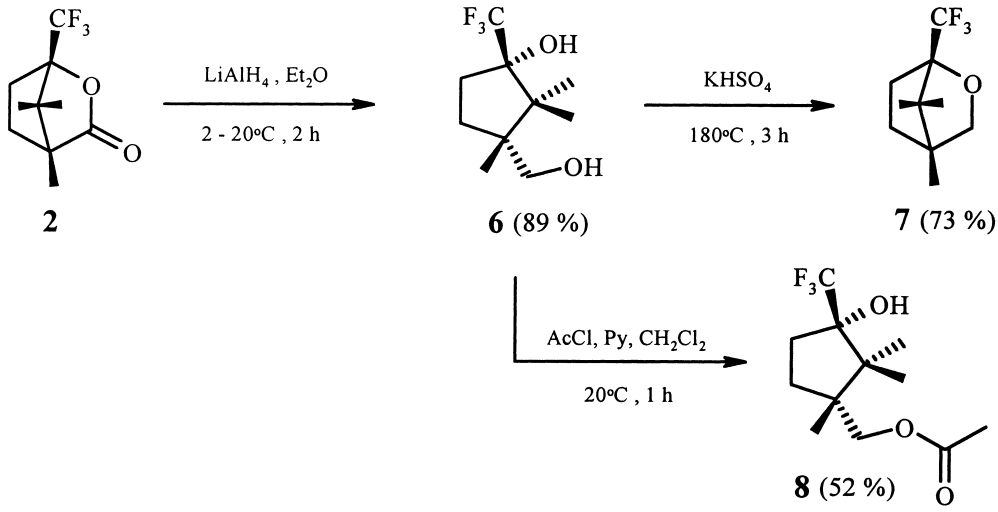


high yield. Dehydration of diol **6** with anhydrous $KHSO_4$ at 180°C afforded the bicyclic ether, (1*R*,4*S*)-(−)-3-oxa-4-(trifluoromethyl)bornane (**7**). The hydroxy groups in the diol **6** showed quite different reactivities. Thus, acetylation with a five-fold excess of acetyl chloride proceeded regioselectively at the primary hydroxyl group to give exclusively monoacetylated product **8**. Compounds **2** and **6–8** retain the absolute configuration of the starting acid **1** on both asymmetric carbon atoms. The bicyclic compounds **2** and **7** also retain the negative sign of the optical rotation coefficient [α] while this coefficient for the monocyclic compounds **6** and **8** showed the opposite sign (positive). Further chemistry of compounds **2–8** is being investigated.



3. Experimental

Melting points were determined in capillaries and boiling points were measured during distillation; both are uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively. Chemical shifts are quoted in ppm from internal TMS for ^1H (positive downfield) and from internal $CFCl_3$ (positive upfield). Crude mixture of products were analysed with a Shimadzu GC-14A Chromatograph using a 3.5 m×2 mm column packed with 5% silicone oil SE-52 on Chromosorb G. GS–MS analyses were performed with a Hewlett-Packard 5890 apparatus using a 30 m capillary column coated with a HP5 oil. 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 as 5% solutions in methanol with a JASCO DIP-360 polarimeter using a 100 mm cell.

(1*S*,4*R*)-(−)-camphanic acid (**1**) was synthesised by following the literature procedure [3].

3.1. Reaction of (1S,4R)-(−)-camphanic acid (1) with sulphur tetrafluoride

(1*S*,4*R*)-(−)-camphanic acid (**1**) (20 g, 0.1 mol) was placed in a 250 ml capacity stainless steel autoclave fitted with a needle valve, the autoclave was cooled in an acetone-dry ice bath, evacuated, then sulphur tetrafluoride (32 g, 0.3 mol) was condensed into it. The autoclave was left at ambient temperature (20–22°C) for 14 days (shaken occasionally). After completion of the reaction, gaseous products were let off (SF_4, SOF_2, HF) and a brown oily residue was washed out with CH_2Cl_2 (180 ml) into a polyethylene container, sodium fluoride (30 g) was added and the mixture was stirred overnight to remove HF. Precipitates were filtered off and the filtrate was concentrated on a rotary evaporator affording a yellow oily residue containing some solid material (elemental sulphur). This mixture was stirred with hexane (200 ml) for half an hour and filtered. The GC–MS analysis of the hexane solution revealed the presence of compound **2** as the main component (84%) together with a number of minor components of which the most abundant

