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A New and Efficient Synthesis of Trifluoromethyl Ketones from Carboxylic Acids. Part I.

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Abstract : Trifluoromethyl ketones can be prepared in good yield from primary carboxylic acid chlorides by reaction with pyridine and trifluoroacetic anhydride followed by aqueous work up.

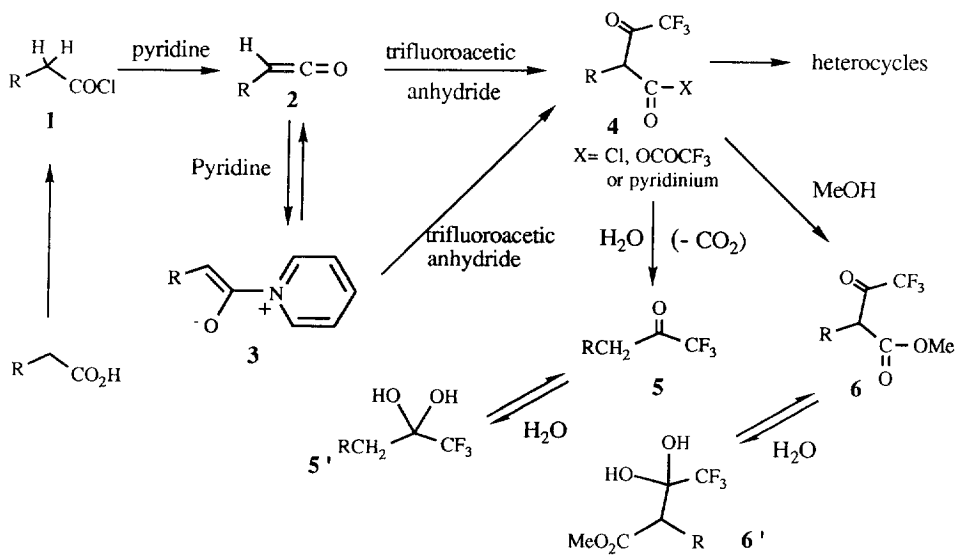
The introduction of fluorine into organic molecules often results in a dramatic modification of their physical and chemical properties as well as of their biological activity profile.[1] It is not surprising therefore that the search for practical and high yielding methods for the obtention of fluoro compounds has been an area of intense activity in the past few decades.[1,2] Trifluoromethyl ketones in particular have emerged as valuable intermediates and targets.[2] Many such compounds have been found to possess a marked inhibitory effect on hydrolytic enzymes such as acetyl cholinesterase, juvenile hormone esterase, proteases, or phospholipases.[3] We recently described in preliminary form a simple, mild, yet efficient process for preparing trifluoromethyl ketones from carboxylic acids.[4] We now wish to give a full account of our work. The application of this approach to the synthesis of a number of trifluoromethyl containing heterocycles is described in the following paper in this issue.

Trifluoromethyl ketones are generally obtained by elaborating simpler fluorine containing molecules. Thus, addition of a Grignard reagent to trifluoroacetic acid or to one of its derivatives,[5] and the decarboxylative hydrolysis of a Claisen type condensation adduct of an ester with ethyl trifluoroacetate[6] are among the oldest and perhaps most popular procedures. Many other methods,[1,2] such as the use of trifluoromethyl organometallic derivatives,[7a] the Wittig reaction with trifluoroacetamide, [7b] or trifluoroacylation of a lithiated sulphone derivative[7c] with ethyl trifluoroacetate followed by desulphonylation, have also been proposed.

All these methods show important limitations as far as compatibility with the functionality of the starting material is concerned. In particular, compounds with more than one carbonyl function or those containing different acidic hydrogens are ill-suited substrates. Mention must be made, however, of the procedure described by Collman and *al* [8] for the preparation of perfluoroalkyl ketones via coupling of an alkyl halide with a perfluoro acyl chloride mediated by disodium tetracarbonyl ferrate, in which

unprotected ketones or ester functions can be present. More relevant to our approach are several modifications of the Dakin-West reaction[9] which lead to α-amino trifluoromethyl ketone derivatives.

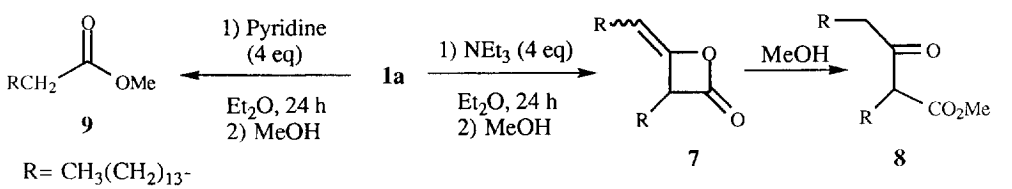
The process we have developed complements existing procedures and appears to be tolerant of various functional groups. It is based on the fact that ketenes can act as weak nucleophiles in the presence of very reactive electrophilic reagents — trifluoroacetic anhydride in our case. Thus, as outlined in Scheme 1, dehydrohalogenation of an acid chloride by pyridine produces a ketene, **2** , or its synthetic equivalent **3**, which can be captured by trifluoroacetic anhydride to yield a highly reactive species **4**. Depending on the work up, the latter can then be converted into a trifluoromethyl ketone, a trifluoromethyl keto ester or even to a number of trifluoromethylated heterocycles, the latter aspect being the subject of part II of this work.



