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Improved synthesis of D,L-fluorocitric acid

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ABSTRACT

We propose a decagram synthesis of commercially unavailable fluorocitric acid. The synthesis begins with benzyl fluoroacetate, which is converted to dibenzyl 2-fluoro-3-oxosuccinate, followed by condensation with malonic acid or its monobenzyl ester and subsequent hydrogenolysis.

1. Introduction

Traditionally, clinicians have treated unresponsive patients by prescribing several different drugs to activate multiple therapeutic mechanisms. An alternative strategy would be implementation of a single multifunctional chemical entity that is able to modulate multiple targets simultaneously. The basic principles and methodologies for the design of multifunctional drugs have been reviewed [1–6].

Evidence has been provided that the activation of astrocytes in the spinal cord is involved in the modulation of neuropathic pain. An inhibitor of glia metabolism – barium fluorocitrate reduces astrocyte activation and significantly attenuated the development of pain hypersensitivity [7–18].

We hypothesized that bifunctional investigational tools could be represented as ionic compounds – pharmaceutical salts, which could be composed by an interaction of any opioid agonist as the organic base with the classical glial inhibitor, fluorocitric acid, as the acid.

A possible advantage of this approach would be that after dissociation, both counterions will be able to act simultaneously and independently at their appropriate targets. The main barrier for checking this hypothesis is the commercial unavailability of fluorocitric acid. Here we describe the design and the methodology of a large scale (multiple grams) method for the preparative synthesis of fluorocitric acid.

2. Results and discussion

We started with the first published method of the synthesis of fluorocitric acid (Scheme 1), in which diethyl oxalate was condensed with ethyl fluoroacetate to give oxalylfluoroacetic ester **1** and, as a minor product, α,α′-difluorocitric ethyl ester **2** [19]. The previously described procedure was modified to give high yields of pure oxalylfluoroacetic ester **1**, which then was used as a carbonyl component in the Reformatsky reaction with ethyl zincbromoacetate. The Reformatsky reaction led to a multicomponent mixture, from which a small amount of pure product – triethyl fluorocitrate **3** was separated and hydrolyzed under acidic conditions to give fluorocitric acid. In contrast to published studies, the product could be isolated only as its barium salt. Analogous results were previously described by hydrolysis under basic conditions using 100% excess of sodium hydroxide, then passing the basic solution through a strong cation-exchange column [20]. In addition to the problem of low yields of triethyl fluorocitrate **3** in the Reformatsky reaction, there are two additional problems when utilizing this method. The first problem concerns transformations **3** → **4** and **3** → **5** (Scheme 1), in which it is very hard to achieve the full hydrolysis of the triprotic acid ester. We have tried to implement a variety of methods and conditions of acidic and basic hydrolysis, changing acids, bases, solvents and temperatures, but could not obtain pure fluorocitric acid **5** in satisfactory yields. The second problem concerns the very high hydrophilicity of obtained product, which makes it practically impossible to perform an efficient extraction into an organic solvent.

Another approach for the synthesis of fluorocitric acid **5** was undertook implementing a method of synthesis [21,22], in which instead of a Reformatsky reaction, the Doebner modification of the Knoevenagel reaction of oxalylfluoroacetic ester **1** with malonic acid is employed (Scheme 2). We have extended this reaction, and for the synthesis of the triethyl ester of fluorocitric acid **3**, instead of malonic acid, its monoethyl ester was used. This approach allowed us to obtain excellent yields of pure **3** and **6**, but hydrolysis of both triethyl ester **3** and diethyl ester **6** faced the same problems and we could isolate the fluorocitric acid **5** only as a barium salt with low yields.