were **3** (4.5%), **4** (2%) and **5** (6.5%). A 5% aqueous solution of KOH (100 ml) was added and the two phases were vigourously mixed together for 2 h. The organic layer was separated, washed with water (3×50 ml) and dried over $MgSO_4$. Compounds **3**, **4** and **5** were not detected by GLC. The solvent was distilled off on a water bath and the residue was vacuum distilled to afford **2** as a white waxy material (solidifies in a water condenser) possessing mild camphor like smell.

(1*R*,4*S*)-(−)-3-oxa-4-trifluoromethylcamphor (**2**): Yield: 10.7 g (48.2%). GLC purity: 98.5%. B.p. 92°C/5 Torr; 65–66°C/2 Torr. M.p.=38–40°C. IR (CCl_4) (cm^{-1}): 1807.8 (vs, C=O). $[\alpha]_D^{22}=-1.4$ (*c*=5, MeOH). Analysis: Found: C, 54.0; H, 6.05; F, 25.7%. $C_{10}H_{13}F_3O_2$ (222.21) requires: C, 54.05; H, 5.9; F, 25.65%. ^{1}H NMR: 1.07 (brs, 2×CH_3); 1.12 (s, CH_3); 1.65–1.8 (m, 1H); 1.82–2.1 (m, 2H); 2.2–2.35 (m, 1H) ppm. ^{19}F NMR: 73.45 (s, CF_3) ppm. MS (70 eV) *m/z* (rel.int., ion): 222 (1, M^+); 194 [47, $(M–CO)^+$]; 179 [9, $(M-CO-CH_3)^+$]; 163 [100, $(M-CO_2-CH_3)^+$]; 109 (21, $C_8H_{13}^+$); 83 (78, $C_6H_{11}^+$); 82 (44, $C_6H_{10}^+$); 69 (17, CF_3^+); 67 (18, $C_5H_7^+$); 55 (41, $C_4H_7^+$); 41 (35, $C_3H_5^+$).

(1*R*,4*S*)-camphanoyl fluoride (**3**): GC–MS *m/z* (rel.int., ion): 200 (<1, M^+); 172 [80, $(M–CO)^+$]; 141 [95, $(M-CO_2-CH_3)^+$]; 113 (70, $C_7H_{10}F^+$); 109 (100, $C_8H_{13}^+$); 83 (90, $C_6H_{11}^+$); 69 (33, CF_3^+); 67 (35, $C_5H_7^+$) 55 (80, $C_4H_7^+$); 41 (85, $C_3H_5^+$).

(1*R*)-3-(trifluoromethyl)camphonenoyl fluoride (**4**): GC–MS *m/z* (rel.int., ion): 224 (5, M^+); 196 [5, $(M–CO)^+$]; 177 [100, $(M–COF)^+$]; 135 (15, $C_6H_6F_3^+$); 127 (20, $C_8H_{12}F^+$).

(1*R*)-3,4-dehydrocamphoroyl difluoride (**5**): GC–MS *m/z* (rel.int., ion): 202 (5, M^+); 174 [8, $(M–CO)^+$]; 155 [40, $(M–COF)^+$]; 127 (100, $(M–COF–CO)^+$]; 107 (55, $C_8H_{11}^+$); 91 (30, $C_7H_7^+$).

