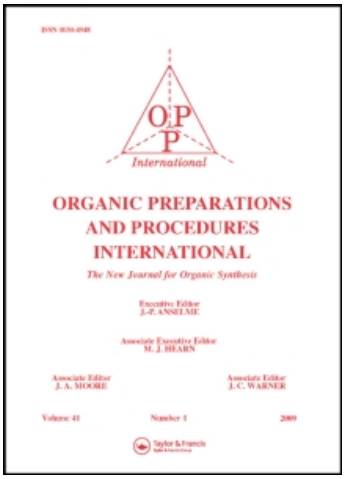

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EXPEDIENT SYNTHESIS OF (1R,3S)-(+)-3-(TRIFLUOROMETHYL)CAMPHONANIC ACID AND DERIVATIVES

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4. J. S. Cha, J. M. Kim, J. H. Chun, S. Y. Kwon and J. C. Lee, *ibid.*, **19**, 730 (1998).

5. J. S. Cha, J. M. Kim, J. H. Chun, S. Y. Kwon and S. D. Cho, *ibid.*, **19**, 1301 (1998).

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EXPEDIENT SYNTHESIS OF (1R,3S)-(+)-3-(TRIFLUOROMETHYL)CAMPHONANIC ACID AND DERIVATIVES

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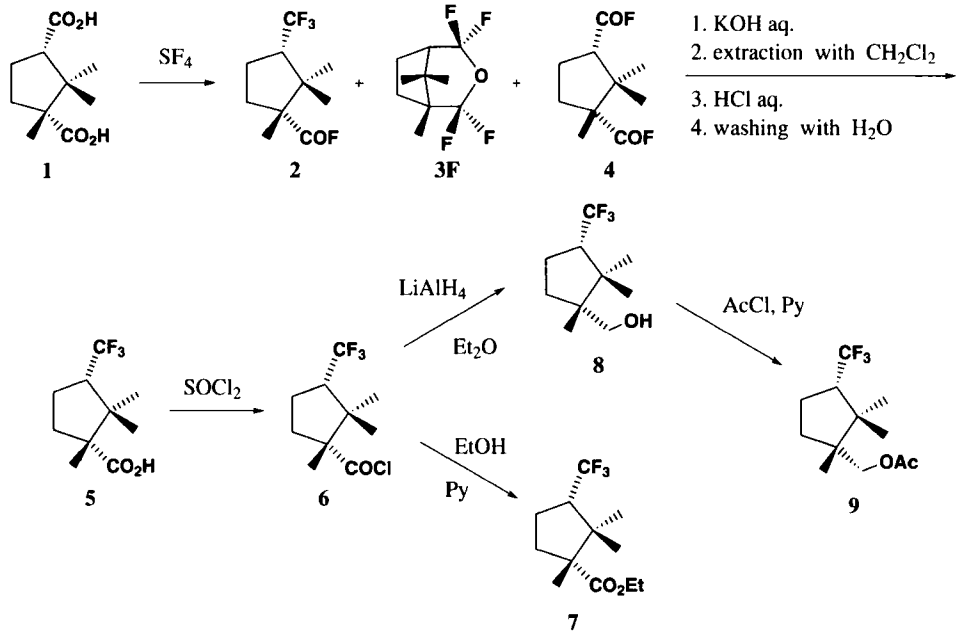
Monoterpenes, particularly camphor and its derivatives such as cyclopentanoids, are versatile, chiral and enantiopure starting materials in natural product synthesis.[1] Recently, there is a growing interest in fluorinated derivatives of terpenic compounds which could serve as synthetic intermediates, mechanistic and ^{19}F NMR probes.[2-5] A preceeding paper[6] described a sulfur tetrafluoride fluorination of (1R,3S)-(+)-camphoric acid (**1**). This reaction resulted in a mixture of (1R,3S)-(+)-3-(trifluoromethyl)camphonanoyl fluoride (**2**), bicyclic tetrafluoroether (**3**) and camphoroyl difluoride (**4**) in ratios depending on the conditions used. The major and most interesting compound **2** was isolated by column chromatography and subsequently hydrolyzed to (1R,3S)-(+)-3-(trifluoromethyl)-camphonanic acid (**5**). This procedure is, however, inconvenient for a larger scale preparation of **5**. We now describe a simple and expedient method for the separation of the crude mixture of products resulting from the reaction of camphoric acid (**1**) with SF_4. This procedure affords pure **5** in good yield as the only product. The preparation of simple derivatives of **5** is also reported.