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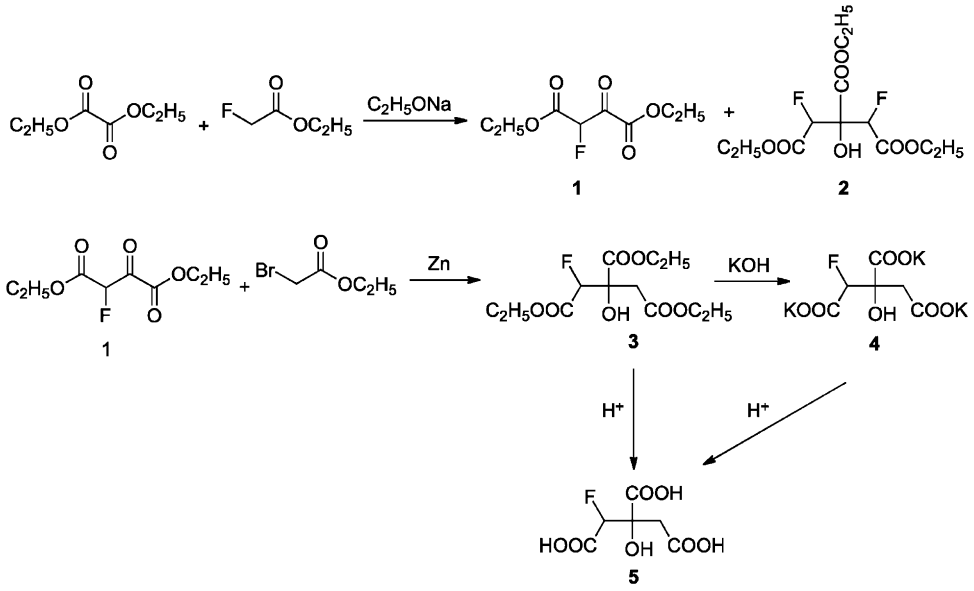
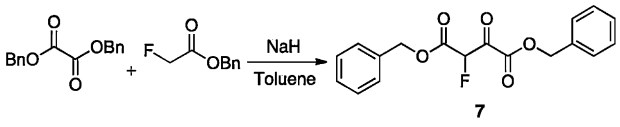
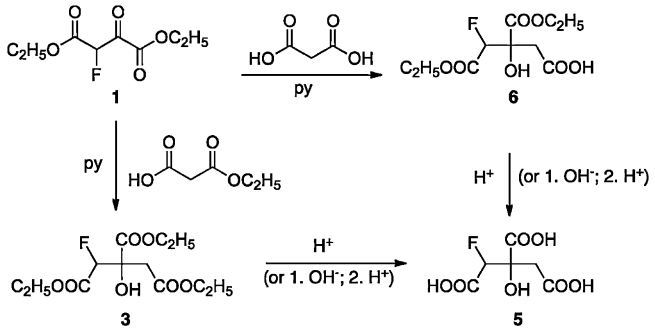


Scheme 1. Implementation of the Reformatsky reaction in the synthesis of fluorocitric acid.

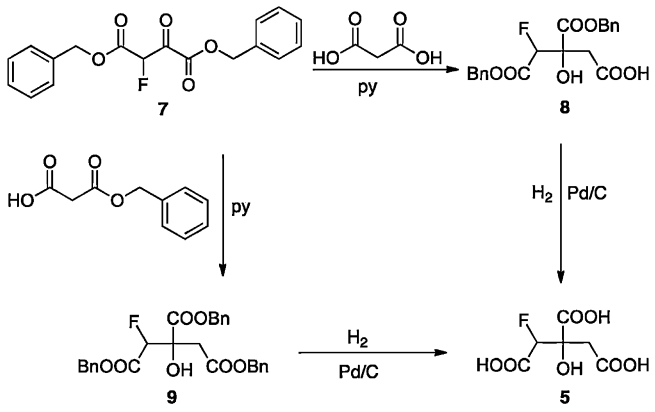
However, we found that replacing the hydrolysis procedure by hydrogenation could be a good solution to the problem (Scheme 3), and for this purpose the synthesis of dibenzyl **8** and tribenzyl **9** esters of fluorocitric acid were developed. The starting material for their synthesis – dibenzyl 2-fluoro-3-oxosuccinate **7** has been prepared from dibenzyloxalate and benzyl fluoroacetate (Scheme 4).



Scheme 4. Synthesis of dibenzyloxalylfluoroacetic ester.