3.2. (1R,3S)-(+)-3-Hydroxy-1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanemethanol (6)

A solution of (1*R*,4*S*)-(−)-3-oxa-4-trifluoromethylcamphor (**2**) (6.3 g, 0.028 mol) in dry ether (30 ml) was added dropwise (15 min) to a stirred suspension of $LiAlH_4$ (1.4 g, 0.037 mol) in ether (150 ml) precooled to 2–3°C under nitrogen atmosphere (slightly exothermic reaction), then the reaction mixture was stirred for 1 h at 5–8°C after which it was slowly (1 h) warmed up to ambient temperature. Diluted hydrochloric acid (ca. 10%, 150 ml) was slowly added and a two-phase mixture was stirred until the water phase became fully transparent. The layers were separated, the water phase was washed with ether (3×50 ml). The combined ether phases were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a colourless solid which was recrystallised from hexane to afford large crystals possessing a mould like smell. Yield: 5.65 g (89.2%). GLC purity: 99.65%. M.p. 103–105°C. IR (CCl_4) (cm^{-1}): 3338.4 and 3123.2 (br, OH). $[\alpha]_D^{22}=+12.1$ (*c*=5, MeOH). Analysis: Found, C, 53.2; H, 7.6; F, 25.1%. $C_{10}H_{17}F_3O_2$ (226.24) requires: C, 53.1; H, 7.6; F, 25.2%. ^{1}H NMR: 0.85 (s, CH_3); 1.01 (q, $^5J_{HF}$=2.6 Hz, CH_3); 1.06 (s, CH_3); 1.52–1.83 (m, 2H); 1.92–2.12 (m, 1H); 2.18–2.34 (m, 1H); 3.30 and 3.60 (AB system, J_{AB}=10.7 Hz, CH_2O); 4.18 (brs, OH); 6.24 (brs, OH) ppm. ^{19}F NMR: 74.4 (s) ppm. MS (70 eV) *m/e* (rel.int., ion): 226 (<1, M^+); 208 [<1, $(M-H_2O)^+$]; 194 [23, (23, $(M-CH_2OH_2)^+$]; 177 [100, $(M-H_2O-CH_2OH)^+$]; 163 (54, $C_8H_{10}F_3^+$) 135 ($18, C_6H_6F_3^+$); 109 ($12, C_8H_{13}^+$); 96 ($26, C_7H_{12}^+$); 83 ($71, C_6H_{11}^+$); 71 ($20, C_4H_7O^+$); 69 (12, CF_3^+); 67 (15, $C_5H_7^+$); 55 (49, $C_4H_7^+$); 43 (22, $C_3H_7^+$); 41 (31, $C_3H_5^+$).

3.3. (1S,4R)-(−)-3-Oxa-4-(trifluoromethyl)bornane (7)

The diol **6** (1.1 g, 5 mmol) and potassium hydrogen sulphate (5.0 g, 37 mmol) freshly dried at 200°C were ground together, then placed at the bottom of a glass tube (ϕ=20 mm, *l*=200 mm) and covered by a layer of potassium hydrogen sulphate (3.5 g). The tube was sealed and slowly heated on an oil bath to 180°C and then kept at the same temperature for 3 h. A liquid product condensed at the upper, cooler part of the tube. After cooling to ambient temperature, ether was added (20 ml), and the solid material was filtered off, then the solid material was washed with ether (5 ml). The GC–MS analysis of the combined ether solutions revealed a single component. The solvent was distilled off on a water bath and the residue was vacuum distilled to afford a white low melting crystalline solid possessing a mild terpenic smell. Yield: 0.76 g (73%). GLC purity: >99%. B.p. 64°C/18 Torr. M.p.=ca. 32°C. IR (CCl_4): no OH absorption. $[\alpha]_D^{20}=-10.7$ (*c*=5, MeOH). Analysis: Found, C, 57.5; H, 7.3; F, 27.5%. $C_{10}H_{15}F_3O$ (208.22) requires: C, 57.7; H, 7.25; F, 27.4%. ^{1}H NMR: 0.89 (s, CH_3); 1.00 (s, CH_3); 1.03 (q, *J*=1.3 Hz, CH_3); 1.45–2.18 (m, 4H); 3.57 and 3.73 (AB system, J_{AB}=7.0 Hz, CH_2) ppm. ^{19}F NMR: 74.2 (s) ppm. MS (70 eV) *m/e* (rel.int., ion): 208 (10, M^+); 193 [4, $(M-CH_3)^+$];193 [4, $(M-CH_3)^+$]; 163 [11, $(M-CH_3-CH_2O)^+$]; 96 (100, $C_7H_{12}^+$); 83 (50, $C_6H_{11}^+$); 55 (15, $C_4H_7^+$); 41 (10, $C_3H_5^+$).