In the present procedure, a mixture of **2**, **3** and **4** is hydrolyzed with aqueous KOH and then the non-hydrolyzable compound (**3**) and other minor base insoluble impurities are removed by extraction with an organic solvent. Acidification of the basic solution gives a mixture of free acids **1** and **5** which are easily separated owing to the drastic difference in their solubility in aqueous media. Acid **5** is practically insoluble in water and could be isolated from **1** by washing with warm water.

The attempted acid-catalyzed esterification of **5** with methanol or ethanol failed presumably due to steric hindrance. However, treatment of **5** with $SOCl_2$ afforded the respective acid chloride **6** nearly quantitatively. Acid chloride **6** reacts in a conventional way with alcohols. Reaction with ethanol gave ester **7**. Reduction of **6** with $LiAlH_4$ yielded alcohol **8** which upon treatment with acetyl chloride gave acetate **9**. Compounds **5-9** exhibit high optical activity. With the exception of **5** and **6**,

these compounds possess a characteristic camphor like odor. The use of acid chloride **6** and alcohol **8** as the ^{19}F NMR probes for determining enantiomeric ratios of chiral compounds is under investigation.



EXPERIMENTAL SECTION

Mps were determined in open capillaries and boiling points during distillation; both are uncorrected. ^1H- and ^{19}F-NMR spectra were recorded in $CDCl_3$ with a Varian Gemini spectrometer at 200 and 188 MHz, respectively; chemical shifts are in p.p.m. from internal TMS for protons and from internal $CFCl_3$ for fluorine nuclei (positive upfield). Mass spectra were obtained with an AMD-604 spectrometer at 70 eV and IR spectra were measured with a Perkin-Elmer Spectrum 2000 instrument. Optical rotations were measured at ambient temperature with a JASCO DIP-360 digital polarimeter using a 100 mm cell. GLC analyses were carried out with a Shimadzu GC-14A chromatograph using a 3.5 m x 2 mm column packed with 5% silicon oil SE-52 on Chromosorb G.

(1R,3S)-(+)-3-(Trifluoromethyl)camphonanic Acid (5).- (1R,3S)-(+)-Camphoric acid (**1**) (48 g, 0.24 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 sulfur tetrafluoride (168 g, 1.6 mol) was condensed into it. The autoclave was agitated at ambient temperature (20-25°) for ten days. After completion of the reaction, gaseous products were let off (SF_4, SOF_2, HF) and the brown semisolid residue was poured into a 10% aqueous solution of potassium hydroxide (500 mL) and stirred overnight at ambient temperature. The mixture was washed with CH_2Cl_2 (3 x 50 mL) to remove base insoluble impurities, the aqueous solution was separated, boiled with charcoal, filtered, strongly acidified with hydrochloric acid and left in a refrigator (5-10°) for two hours. A brownish precipitate was separated by filtration. The solid material was stirred with water (400 mL) at 40° for 15 minutes and

filtered. This operation was repeated three time (removal of unreacted camphoric acid). The brownish colored solid material was dried over P_4O_{10} under vacuum to constant weight (35 g). Crystallization from *n*-hexane (250 mL) with small amount of charcoal gave a white-yellowish product which was recrystallized from acetone (charcoal added) to give a colorless product. Yield: 26.2 g (49%). $[\alpha]_D^{21}$ = +53.1 (c = 5, MeOH). Elemental analysis, spectral data and physical properties were with agreement with the reported data.[6]

(1R,3S)-(+)-3-(Trifluoromethyl)camphonanoyl Chloride (6).- Acid (**5**) (11.2 g, 0.05 mol) and thionyl chloride (25 g, 0.21 mol) were refluxed for 1.5 hours (evolution of gases ceased after 1 hour), an excess of $SOCl_2$ was distilled off under atmospheric pressure and the residue was vacuum distilled to give a colorless liquid. Yield: 11.1 g (92%), bp. 78-80°/8 Torr.