Scheme 1

The use of ketenes as nucleophiles is well precedented,[10] although this aspect of ketene chemistry has been rather neglected in spite of its tremendous synthetic potential. We sought to exploit this property by generating the ketene by deprotonation of an acyl chloride using a weak organic base such as pyridine and trapping it with trifluoroacetic anhydride; the latter, lacking a hydrogen in α position, can only react with pyridine to give N-trifluoroacetylpyridium trifluoroacetate, itself a strong trifluoroacetylating agent. Whatever the acylating species, ketene **2** would evolve finally into the β-dicarbonyl intermediate **4**. It must be mentioned that a precedent for such a process can be found in the reaction of ketene itself with trifluoroacetyl chloride, described in a patent many years ago.[11a] In addition, a few examples of the reaction of acid chlorides with ketene itself[11b] or with diphenyl ketene[11c] are known and Viehe and his colleagues have reported the reaction of acid chlorides with phosgene iminium salts in the presence of triethylamine.[11d]

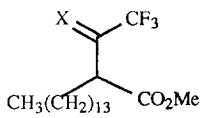
The choice of pyridine as base was not totally innocent since we expected that the ketene-pyridine adduct **3** would in fact be a better nucleophile than the ketene. At the beginning of the century, Staudinger[12a] found that pyridine reacts with diphenyketene to yield an addition product which, on heating, gives back the starting materials. Dimethylketene reacts similarly with quinoline, whereas ketene itself affords irreversibly a tricyclic adduct.[12b] Later work, especially by the group of Wynberg[13] on the reaction of ketene itself with chloral, has shown the importance of pyridine type bases in enhancing the nucleophilicity of the ketene through such adducts. Another condition, crucial for the success of our approach, is that the substituted ketene, generated *in situ* from the acid chloride by the base, must react faster with the trifluoroacylating agent than with itself. It is a well known fact that ketenes (especially aldoketenes) generally dimerise more or less rapidly to produce primarily a cyclobutanedione which can rearrange into the more stable β-lactone.[14] It is interesting to note in this respect that such dimers may be obtained from an acid chloride by treatment with a weak base such as triethylamine but not normally with pyridine type bases which appear to inhibit the dimerisation[14c] presumably because of the formation of the above mentioned adduct **3**. We have confirmed these earlier observations in the case of palmitoyl chloride (Scheme 2) which on treatment with triethylamine produced indeed the β-lactone **7** (this on prolonged contact with methanol gives ketoester **8**). In contrast, the same treatment with pyridine only afforded methyl palmitate **9** on quenching with methanol. Under these conditions, either the concentration of the ketene becomes too low or it reacts completely with pyridine to yield the betain **3a** adduct (see Scheme 1) which apparently does not dimerise, or only very slowly.



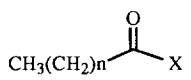
Scheme 2

As anticipated from the mechanistic manifold of Scheme 2, addition of pyridine to a mixture of palmitoyl chloride **1a** and trifluoroacetic anhydride at room temperature in dichloromethane followed by quenching the intermediate adduct **A** (which can be the acid chloride, a mixed anhydride or even an N-acylpyridinium salt as indicated in scheme 2) with methanol gave the expected ketoester **6a** in 78%. This compound spontaneously formed a hydrate on contact with moisture either on chromatography or simply on standing. When an aqueous quench was used, the corresponding keto acid underwent spontaneous decarboxylation to the trifluoromethyl ketone **5a** in 66% yield. The crude yield became essentially quantitative (86% isolated) when ether or toluene, where pyridinium hydrochloride is less soluble, was used as solvent. Formation of the hydrate on silica gel, well known for trifluomethyl ketones,[3a] is responsible for the lowering of the yield.

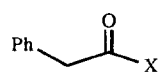
We thus have in hand a convenient and mild process for converting a carboxylic acid, via its chloride, into a trifluoromethyl ketone. The scope of this approach is illustrated by examples **5b-h**; the yield of isolated product is shown next to the structure number. In most cases, the crude yield was essentially quantitative, with losses during purification being again due to problems of hydration. Normally the reaction is performed at room temperature (or 0°C in the case of **5d**) using an excess of both pyridine (7-8 eq.) and trifluoroacetic anhydride (5-6 eq.). This excess may be decreased in large scale but for small scale preparations, we found the minimum to be 2 eq. of trifluoroacetic anhydride and 4 eq. of pyridine. Exception must be made of phenylacetyl chloride **1c** which has especially acidic α-hydrogens. When the reaction was carried at room temperature or at 0°C, only tarry materials were formed. Lowering the reaction temperature to -60°C allowed the obtention of 40% isolated yield of the desired trifluoromethyl ketone **5c** (the yield is higher, ca 65%, if it is based on percent conversion).



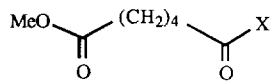
6a: X= O (78%)
6'a: X=$(OH)_2$



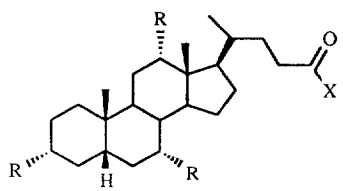
1a: X= Cl ; n=14
5a: X=CF_3; n=14 (86%)
1b: X= Cl ; n=16
5b: X=CF_3; n=16 (73%)



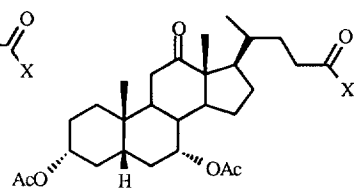
1c: X= Cl
5c: X=CF_3 (40%)



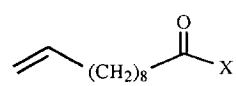
1d: X= Cl
5d: X=CF_3 (54%)



1e: X= Cl ; R=H
5e: X=CF_3; R=H (60%)
1f: X= Cl ; R=OAc
5f: X=CF_3; R=OAc (67%)