Scheme 2. Implementation of the Knoevenagel–Doebner reaction in the synthesis of fluorocitric acid.



Scheme 3. Synthesis of tribenzyl **9** and dibenzyl **8** esters of fluorocitric acid.

Condensation of dibenzyl 2-fluoro-3-oxosuccinate **7** with malonic acid and the malonic acid monobenzyl ester in pyridine gave good yields of the dibenzyl **8** and tribenzyl **9** esters of fluorocitric acid. Hydrogenolysis of both of compounds gave excellent yields of fluorocitric acid **5**.

Compounds **2**, **3**, **5**, **6**, **7**, **8**, **9** had interesting ^{1}H and ^{13}C NMR spectra due to spin–spin coupling of ^{19}F, a spin- nucleus. The observed ^{1}H and ^{13}C signals gave doublets by ^{19}F, through 1–4 bonds. The following coupling constants were observed: $^{1}J_{CF} \sim 200$ Hz, $^{2}J_{CF} \sim 20$ Hz, $^{3}J_{CF} \sim 5$ Hz, $^{2}J_{HF} \sim 50$ Hz, $^{4}J_{HF} \sim 0$–5 Hz, $^{2}J_{HH} \sim 10$–15 Hz, $^{3}J_{HH} \sim 6$–8 Hz. The magnitude of the coupling constant due to fluorine increases with proximity to the ^{19}F nucleus, which aided in the assignment of carbonyl resonances in the ^{13}C NMR.

Compound **5** was characterized by ^{1}H, ^{13}C, and ^{19}F NMR and by ^{1}H–^{13}C HSQC. In the ^{1}H spectrum, the OH protons were not observed due to exchange with CD_3OD and one of the methylene protons was observed to have a $^{4}J_{HF}$ coupling of 0.9 Hz. In the ^{1}H-decoupled HSQC spectrum, the ^{1}H–$^{13}C(^{19}F)$ showed two cross-peaks in an anti-diagonal correlation. The separation between the peaks in the F2 dimension corresponds to the $^{2}J_{HF}$ coupling (47.4 Hz) and the separation between the peaks in the F1 dimension corresponds to the $^{1}J_{CF}$ coupling (−193.2 Hz). Both coupling constants are consistent with the magnitude and sign of known constants [23]. ^{19}F NMR spectrum showed five doublets of different intensities (25:1:90:15:15) with $^{2}J_{HF} = 47.5$ Hz.

3. Conclusions

Bulk synthesis of commercially unavailable fluorocitric acid has been proposed starting from readily synthesized dibenzyl 2-fluoro-3-oxosuccinate, followed by condensation with malonic acid or its monobenzyl ester and subsequent hydrogenolysis.

4. Experimental

4.1. General remarks

The compounds were characterized by ^{1}H and ^{13}C NMR. All standard ^{1}H and ^{13}C NMR experiments were performed on Bruker DRX-600 equipped with a Narolac 5 mm probe at 298 K. ^{19}F NMR was performed on Varian Unity-300 using 10 μL trifluoroacetic acid as an internal standard referenced at −78.5 ppm. Multiple resonances were observed in some spectra, due to conformers, diastereomers, or different protonation states; the largest signal was reported for chemical shift and multiplicity. Chemical shifts for ^{1}H and ^{13}C NMR are reported with respect to TMS at 0.00 ppm. Coupling constants are reported in hertz. Fluorine is a spin- nucleus and was not decoupled for NMR experiments.

The compounds were analyzed by GC–MS measurement using a Micromass GCT instrument (with a DB5 column) with standard GC and electron impact (EI) ionization (70 eV) conditions. In most cases, the molecular ion was not detected, thus electrospray ionization (ESI) was used to determine accurate masses for the protonated molecules ([M+H]+) on a Bruker 9.4 T Apex Qh Fourier transform ion cyclotron resonance (FT-ICR) instrument. The accuracy of these measurements, i.e., the chemical formulae determinations, were <2.0 ppm.

The purity of compounds was determined by TLC on silica gel plates (Analtech 02521), solvent system MeOH:$CHCl_3$ 1:4. Melting points are uncorrected.