3.4. (1R,3S)-(+)-1-acetoxymethyl-3-hydroxy-1,2,2-trimethyl-3-(trifluoromethyl)cyclopentane (8)

A solution of acetyl chloride (4 g, 50 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of the diol **6** (2.2 g, 10 mmol) and pyridine (4 g, 50 mmol) in CH_2Cl_2 (15 ml). An exothermic reaction occurred and fine precipitate of C_5H_5N..HCl immediately formed. The reaction mixture was stirred at ambient temperature for 1 h, then poured into cold water (60 ml) and acidified with hydrochloric acid (ca. 2 ml). The bottom organic layer was separated, washed with water followed by 10% aqueous $NaHCO_3$ and again with water and dried over $MgSO_4$. Evaporation of the solvent gave a crystalline solid possessing strong smell of acetic acid. The solid was mixed with triethylamine (6 ml) and stirred at 40–50°C for 1 h. The homogeneous solution was poured into water (100 ml) to

afford white precipitate which was filtered off and dried over P_4O_{10} in vacuo to give **8** (2 g, m.p. 109–111°C). Recrystallization from hexane (ca. 40 ml) gave fine, odourless crystals. Yield: 1.4 g (52%). GLC purity: >99%. M.p.=112–114°C. IR (CCl_4) (cm^{-1}): 1720.3(s) and 1741.5(vs) (C=O); 3462.6 (broad, hydrogen bonded OH) and 3603.7 (sharp, free OH). $[\alpha]_D^{20}=+9.5$ (c=5, MeOH). Analysis: Found: C, 53.6; H, 7.3; F, 21.25%. $C_{12}H_{19}F_3O_3$ (268.28) requires: C, 53.7; H, 7.15; F, 21.25%. ^{1}H NMR: 0.97 (s, CH_3); 1.00 (q,^{5} J_{HF}=2.6 Hz, CH_3); 1.04 (s, CH_3); 1.45–1.8 (m, 1H); 1.85–2.0 (m, 1H); 2.08 (s, $COCH_3$); 2.25–2.4 (m, 2H); 3.95 and 4.48 (AB system, J_{AB}=11.0 Hz, CH_2O) ppm. The spectrum contains also two sharp signals at 1.64 and 2.33 ppm which disappear on addition of a drop of D_2O and appear again after addition of H_2O; they could be assigned to a hydrogen bonded and free OH groups. ^{19}F NMR : 75.3 (s) ppm.

MS (70 eV) *m/e* (rel.int., ion): 268 (<1%, M^+); 250 [6, $(M-H_2O)^+$]; 225 [8, $(M-CH_3O)^+$]; 208 [4,$(M-CH_3CO_2H)^+$]; 195 [17,$(M-CH_3CO_2CH_2)^+$]; 177 (100, $C_9H_{12}F_3^+$); 96 (34, $C_7H_{14}^+$); 83 (28, $C_6H_{11}^+$); 71 (9, $C_4H_7O^+$); 68 (10, $C_5H_8^+$); 55 (14, $C_4H_7^+$); 43 (60, CH_3CO^+).

References

[1] W. Dmowski, T. Kozłowski, J. Fluorine Chem. 83 (1997) 187.
[2] W. Dmowski, K. Piasecka-Maciejewska, Org. Prep. Proc. Int. 31 (1999) 207.
[3] H. Gerlach, D. Kappes, R.K. Boeckman Jr., G.N. Maw, Org. Syntheses 71 (1993) 48.
[4] W. Dmowski, Introduction of Fluorine in Organic Compounds Using Sulfur Tetrafluoride, in: Houben-Weyl: Methods in Organic Chemistry, vol. E10 a, Stuttgart, 1999.