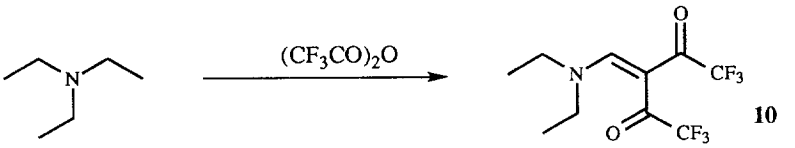
1g: X= Cl
5g: X=CF_3 (67%)



1h: X= Cl
5h: X=CF_3 (75%)

The reaction takes place under essentially neutral conditions, so that groups other than the acid chloride are not normally affected. Examples **5d**, **5f**, and **5g**, demonstrate the compatibility of this method with the presence of ketones and esters and where the classical Claisen condensation is almost certainly bound to fail. Moreover, even though we have employed the acid chloride throughout, this is not absolutely necessary. The acid chloride can in fact be replaced with the sodium salt of the acid since the mixed anhydride formed with trifluoroacetic anhydride can act as the precursor to the ketene. This variant, which should be useful for fragile molecules that do not withstand the conditions necessary for acid chloride formation, is illustrated for palmitic acid. Thus from sodium palmitate, we succeeded in obtaininng an unoptimized 60% yield of pentadecyl trifluoromethyl ketone **5a**.

We have found that pyridine may be replaced with collidine without a significant modification in the yield but triethylamine was not suitable. In fact, we observed that triethylamine reacted with trifluoroacetic anhydride through what appears to involve a hydride transfer to give compound **10**, a reaction that was first discovered by Schreiber[15] a few years ago.



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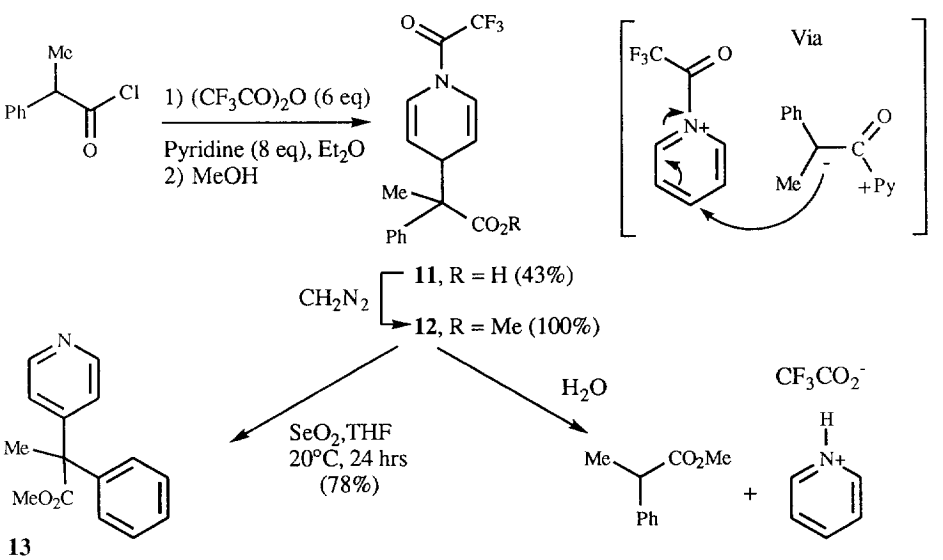
So far, and for reasons which are still not clear, the reaction has failed with α,β unsaturated and secondary acid chlorides. With the latter compounds, the reaction may be reversible or prevented for steric reasons. Interestingly, under the usual conditions, 2-phenyl propionyl chloride furnished an adduct with pyridine in 43% yield for which structure **11** was assigned on the basis of its spectroscopic properties, and further confirmed by esterification with diazomethane to give **12** followed, either by hydrolysis to yield methyl 2-phenylpropionate and pyridinium trifluoroacetate, or, more usefully, by aromatisation into **13** with selenium dioxide. The formation of compound **11** is almost certainly another illustration of the reaction of a ketene (or perhaps better its pyridine adduct) as a nucleophile, this time with pyridinium trifluoroacetate (Scheme 3). We have not yet examined the generality of this reaction as a route to derivatives of type **11** or **13** which are not easily accessible otherwise.



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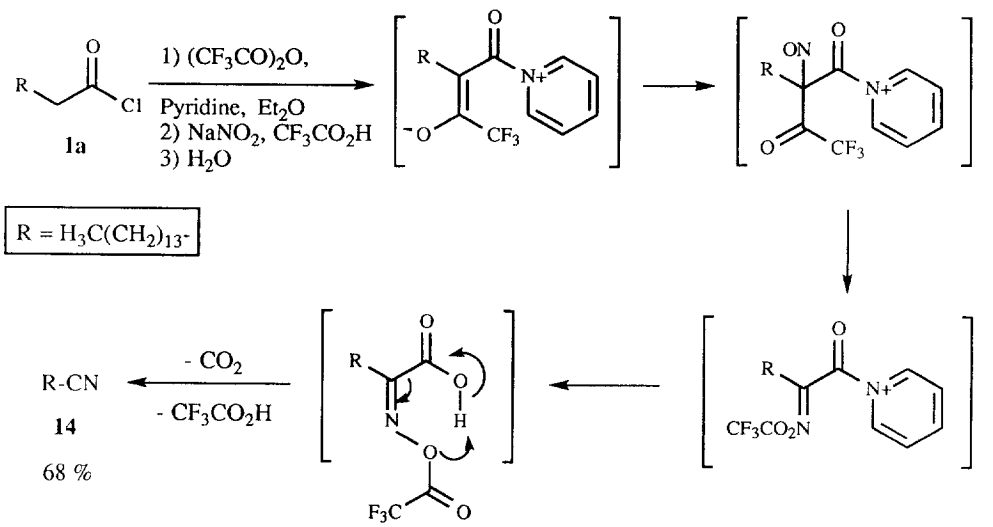
Scheme 3