IR (film): 1787 cm^{-1} (vs, COCl). $[\alpha]_D^{21}$ = +38.1 (c = 5, *n*-hexane)

Anal. Calcd for $C_{10}H_{14}ClF_3O$: C, 49.50; H, 5.81; Cl, 14.61; F, 23.49

Found: C, 49.18; H, 5.88; Cl, 14.76; F, 23.44

^1H NMR (200 MHz, in $CDCl_3$): δ 1.11 (q, $^5J_{HF}$ = 1.9 Hz, CH_3); 1.35 (s, CH_3); 1.38 (d, J_{HH} = 0.9 Hz, CH_3); 1.65-1.80 (complex, 1H); 1.85-2.00 (complex, 2H), 2.48-2.78 (complex, 1H); 2.60 (q, $^3J_{HF}$ = 9.8 Hz, CH). ^{19}F NMR (188 MHz, in $CDCl_3$): δ 65.35 (d, $^3J_{HF}$ = 9.8 Hz, CF_3).

MS (70 eV) m/e (rel.int., ion): 244,242 (0.6; 1.8, M^+); 224,222 (0.9; 2.5, M-HF); 207 (13, M-Cl); 179 (95, M-COCl); 163 (73, $C_8H_{10}F_3^+$); 138 (100, $C_6H_9F_3^+$); 120,118 (11;36, $C_6H_{11}Cl^+$); 107,105 (17;51, $C_5H_{10}Cl^+$); 83 (21, $C_6H_{11}^+$); 79,11 (5;15, $C_4H_7Cl^+$); 69 (40, $C_5H_9^+$ and CF_3^+); 55 (44, $C_4H_7^+$); 43 (24, $C_3H_7^+$); 41 (35, $C_3H_5^+$).

Ethyl (1R,3S)-(+)-3-(Trifluoromethyl)camphonanoate (7).- Pyridine (0.6 g, 7.6 mmol) was added dropwise to a stirred solution of acid chloride (**6**) (1.8 g, 7.4 mmol) in commercial anhydrous ethanol (5 mL); an exothermic reaction occured (periodical cooling with tap water was applied). The solution was left at ambient temperature for two hours after which time it was mixed well with 1% hydrochloric acid (30 mL). The organic material was extracted with ether (2 x 20 mL). The extract was washed with 5% $NaHCO_3$ (20 mL) followed by water and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue was vacuum distilled to give a colorless oil. Yield: 1.3 g (70%). GLC purity: >98%, bp. 66-68°/2 Torr. IR (film): 1727.7 cm^{-1} (vs, C=O). $[\alpha]_D^{21}$ = +31.8 (c = 5, EtOH).

Anal. Calcd for $C_{12}H_{19}F_3O_2$: C, 57.13; H, 7.59; F, 22.59. Found: C, 57.09; H, 7.67; F, 22.53

^1H NMR (200 MHz, in $CDCl_3$): δ 0.94 (q, $^5J_{HF}$ = 1.9 Hz, CH_3); 1.20 (broad s, CH_3); 1.26(s, CH_3); 1.28 (t, $^3J_{HH}$ = 7.1 Hz, CH_3); 1.54 (complex, 1H); 1.90 (complex, 2H); 2.58 (q, $^3J_{HF}$ = 10.0 Hz, CH); ca. 2.7 (complex, 1H); 4.15 (q, $^3J_{HH}$ = 7.1 Hz, CH_2). ^{19}F NMR (188 MHz, in $CDCl_3$): δ 65.3 (d, $^3J_{HF}$ = 10.0 Hz). MS (70eV) m/z (rel.int., ion): 252 (10, M^+); 237 (4, M-CH_3); 207 (7, M-EtO); 179 (62, M-CO_2Et); 115 (100, $C_6H_{11}O_2^+$); 87 (65, $C_4H_7O_2^+$); 69 (10, CF_3^+); 55 (36, $C_4H_7^+$); 43 (25, $C_3H_7^+$); 41 (26, $C_3H_5^+$).