4.2. General procedure for the synthesis of oxalylfluoroacetic diethyl ester (1)

To a cooled (ice bath) stirred solution of sodium ethoxide, prepared from 3.105 g (0.135 mol) of sodium and 75 mL of dry ethanol was added dropwise diethyl oxalate 14.6 g (0.1 mol) in equal volume of dry ethanol and after 15 min, a solution of 10.6 g (0.1 mol) ethyl fluoroacetate[1] in 15 mL of dry ethanol was added. The mixture was stirred additional 2–3 h allowing come to room temperature and left for a night. Next day 75 mL of dry ether was added to the mixture, precipitated salt was filtered off washed with dry ether and placed in 150 mL of ether. The mixture was cooled (ice bath) and the obtained salt was hydrolyzed with 10% solution of HCl (0.135 mol). Ether layer was separated, dried on $MgSO_4$ and after evaporation of the solvent products were distilled giving two fractions. Both of the fractions are identical to previously described samples [1–3].

4.2.1. Analysis of Fraction 1

Oxalylfluoroacetic diethyl ester **1**. 110–112 °C (5 mm Hg) 17.5 g (69.4%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96 (d, 47.3 Hz, 1H), 4.48–4.36 (m, 2H), 4.36–4.25 (m, 2H), 1.44–1.36 (m, 3H), 1.34–1.27 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.77 (d, 20.6 Hz), 163.08 (d, 23.5 Hz), 159.49 (s), 88.16 (d, 197.3 Hz), 63.43 (s), 63.14 (s), 13.85 (s).

4.2.2. Analysis of Fraction 2

α,α′-Difluorocitric ethyl ester **2**. 140–160/5, 4.5 g (12.6%). Crystalline solid, m.p. 68–69 °C.

^{1}H (600 MHz, $CDCl_3$): δ 5.39 (d, 47.5 Hz, 1H), 5.29 (d, 47.5 Hz, 1H), 4.44–4.22 (m, 6H), 1.41–1.28 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.55 (d, 6.7 Hz), 167.55 (t, 5.1 Hz), 166.09 (d, 23.4 Hz), 165.82 (d, 20.0 Hz), 165.66 (d, 20.1 Hz), 88.88 (dd, 196.4, 5.0 Hz), 88.45 (dd, 158.3, 3.2 Hz), 87.90 (d, 6.4 Hz), 87.25 (dd, 197.7, 6.4 Hz), 78.64 (t, 19.9 Hz), 77.79 (dd, 22.0, 19.5 Hz), 63.71 (s), 62.43 (s), 62.33 (s), 13.87 (s), 13.80 (s). EI-MS: *m*/*z* 381; HRMS calcd for $C_{23}H_{29}N_2O_3$: 381.2178; found (ESI, $[M+H]^+$): 381.2183.

4.3. General procedure for Reformatsky reaction: D,L-fluorocitric acid triethyl ester (3)

4.3.1. Method 1

A typical 0.05 mol scale procedure was performed as follows. The activated Zn metal dust 6.4 g (0.1 mol) was placed in a reaction flask, its surface was covered with dry THF, a couple of crystals of iodine, and a couple of drops of ethyl 2-bromoacetate was added and the mixture was heated up to boiling temperature of THF and the vapours of iodine disappeared. At that moment a solution of oxalylfluoroacetic ester **1** 10.3 g (0.05 mol) was added in 30 mL of THF and on stirring and boiling 9.185 g (0.055 mol) of ethyl 2-bromoacetate in equal volume of THF was added dropwise during 30 min. The reaction initiated typically after addition of 20–30% of the total amount of ethyl 2-bromoacetate and started to boil very violently. It is obvious that this process could not be scaled up due to its unpredictable point of initiation, which made efficient cooling impossible. The reaction mixture was heated to reflux additional one hour until obtaining a clear yellowish-orange solution and left for the night at room temperature. Next day it was filtered, THF was evaporated and 75 mL of chloroform was added to remaining residue. The mixture was cooled (ice bath) and on stirring 0.2 mol of H_2SO_4 as a 5% solution was added. The chloroform solution was separated, dried on $MgSO_4$ and the solvent was evaporated. Attempts to distill the remaining polycomponent mixture (TLC) resulted in intensive tarification. Column chromatography also was inefficient. A small quantity 1–1.5 g (7–10%) of product **3** was crystallized during a couple of days, which was separated via filtration affording the desired Reformatsky products in pure form and used in following steps. Ten experiments have been performed with changes of solvents, order of adding of reagents, etc., which confirmed that the proposed procedure was not practical of for preparative scale preparations.