This approach to the synthesis of trifluoromethylketones from primary carboxylic acids is simple and efficient. It has for example been recently applied by researchers at Merck-Frosst[16] for exchanging the carboxylic function in arachidonic acid with a ^{13}C-labelled trifluoromethyl group on a very small scale. Longer perfluorinated chains could in principle be introduced by replacing trifluoroacetic anhydride with the appropriate perfluorinated anhydride. We have illustrated in one example the capture of the first intermediate (i.e. **4** in scheme 1) with methanol to give a highly useful trifluoromethyl ketoester (e.g. **6a**). Methanol, of course may be replaced by a host of other nucleophiles to give a variety of products. The following paper in this issue will present the preparation of a number of heterocyclic systems. Another, interesting variation, is to react the same intermediate **4** with another strong electrophile such as for example a nitrosonium ion. This species can be generated *in situ* by adding sodium nitrite followed by trifluoroacetic acid. Under these conditions, starting from palmitoyl chloride **1a**, nitrosation and fragmentation of the nitroso intermediate took place to give pentadecanenitrile **14** in 68% yield (Scheme 4). This one pot shortening by one carbon of a carboxylic acid is analogous to the reaction of ketenes with nitrosyl chloride / pyridine we reported[17] a few years ago in connection with a project concerning the degradation of the bile acid side chain. A plausible mechanism is outlined in Scheme 4.



Scheme 4

EXPERIMENTAL SECTION

All reactions were performed under an inert atmosphere (nitrogen or argon). Melting points were determined with a Köfler or a Reichert hot stage apparatus. ^1H and ^{13}C n.m.r. spectra are for deuteriochloroform solutions with tetramethylsilane as internal standard (δ ppm). Optical rotations are for chloroform solutions. I.R. spectra are of Nujol mulls unless otherwise stated. Mass spectra (electron

impact) were recorded on MS 50 or VG ZAB spectrometers. MATREX 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

Methyl 2-(trifluoroacetyl)hexadecanoate (6a) and methyl 2-(2,2,2-trifluoro-1,1-dihydroxyethyl) hexadecanoate (6'a). To a solution of trifluoroacetic anhydride (1.6 ml; 11.3 mmol) in anhydrous dichloromethane (25 ml) were added successively hexadecanoyl chloride (1.15 ml; 3.8 mmol) and pyridine (1.2 ml; 14.8 mmol). The reaction mixture was stirred for 2 hrs at 20°C. Methanol (10 ml) was then added and stirring was continued for 30 min. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane The usual work-up afforded a crude residue (1.2 g) which was purified by silica gel chromatography (eluent dichloromethane/petroleum ether; 50/50) to yield a white crystalline powder (1,08 g; 78%) which was constituted of a mixture of trifluoromethyl ketone **6a** and hydrated form **6'b**, as shown by n.m.r.

Methyl 2-(trifluoroacetyl)hexadecanoate **6a**: m.p.: 50-5°C (crude); IR (cm^{-1}): 3450; 2920; 1770; 1750; 1450.(film); n.m.r. ^1H : 4.8 (s); 4.2 (s); 3.86 (s); 3.83 (s); 3.79 (s); 3.75 (s) (3H); 1.85-2.05 (m, 2H); 1.25 (s, 24H); 0.88 (t, J = 6,0 Hz, 3H); n.m.r. ^{13}C: 187.0 (q, J = 142 Hz); 175.8; 167.9; 125.7; 120.0; 118.5; 112.5; 94.02 (q, J = 128 Hz); 53.0; 52.5; 47.9; 32.1; 29.8; 29.5; 29.4; 29.3; 29.2; 28.0; 27.2; 26.8; 25.1; 22.8; 14.2.

When exposed for several months to atmospheric moisture, the above mixture gave hydrate **6'b** as a single product. Dissolution of the latter in chloroform gave back the same mixture of products after few hours.

Methyl 2-(2,2,2-trifluoro-1,1-dihydroxyethyl)hexadecanoate **6'b**: m.p.: 52-5°C; IR (cm^{-1}), film: 3450; 2920; 1770; 1750; 1450; n.m.r. ^1H : 5.02 (s, 1H); 4.57 (s, 1H); 3.74 (s, 3H); 2.94 (dd, J = 4.5 Hz, J = 10.9 Hz, 1H); 1.81-1.64 (m, 2H); 1.22 (s, 24H); 0.84 (t, J = 6,6 Hz); n.m.r. ^{13}C: 175.9; 122.8 (q, J = 287 Hz); 94.0 (q, J = 32.5 Hz);52.5; 47.9; 32.1; 29.8; 29.5; 29.4; 27.2; 26.7; 22.8; 14.2; M.S.: 366 (M^+ - H_2O), 334 (M^+ - CH_4O), 328, 297 (M^+ - CF_3), 239, 183, 171; H.R.M.S.: peak: $C_{19}H_{33}F_3O_3^+$, calc.: 366.23817; found: 366.2370.