(1R,3S)-(+)-1,2,2-Trimethyl-3-(trifluoromethyl)-1-cyclopentanemethanol (8).- A solution of acid chloride (**6**) (9.7 g, 0.04 mol) in dry ether (50 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.3 g, 0.06 mol) in ether (150 mL) precooled to 2-3° under nitrogen (slightly exothermic reaction). The reaction mixture was stirred at ambient temperature for two hours. Diluted hydrochloric

acid (*ca.* 10%, 300 mL) was slowly added and a two-phase mixture was stirred until the water phase became fully transparent (overnight). The layers were separated, the water phase was washed with ether (3 x 50 mL) and the organic solvent was dried over $MgSO_4$. The solvent was removed under atmospheric pressure and the residue was distilled to give a colorless solid (solidifies in a water condenser). Yield: 6.8 g (81%). GLC purity: 99.95%, bp. 76-78°/ 4 Torr, mp. 45-46°. IR (CCl_4) : 3641.4 (sharp), 3506 cm^{-1} (broad); no carbonyl absorption. $[\alpha]_D^{21} = +34.9$ (c = 5, MeOH).

Anal. Calcd for $C_{10}H_{17}F_3O$: C, 57.13; H, 8.15; F, 27.11. Found, C, 57.11; H, 8.27; F, 27.13

^1H NMR (200 MHz, in $CDCl_3$): δ 0.99 (q, $^5J_{HF}$ = 1.8 Hz, CH_3); 1.02 (s, CH_3); 1.12 (s, CH_3); *ca.* 1.5 (broad, OH); 1.35-1.50 (complex, 1H); 1.6-2.05 (complex, 2H); 2.50-2.72 (complex, 1H); 2.54 (q, $^3J_{HF}$ = 10.3 Hz, CH); 3.54 (AB system, J_{AB} = 10.8 Hz, CH_2O). ^{19}F NMR (188 MHz, in $CDCl_3$): δ 65.0 (d, $^3J_{HF}$ = 10.2 Hz). MS (70 eV) m/e (rel.int., ion): 210 (4, M^+); 193 (4, M-OH); 179 (93, M-CH_2OH); 163 (16, $C_8H_{10}F_3^+$); 71 (100, $C_4H_7O^+$); 68 (43, $C_5H_8^+$); 55 (47, $C_4H_7^+$); 43 (54, $C_3H_7^+$); 41 (40, $C_3H_5^+$).

(1R,3S)-(+)-1,2,2-Trimethyl-3-(trifluoromethyl)-1-cyclopentanemethyl Acetate (9).- A solution of acetyl chloride (0.45 g, 5.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise (15 minutes) to a stirred solution of alcohol (**8**) (1.1g, 5.2 mmol) and pyridine (0.45 g, 5.7 mmol) in CH_2Cl_2 (10 mL) precooled to 5°. The temperature slowly increased to 8° and after a few minutes a fine precipitate of Py.HCl began to form. The reaction was allowed to warm to ambient temperature and was stirred for additional two hours. The reaction mixture was washed with 5% hydrochloric acid (2 x 30 mL) followed by 5% $NaHCO_3$ and finally by water and dried over $MgSO_4$. The solvent was removed under atmospheric pressure and the residue was distilled to give a colorless oil. Yield: 0.8 g (61%). GLC purity: 98%, bp. 105-106°/ 6 Torr.

IR (film) : 1744.3 cm^{-1} (vs, C=O). $[\alpha]_D^{21} = +29.7$ (c = 5, MeOH).

Anal. Calcd for $C_{12}H_{19}F_3O_2$: C, 57.13; H, 7.59; F, 22.59. Found: C, 57.09; H, 7.67; F, 22.56

^1H NMR (200 MHz, in $CDCl_3$): δ 0.98 (q, $^5J_{HF}$ = 1.75 Hz, CH_3); 1.00 (s, CH_3); 1.13 (s, CH_3); 1.4-2.05 (complex, 4H); 2.07 (s, CH_3O); 2.58 (m, $^3J_{HF}$ = 10.2 Hz, CH); 3.97 (s, CH_2O).