4.3.2. Method 2

Oxalylfluoroacetic ester **1** (7.725 g, 0.0375 mol) was added over a period of 30 min to a solution of malonic acid monoethyl ester (4.95 g, 0.0375 mol) in 10 mL of pyridine. The reaction mixture was stirred at room temperature for 2 h, then heated on a steam bath for ∼30 min until evolution of CO_2 ceased. The pyridine was evaporated, and 75 mL of ether was added to the remaining residue. The traces of pyridine was extracted with 5% HCl 2× 10 mL, excess of malonic acid monoethyl ester washed out with 5% $NaHCO_3$ solution 2× 10 mL. This organic phase was dried with $MgSO_4$. After removal of ether 7.7 g (70%) of pure triethyl monofluorocitrate **3** was obtained.

4.3.3. Spectroscopic data for D,L-fluorocitric acid triethyl ester (3)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.10 (d, 47.3 Hz, 1H), 4.32 (q 7.2 Hz, 2H), 4.26 (q, 7.8 Hz, 2H), 4.15 (q, 7.2 Hz, 2H), 3.21–2.85 (m, 2H), 1.33 (t, 7.1 Hz, 3H), 1.30 (t, 7.6 Hz, 3H), 1.25 (t, 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.73 (d, 6.1 Hz), 169.39 (s), 165.90 (d, 24.7 Hz), 90.90 (d, 197.4 Hz), 76.15 (d, 19.9 Hz), 62.94 (s), 62.03 (s), 61.10 (s), 39.60 (d, 6.2 Hz), 13.97 (s), 13.92 (s), 13.88 (s). [M+H]+, $C_{12}H_{20}FO_7$, calculated: 295.11876; measured: 295.11909 (1.1 ppm error).

4.4. Synthesis of D,L-fluorocitric acid diethyl ester (6)

4.4.1. General procedure for synthesis of D,L-fluorocitric acid diethyl ester (6)

Oxalylfluoroacetic ester **1** (15.4 g, 0.075 mol) was added over a period of 30 min to a solution of malonic acid (8.0 g, 0.075 mol) in

[1] *Caution*: Ethyl fluoroacetate is a highly toxic compound.

20 mL of pyridine. The reaction mixture was stirred at room temperature for 2 h, then heated on a steam bath for ~30 min until evolution of CO_2 ceased. Pyridine was evaporated, and 75 mL of ether was added to remaining residue. The traces of pyridine was extracted with 5% HCl 2× 10 mL. Fluorocitric acid diethyl ester was extracted out with 5% $NaHCO_3$ solution 2× 20 mL. The water solution was cooled (ice bath), ether (75 mL) was added, and then it was acidified with 0.075 mol of 10% HCl. The organic phase was separated, dried with $MgSO_4$. After removal of ether 13.7 g (69%) of pure fluorocitric acid diethyl ester **6** was obtained. All attempts to obtain the free D,L-fluorocitric acid **5** by acidic (HCl, H_2SO_4) or basic (NaOH, KOH) hydrolysis varying the temperature and time regimes of both the triethyl and diethyl esters of fluorocitric acids failed.

4.4.2. Spectroscopic data for D,L-fluorocitric acid diethyl ester (6)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (bs, 2H), 5.09 (d, 47.3 Hz, 1H), 4.33–4.21 (m, 4H), 3.09 (d, 4.8 Hz, 1H), 3.04 (s, 1H), 1.31 (t, 7.2 Hz, 3H), 1.29 (t, 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.31 (s), 170.74 (d, 6.4 Hz), 166.06 (d, 24.4 Hz), 90.96 (d, 198.2 Hz), 76.11 (d, 19.9 Hz), 63.41 (s), 62.40 (s), 39.48 (d, 6.2 Hz), 14.08 (s), 13.99 (s).