1,1,1-Trifluoro-2-heptadecanone (5a). Three procedures were used to prepare this compound:

Method A To a solution of trifluoroacetic anhydride (3.2 ml; 22.6 mmol) in anhydrous dichloromethane (30 ml), were added successively hexadecanoyl chloride (1.15 ml; 3.8 mmol) and pyridine (2.4 ml; 29.6 mmol). The reaction mixture was stirred at 20°C for 1 hour (TLC monitoring as above) then water (10 ml) was added cautiously and stirring was continued until the evolution of carbon dioxide ceased. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane . The usual work-up afforded a crude residue (1.26 g) which was purified by silica gel chromatography (eluent dichloromethane) to yield **5a** (770 mg; 66%) as a white solid; m.p.: 25-26°C (after distillation under vacuum); IR (cm^{-1}), film: 2910, 2880, 1760, 1460, 1210, 1150; n.m.r. ^1H : 2.70 (t, J=7.3 Hz, 2H); 1.67 (t, J=7.0 Hz, 2H); 1.27 (s, 24H); 0.88 (t, J=6.7 Hz, 3H); n.m.r. ^{13}C: 36.5; 32.1; 29.8-29.3 (several peaks); 28.7; 22.8; 22.7; 14.5; M.S.: 308 (M^+), 239 (M^+ - CF_3). Calc. for $C_{17}H_{31}F_3O$: C, 66.20; H, 10.13%. Found: C: 66.29 ; H, 10.24 %).

Method B To a solution of trifluoroacetic anhydride (3.04 ml; 21.5 mmol) in anhydrous dichloromethane (30 ml), were added successively sodium hexadecanoate (1g; 3.5 mmol) and pyridine (2.3 ml; 28.4 mmol). The reaction mixture was stirred at 20°C for 2 hrs. Water (10 ml) was added cautiously and stirring was continued until the evolution of carbon dioxide ceased. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane . The same work-up procedure as above afforded a crude residue which was purified by silica gel chromatography (eluent dichloromethane) to yield **5a** (650 mg, 60%).

Method C To a solution of trifluoroacetic anhydride (2.75 ml; 19.5 mmol) in anhydrous ether (30 ml), were added successively hexadecanoyl chloride (1 ml; 3.3 mmol) and pyridine (2.1 ml; 26 mmol). The reaction mixture was stirred at 20°C for 30 min. (TLC monitoring as above) then water (10 ml) was added cautiously and stirring was continued until the evolution of carbon dioxide ceased. The reaction mixture was poured into water (150 ml) and extracted with ether. The usual work-up afforded a

crude residue (1.18 g), the n.m.r. spectrum of which is identical to that of pure **5a**. However, silica gel chromatography (eluent dichloromethane) gave only 86% of **5a** (870 mg) .

1,1,1-Trifluoro-2-nonadecanone (5b). To a solution of stearic acid **2a** (1 g.; 3,3 mmol) in anhydrous dichloromethane (10 ml) was added oxalyl chloride (1.15 ml; 3.8 mmol). The reaction mixture was stirred at 20°C for 2 hrs. Solvent and excess oxalyl chloride were removed by distillation under reduced pressure. The residue was taken up in dry dichloromethane (30 ml). To this solution trifluoroacetic anhydride (3 ml, 21.2 mmol.) was added. Pyridine was then added at 0°C. The cooling bath was removed and the reaction monitored by TLC as above. After 1 hour, water (10 ml) was added cautiously and stirring was continued until carbon dioxide evolution had ceased. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane. The usual work-up afforded a crude residue (1.26 g) which was purified by silica gel chromatography (eluent dichloromethane) to yield **5b** (820 mg; 73%) as a white solid; m.p.: 26-8°C (after sublimation under vacuum); IR (cm^{-1}), film: 2900; 2820; 1760; 1450; 1200; 1140; n.m.r. ^1H : 2.69 (t, J = 7.2 Hz, 2H); 1.67 (t, J = 6.9 Hz, 2H); 1.27 (s, 28H); 0.88 (t, J=6.7 Hz, 3H); n.m.r. ^{13}C: 191.4 (q, J = 35 Hz); 115.8 (q, J = 292 Hz); 36.4; 32.2; 29.9; 29.6; 29.4; 29.0; 22.9; 22.6; 14.1; M.S.: 336 (M^+), 312, 267 (M^+ - CF_3). (Calc. for $C_{19}H_{35}F_3O$: C, 67.82; H, 10.49 %. Found: C, 67.68; H: 10.58 %).

1,1,1-Trifluoro-3-phenyl-2-propanone (5c). To a solution of trifluoroacetic anhydride (3.2 ml; 22.6 mmol) in anhydrous dichloromethane (20 ml), cooled at -66°C (dry-ice/ chloroform bath) were added successively phenylethanoyl chloride (1 ml, 8.0 mmol) and pyridine (1.22 ml; 15.1 mmol). The reaction mixture was stirred vigourously at -66°C for 9 hrs.Water (1 ml) was added and cooling bath removed. When the temperature of the reaction mixture reached 20°C, it was poured into water (50 ml) and extracted with dichloromethane . The crude residue was a mixture of phenylacetic acid and ketone **5c** (molar ratio 35:65). Silica gel chromatography (eluent ether/triethylamine) afforded the known[6f,18] **5c** (600 mg; 40%, colourless oil; IR (cm^{-1}), film: 1760; 1490; 1450; 1150; n.m.r. ^1H : 7.4-7.25 (m, 3H); 7.2-7.1 (m, 2H)); 3.96 (s, 2H); n.m.r. ^{13}C: 188.9 (q, J = 35 Hz);130.5; 129.7; 129.0; 128.6; 128.3; 128.0;115.9 (q, J = 293 Hz); 43.0.