^{19}F NMR (188 MHz, in $CDCl_3$) δ: 65.05 (d, $^3J_{HF}$ = 10.2 Hz). MS (70eV) m/z (rel.int., ion): 252 (2, M^+); 210 (32, M-CH_2CO); 192 (18, M-CH_3CO_2H); 179 (17, M-$CH_3CO_2CH_2$); 177 (25, $C_9H_{12}F_3^+$); 71 (18, $C_4H_7O^+$); 69 (14, CF_3^+); 68 (68, $C_5H_8^+$); 55 (18, $C_4H_7^+$); 43 (100, CH_3CO^+; $C_3H_7^+$).

REFERENCES

1. Th. Money, in *"Organic Synthesis Theory and Applications"*, Vol. 3, p. 1-83, T. Hudlicky Ed. JAI Press Inc., Greenwich, London, 1996.

2. Y. Hanzawa, M. Suzuki, Y. Kobayashi and T. Taguchi, *J. Org. Chem.*, **56**, 1718 (1991).

3. T. Shinada, N. Sekiya, N. Bojkova and K. Yoshihara, *Synlett*, 1247 (**1995**).

4. S. Watanabe, T. Fujita, M. Sakamoto, Y. Mina and T. Kitazume, *J. Fluorine Chem.*, **73**, 21 (1995).

5. S. Watanabe, T. Fujita, M. Sakamoto, M. Takeda, T. Kitazume and T. Yamazaki, *J. Fluorine Chem.*, **82**, 1 (1997).

6. W. Dmowski and T. Kozlowski, *J. Fluorine Chem.*, **83**, 187 (1997).

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(R)-2-HYDROXY-3-TRIPHENYLMETHYLTHIOPROPANOIC ACID, AN INTERMEDIATE IN THE SYNTHESIS OF HYDROXY ANALOGS OF OXYTOCIN

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(10/13/98)

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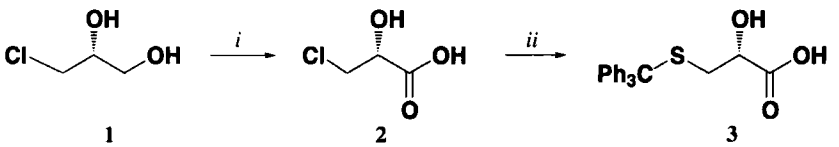
For our ongoing vasopressin and oxytocin (OT) projects, we needed to synthesize the potent oxytocin agonist [L-Hmp[1],Thr[4]]OT as a reference compound. The peptide, proposed by Manning's group in the mid-seventies,[1] is an analog of 4-threonine oxytocin in which a hydroxyl group replaces the N-terminal amino group. In the original synthesis of the peptide, (R)-2-hydroxy-3-benzylthiopropanoic acid was used. This protected hydroxythioacid was obtained in three steps by the procedure of Hope and Walti[2] which comprises a) oxidation of racemic 3-chloro-1,2-propanediol with nitric acid; b) conversion of the obtained D,L-β-chlorolactic acid to D,L-β-benzylthiolactic acid and c) resolution of the racemic mixture by crystallization of diastereoisomeric salts with brucine. An earlier attempt to synthesize this compound by nitrous acid deamination of (R)-S-benzylcysteine[3] resulted in a substance with different physicochemical properties due to thiiran formation.[4] Most recently, the synthesis of (S)-2-hydroxy-3-*tert*-butylthiopropanoic acid by regioselective epoxide ring opening of potassium glycidate was reported.[5]

For continuous-flow mode of peptide synthesis,[6] an acid labile S-protecting group was needed. The S-trityl group,[7] which can be removed with TFA, was a preferred candidate. The synthesis of (R)-2-hydroxy-3-S-triphenylmethylthiopropanoic (**3**) acid does not appear to have been reported and none of the methods used for the synthesis of (R)-2-hydroxy-3-benzylthiopropanoic acid appeared directly applicable to the synthesis of (**3**). A convenient, high-yield synthesis of (**3**) from (R)-3-chloro-1,2-propanediol (**1**) in only two steps is described here (*Scheme*).



1 **2** **3**

i) HNO_3; *ii)* NaH, TrtSH, DME