4.5. Synthesis of dibenzyl 2-fluoro-3-oxosuccinate (7)

4.5.1. General procedure for synthesis of dibenzyl 2-fluoro-3-oxosuccinate (7)

To a cooled (ice bath) stirred solution of 0.0625 mol of sodium hydride, in 100 mL of dry toluene was added dibenzyl oxalate 13.5 g (0.05 mol) and after stirring for 15 min solution of 8.4 g (0.05 mol) of benzyl fluoroacetate[2] [4] in 15 mL of dry toluene was added dropwise. The mixture was stirred an additional 2–3 h allowed to come to room temperature and then heated under reflux for 15 min and left for a night at room temperature. The solution was cooled the next day (ice bath) and to it was added 5 mL of ethanol to the mixture, and then, 0.0625 mol of 10% HCl solution. The toluene layer was separated, dried on $MgSO_4$ and after evaporation of the toluene and benzyl alcohol the residue was mixed with hexanes and cooled on dry ice. The solid material was separated at room temperature and excess of hexanes was evaporated giving 15.05 g (91.2%) of mixture of D,L-dibenzyl 2-fluoro-3-oxosuccinate **7**. Attempts to distill the product led to decomposition.

4.5.2. Spectroscopic data for dibenzyl 2-fluoro-3-oxosuccinate (7)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46–7.06 (m, 10H), 5.23 (d, 48.1 Hz, 1H), 5.19–4.93 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.49 (s), 167.94 (d, 2.4 Hz), 166.14 (d, 24.0 Hz), 136.95 (s), 136.61 (s), 128.67 (s), 128.61 (s), 128.52 (s), 128.30 (s), 128.27 (s), 88.61 (d, 188.1 Hz), 68.75 (s), 68.60 (s).

4.6. Synthesis of D,L-fluorocitric acid dibenzyl ester (8)

4.6.1. General procedure for synthesis of D,L-fluorocitric acid dibenzyl ester (8)

Dibenzyl 2-fluoro-3-oxosuccinate **7** (3.3 g, 0.01 mol) was added over a period of 30 min to a solution of malonic acid 1.04 g, (0.01 mol) in 5 mL of pyridine. The reaction mixture was stirred at room temperature for 2 h, then heated on a steam bath for ~30 min until evolution of CO_2 ceased. Pyridine was evaporated, and 50 mL of ether was added to remaining residue. The traces of pyridine were extracted with 5% HCl (2× 5 mL), and the solution washed with water. To the organic part was added 0.02 mol of $NaHCO_3$ as 5% solution. The ether layer was separated, and to the cooled (ice bath) alkali water suspension was added a new portion of ether (50 mL) and it was acidified with 10% H_2SO_4. The organic layer was separated and dried with $MgSO_4$. After removal of ether 2.7 g (69%) of pure dibenzyl 2-fluoro-3-oxosuccinate **8** was obtained.

4.6.2. Spectroscopic data for D,L-fluorocitric acid dibenzyl ester (8)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.20 (m, 10H), 5.15 (d, 13.5 Hz, 1H), 5.12 (d, 47.1 Hz, 1H), 5.12 (d, 11.3 Hz, 1H), 5.10 (d, 11.9 Hz, 1H), 5.04 (d, 11.9 Hz, 1H), 3.07 (d, 16.5 Hz, 1H), 3.02 (d, 16.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.04 (s), 170.57 (d, 6.2 Hz), 165.82 (d, 25.0 Hz), 134.48 (s), 134.39 (s), 128.89 (s), 128.87 (s), 128.84 (s), 128.75 (s), 128.73 (s), 128.68 (s), 90.88 (d, 198.3 Hz), 76.25 (d, 20.0 Hz), 68.97 (s), 68.00 (s). EI-MS: m/z 381; HRMS calcd for $C_{23}H_{29}N_2O_3$: 381.2178; found (ESI, $[M+H]^+$): 381.2183.