Methyl 7,7,7-trifluoro-6-one-heptanoate (5d). To a solution of adipic acid monomethylester **4a** (1 ml; 6.5 mmol) in anhydrous dichloromethane (10 ml) was added oxalyl chloride (0.9 ml; 10.3 mmol) and the resulting mixture stirred for two hours at 20°C. The solvent and excess oxalyl chloride were evaporated under reduced pressure and the residue taken up in dichloromethane (40 ml) and treated with trifluoroacetic anhydride (5.6 ml; 39.6 mmol). The mixture was cooled to 0°C, pyridine (4.4 ml; 54.4 mmol) was added, and stirring continued at 0°C for 20 min. Water (10 ml) was then added cautiously and after stirring at 20°C for one hour, the reaction mixture was poured into water (50 ml) and extracted with dichloromethane. The usual work-up afforded a crude residue which was purified by silica gel chromatography [eluent dichloromethane/petroleum ether (50/50)] to give **5d** (740 mg; 54%) as a colourless oil; IR (cm^{-1}): 3400; 2930; 1760; 1720; 1430; n.m.r. ^1H : 3.68 (s, 3H); 2.78 (t, J = 6.3 Hz); 2.37 (t, J = 6.5 Hz); 1.85-1.6 (m, 4H); n.m.r. ^{13}C: 191.0 (q, J= 35 Hz); 173.4; 115.5 (q, J= 292 Hz); 51.3; 35.8; 33.3; 23.8; 21.7.; M.S.: 212 (M^+); 181 (M^+ - MeO); 153 (M^+ - CO_2Me); 143 (M^+ - CF_3); 115 (M^+ - $COCF_3$); H.R.M.S.: peak:$C_7H_{11}O_3^+$; calc.: 143.07082; found: 143.0708.

25,25,25-Trifluoro-5β-homocholan-24-one (5e). To a solution of cholanic acid (300 mg) in anhydrous dichloromethane (20 ml) oxalyl chloride (0.3 ml; 3.5 mmol) was added. The reaction mixture was stirred for two days at 20°C. The solvent and excess oxalyl chloride were evaporated under reduced pressure. Cholanoyl chloride **1e** crystallized in the flask and was used in the next step without further purification.

To a solution of trifluoroacetic anhydride (0.55 ml; 3.9 mmol) in anhydrous dichloromethane (30 ml) were added successively cholanoyl chloride prepared above (210 mg) and pyridine (0.4 ml; 4.9 mmol). The reaction mixture was stirred at 20°C for 25 hrs (TLC monitoring as above) then water (1 ml) was added cautiously and stirring was continued until carbon dioxide evolution had ceased. The reaction

mixture was poured into water (50 ml) and extracted with dichloromethane . The usual work-up afforded a crude residue which was purified by silica gel chromatography (eluent dichloromethane) to give **5e** (137 mg; 60%) as a white solid; m.p.: 118-120°C (ether); $[\alpha]_D^{23}$: +20° (chloroform); IR (cm^{-1}): 2900; 1760; 1450; 1210; 1150 (Nujol); n.m.r. ^1H : 2.85-2.50 (m, 2H); 2.0-1.5(m, 10H); 1.0-1.5(m, 22H); 0.94 (s), 0,92 (s) (6H); 0.65 (s, 3H); n.m.r. ^{13}C: 192.1 (q, J= 35 Hz); 115.7 (q, J= 292 Hz); 56.7; 56.0; 43.8; 42.9; 40.6; 40.4; 37.7; 36.0; 35.5; 35.2; 33.5; 28.5; 28.3; 27.6; 27.4; 27.2; 26.7; 26.1; 24.4; 24.2; 21.5; 21.0; 18.4; 12.2; 0.1; M.S.: 412 (M^+); 397 (M^+ - CH_3); 355, 343(M^+ - CF_3); 302; 217. (Calc. for $C_{25}H_{39}F_3O$: C, 72.78; H, 9.53 %. Found: C, 72.80; H, 9.41 %).

3α,7α,12α-Triacetoxy-25,25,25-trifluoro-5β-cholan-24-one (5f). To a suspension of cholic acid (50 g) in acetic acid (300 ml) were added successively acetic anhydride (170 ml) and perchloric acid (70%, four drops). The reaction mixture was stirred for 24 hrs at 20°C while starting material progressively went into solution. Water (40 ml) was added and stirring continued for 12 hrs. The reaction mixture was then poured into water (500 ml) and extracted with dichloromethane. After the usual work-up the crude residue was completely dried by azeotropic distillation with several portions of toluene affording 3α,7α,12α-triacetoxycholanic acid as a glassy solid which was used without purification in the following step.

To a solution of the triacetate (1.13 g; 2.2 mmol) in anhydrous dichloromethane (15 ml) was added oxalyl chloride (0.35 ml; 4.0 mmol) and the mixture stirred for 18 hrs at 20°C. The solvent and excess oxalyl chloride were evaporated under reduced pressure. The residue was taken up in dichloromethane (30 ml) and trifluoroacetic anhydride (1.8 ml; 12.7 mmol) was added to the resulting solution which was cooled to 0°C before addition of pyridine (1.4 ml; 17.3 mmol). After 90 min, water (10 ml) was added and the resulting mixture poured into water (50 ml) and extracted with dichloromethane. The usual work-up afforded a crude residue which was purified by silica gel chromatography [eluent dichloromethane/petroleum ether (50/50)] gave a mixture of **5f** and the corresponding hydrate **5'f** (860 mg; 67%) as a white solid. To obtain the pure ketone **5f**, the above mixture was refluxed in toluene (10 ml) for 2 hrs and the solvent evaporated under reduced pressure, leaving ketone **5f** as white crystals; m.p.: 69-73°C (ether); $[\alpha]_D^{23}$: +64.6° (chloroform); IR (cm^{-1}): 2910; 1750; 1720; 1370; 1250; 1020; 900; 730.(Nujol); n.m.r. ^1H : 5.09 (s, 1H); 4.90 (s, 1H); 4.65-4.5 (m, 1H); 2.15 (s, 3H); 2.09 (s, 3H); 2.05 (s, 3H);0.93 (s, 3H); 0.55 (s, 3H).; n.m.r. ^{13}C192.1 (q, J= 35 Hz); 170.4; 170.3; 170.2; 115.7 (q, J= 292 Hz); 75.2; 73.9; 70.6; 47.3; 45.0; 43.2; 40.8; 37.6; 34.5; 34.3; 34.2; 33.2; 31.1; 28.7; 28.0; 27.0; 26.7; 25.4; 22.6; 22.4; 21.4; 21.2; 21.2; 17.4; 12.0; M.S. 466 (M^+ - 2 $C_2H_4O_2$); 406 (M^+ - 3 $C_2H_4C0_2$); 391 (M^+ - 3 $C_2H_4C0_2$ - CH_3); 313; 253. (Calc. for $C_{31}H_{45}F_3O_7$: C, 63.46 ; H, 7.73 %; Found C, 63.56 ; H, 7.69 %).

3α,7α-Diacetoxy-25,25,25-trifluoro-5β-homocholane-12,24-dione (5g). To a solution of 3α,7α-diacetoxy-12-one-5β-cholan-24-oic acid[19] (0.510 g; 0.94 mmol) in anhydrous dichloromethane (10 ml) was added oxalyl chloride (0.3 ml; 3.4 mmol) and the resulting mixture stirred for 18 hrs at 20°C. The solvent and excess oxalyl chloride were evaporated under reduced pressure, the residue taken up in dichloromethane (15 ml) and treated with trifluoroacetic anhydride (0.9 ml; 6.4 mmol). The resulting solution was cooled to 0°C and pyridine (0.67 ml; 8.3 mmol) was added. The reaction was allowed to warm to 20°C and kept at this temperature for 2 hrs,. After quenching with a small amount of water (10 ml), the reaction mixture was poured into water (50 ml) and extracted with dichloromethane . The usual work-up afforded a crude residue which was purified by silica gel chromatography (eluent ether) yielding a white solid which consisted of a mixture of **5c** and the corresponding hydrate **5'c**, as indicated by IR. This white solid was refluxed in toluene (10 ml) for 2 hrs. Evaporation of the solvent under reduced pressure afforded pure ketone **5c** (340 mg; 67%) as white crystals; m.p.: 148-151°C (ether/petroleum ether); $[\alpha]_D^{23}$: +69.7° (chloroform); IR (cm^{-1}): 1750; 1720; 1680; 1450; 1370; 1360. (Nujol); n.m.r. ^1H : 4.99 (s, 1H); 4.65-4.47 (m, 1H); 2.03 (s, 3H); 2.01 (s, 3H); 1.05 (s, 6H); 0.87 (d, J= 6.1 Hz, 3H); n.m.r. ^{13}C: 213.6; 191.5 (q, J= 35 Hz); 170.3; 169.9; 115.4 (q, J= 292 Hz);73.3; 70.2; 56.8; 53.4; 52.9; 45.9; 40.2; 37.7: 37.6; 37.3; 35.3; 34.9; 34.6; 34.3; 33.2; 31.1; 27.6; 27.1; 26.3; 23.5; 21.8;

21.1; 18.3; 11.2; M.S.: 542 (M^+); 482 (M^+ - $C_2H_4O_2$); 422 (M^+ - 2 $C_2H_4CO_2$); 315; 269; 229. (Calc. for $C_{29}H_{41}F_3O_6$: C, 64.19 ; H, 7.62 %. Found: C, 64.06 ; H, 7.55 %).

1,1,1-Trifluoro-11-dodecen-2-one (5h). To a solution of trifluoroacetic anhydride (3.95 ml; 28 mmol) in anhydrous ether (35 ml) were added successively 10-undecenoyl chloride **1h** (0.94g; 1.0 ml) and pyridine (3 ml; 37.1 mmol). The reaction mixture was stirred at 20°C for 25 min. (TLC monitoring as above), the reaction mixture was cooled to 0°C and water (10 ml) was added cautiously. The reaction mixture was poured into water (50 ml) and extracted with ether. The usual work-up afforded a crude residue which was purified by silica gel chromatography (eluent ether/petroleum ether (50/50)) thus affording **1h** (1.01g; 75%) contaminated by 10 mole% of undecylenic acid. A pure sample of **1h** was obtained by microdistillation under vacuum; IR (cm^{-1}): 2920; 2850; 1760; 1640; 1210; 1150; n.m.r. ^1H : 5.90-5.70 (m, 1H); 5.03-4.89 (m, 2H); 2.70 (t, J = 7.2 Hz, 2H); 2.10-1.95 (m, 2H); 1.75-1.55 (m, 2H); 1.31 (s, 12H); n.m.r. ^{13}C: 191.5 (q, J= 35 Hz); 139.1; 115.7 (q, J= 292 Hz); 114.2; 36.4; 33.9; 29.2; 29.1; 29.0; 28.8; 22.4.; M.S.: 248 (M^+ + H_2O); 236 (M^+); 189; 172; 147; H.R.M.S.: peak:$C_{12}H_{19}F_3O^+$, calc.: 236.13880; found: 236.1389.