4.7. Synthesis of D,L-fluorocitric acid tribenzyl ester (9)

4.7.1. General procedure for synthesis of D,L-fluorocitric acid tribenzyl ester (9)

Dibenzyl 2-fluoro-3-oxosuccinate **7** (3.3 g, 0.01 mol) was added over a period of 30 min to a solution of malonic acid monobenzyl ester [5] 1.94 g, (0.01 mol) in 5 mL of pyridine. The reaction mixture was stirred at room temperature for 2 h, then heated on a steam bath for ~30 min until evolution of CO_2 ceased. Pyridine was evaporated, and 25 mL of ether was added to remaining residue. The traces of pyridine was extracted with 5% HCl (2× 5 mL), excess of malonic acid monobenzyl ester washed out with 5% $NaHCO_3$ solution (2× 5 mL), water. This ether solution was dried with $MgSO_4$. After removal of ether 3.1 g (64.6%) of pure tribenzyl monofluorocitrate **9** was obtained.

4.7.2. Spectroscopic data for D,L-fluorocitric acid tribenzyl ester (9)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.24 (m, 15H), 5.13 (d, 12.1 Hz, 1H), 5.11 (d, 47.0 Hz, 1H), 5.09 (d, 12.1 Hz, 1H), 5.04 (s, 2H), 5.03 (d, 14.4 Hz, 1H), 4.98 (d, 11.9 Hz, 1H), 3.07 (d, 16.3 Hz, 1H), 3.01 (d, 16.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.51 (d, 6.4 Hz), 169.14 (s), 165.73 (d, 25.0 Hz), 135.15 (s), 134.42 (s), 134.39 (s), 128.65 (s), 128.62 (s), 128.59 (s), 128.57 (s), 128.56 (s), 128.52 (s), 128.39 (s), 128.32 (s), 90.82 (d, 197.9 Hz), 76.31 (d, 19.9 Hz), 68.59 (s), 67.70 (s), 66.88 (s), 39.68 (d, 5.7 Hz). [M+H]+, calculated: 480.1662; measured: 480.1673 (1.3 ppm error).

4.8. Synthesis of D,L-fluorocitric acid (5)

4.8.1. General procedure for synthesis of D,L-fluorocitric acid (5) from 9

3.0 g of tribenzyl monofluorocitrate **9** in 60 mL of ethanol was hydrogenated at the presence of 0.3 g of 10% palladium on charcoal catalyst at 50 psi pressure and at room temperature for 24 h. The catalyst was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue consisted of 1.3 g (100% yield) of D,L-fluorocitric acid **5** as a colorless oil which partly crystallizes on standing during a long time.

4.8.2. General procedure for synthesis of D,L-fluorocitric acid (5) from 8

2.6 g of dibenzyl monofluorocitrate **8** in 52 mL of ethanol was hydrogenated at the presence of 0.26 g of 10% palladium on charcoal catalyst at 50 psi pressure and at room temperature for 24 h. The catalyst was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue consisted of 1.3 g (100% yield) of D,L-fluorocitric acid **5** as a colorless oil which partly crystallizes on standing during a long time.

4.8.3. Spectroscopic data for D,L-fluorocitric acid (5)

^{1}H NMR (600 MHz, CD_3OD) δ 5.20 (d, 47.4 Hz, 1H), 3.05 (d, 16.1 Hz, 1H), 2.91 (dd, 16.0, 0.9 Hz, 1H). ^{13}C NMR (151 MHz,

[2] *Caution*: Benzyl fluoroacetate is a highly toxic compound.

CD_3OD) δ 173.73 (d, 6.5 Hz), 172.87 (s), 169.68 (d, 25.8 Hz), 92.71 (dd, 193.2, 5.8 Hz), 77.40 (d, 20.2 Hz), 40.91 (d, 6.2 Hz). ^{19}F NMR (282 MHz, CD_3OD) δ −78.5 (s, TFA), −202.73 (d, 47.5 Hz).

Acknowledgments

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