2-(1,4-Dihydro-1-trifluoroacetylpyridin-4-yl)-2-phenylpropionic acid (11). To a solution of trifluoroacetic anhydride (2.9 ml; 20.5 mmol) in anhydrous ether (20 ml) were added successively 2-phenylpropanoyl chloride **9** (0.5 ml) and pyridine (2.22 ml; 27.3 mmol), and the resulting mixture was stirred at 20°C for 24 hrs. After cooling to 0°C, methanol (10 ml) was added cautiously then the mixture was poured into water (50 ml) and extracted with ether. The usual work-up afforded a crude residue which was purified by silica gel chromatography (eluent dichloromethane) to give **11** (470 mg.; 43%); IR (cm^{-1}): 3500-2500; 1770; 1690; 1620; 1420; 970; n.m.r. ^1H (400 MHz): 11.2-11.0 (s, 1H exchanged with D_2O); 7.5-7.25 (m, 5H); 7.19 (d, J = 8.5 Hz, 0.5H), 7.05 (d, J = 8.5 Hz, 0.5H); 6.81 (d, J = 8.5 Hz, 0.5H), 6.65 (d, J = 8.6 Hz, 0.5H); 5.50-5.45 (m, 0.5H), 5.33-5.29 (m, 0.5 Hz); 4.68-4.63 (m, 0.5H), 4.49-4.44 (m, 0.5H); 4.04 (s, 1H); 1.57 (s, 3H); n.m.r. ^{13}C: 180.6; 152.4 (q, J= 35 Hz); 139.0; 138.9; 128.8;127.8; 126.4; 123.2; 116.0 (q, J= 292 Hz); 113.8; 112.4; 111.9; 110.5; 53.8; 41.3; 17.0; M.S.: 341 ($M.H_2O^+$); 192; 176; 168.

Methyl 2–(pyridin-4yl)-2-phenylpropionate (13). The same reaction was repeated using 2-phenylpropanoyl chloride (1 ml; 6,8 mmol), trifluoroacetic anhydride (5.8 ml; 41 mmol) and pyridine (4.45 ml; 54.6 mmol). The crude acid **11** was dissolved in a mixture of ether (20 ml) and ethanol (5 ml). In a separate flask, Diazald (9 g.) in ether (50 ml) was slowly added to a solution of potassium hydroxide in a mixture of water (4 ml) and ethanol (13 ml). The mixture was heated to 60°C allowing the ethereal solution of diazomethane to distill into the flask containing acid **11**. Excess acetic acid was then added until nitrogen evolution ceased. Evaporation of the solvents under reduced pressure left a crude residue which was subjected to silica gel filtration, to give methyl 2-(1,4-dihydro-1-trifluoroacetylpyridin-4-yl)-2-phenylpropionate **12** (1.01 g, 42%) as a colourless oil that was used as such in the next step; n.m.r. ^1H : 7.4-7.0 (m, 6H); 6.84-6.77 (m, 0.5H), 6.68-6.60 (m, 0.5H); 5.50-5.45 (m, 0.5 H), 5.33-5.29 (m, 0.5 H); 4.69-4.61 (m, 0.5 H), 4.50-4.43 (m, 0.5H); 4.03 (s, 1H); 3.63 (s, 3H) 1.54 (s, 3H).

Selenium dioxide (150 mg; 1.3 mmol) was added to a solution of ester **12** (0.320 g; 0.90 mmol) in tetrahydrofurane (20 ml) and the mixture stirred for 24 hrs at 20°C then filtered. The filtrate was evaporated to dryness, the residue taken-up in ether (20 ml) and extracted twice with diluted hydrochloric acid (2 X 30 ml, 0.25 N). The aqueous layer was neutralised with saturated aqueous solution of sodium hydrogencarbonate, and extracted with ether. The usual work-up gave compound **13** (0.170 g; 78%) as a colourless oil; IR (cm^{-1}): 2950; 1731; 1594; 1446; 1411; 1244; 700. (film); n.m.r. ^1H : 8.52 (dd, J = 4.7 Hz, J = 1.5 Hz, 2H); 7.35-7.09 (m, 7H); 3.72 (s, 3H); 1.92 (s, 3H); n.m.r. ^{13}C: 174.1; 153.3; 149.5; 142.3; 128.3; 127.6; 127.3; 123.0; 56.1; 52.6; 26.2; M.S.: 241 (M^+); 182 (M^+ - $C_2H_3O_2$); 167 (M^+ - $C_3H_6O_2$). (Calc. for $C_{15}H_{15}NO_2$: C, 74.66 ; H, 6.27; N: 5.80%. Found: C, 74.44; H, 6.39; N: 5.52%).

Pentadecanenitrile (14). To a solution of trifluoroacetic anhydride (2.7 ml; 19.1 mmol) in anhydrous ether (25 ml) were added successively hexadecanoyl chloride (1.0 ml, 3.3 mmol.) then pyridine (2.1 ml; 25.8 mmol.). After stirring at 20°C for 30 min., sodium nitrite (0.250 g., 3.6 mmol.) was added and the reaction mixture cooled to 0°C. Trifluoroacetic acid (2.5 ml) was then added, followed by dropwise addition of water (0.5 ml). As soon as gas evolution has ceased, the reaction mixture was poured into water and extracted with ether. The usual work-up afforded a crude residue which was purified by silica gel chromatography (eluent dichloromethane/petroleum ether: 50/50 --> 100/0) thus yielding nitrile **14** (0.500 g; 68%) as a white solid; m.p.: 20-4°C (cold petroleum ether); IR (cm^{-1}): 2927, 2854, 2251, 1465, 910. (Nujol); n.m.r. ^{1}H : 2.24 (t, J = 7.0 Hz, 2H); 1.65-1.45 (m, 2H); 1.18 (s, 22H); 0,80 (t, J = 6.7 Hz, 3H); n.m.r. ^{13}C: 119.5; 31.8; 29.6; 29.4; 29.2; 28.7; 28.5; 25.3; 22.6; 16.9; 13.9. (Calc. for C15H29N: C, 80.64; H, 13.08; N: 6.27%. Found: C, 80.51; H, 13.16; N, 6.16%).

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