Trifluoroacetylation of Alcohols During NMR Study of Compounds with Bicyclo[2.2.1]heptane, Oxabicyclo[3.3.0]octane and Bicyclo[3.3.0]octane Skeleton

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Abstract: TFA was added to a solution of a bicyclo[2.2.1]heptane azide-alcohol in CDCl₃ to correctly characterize the compound, but during 24 h gave the trifluoro acetylated compound in quantitative yield. NMR spectra of the esterified compound helped us also to correctly attribute the NMR signals to the protons, and also confirmed the identification of the carbon atoms. The study was extended to other 14 compounds containing a primary alcohol group alone or with an ethylene ketal, a δ - or γ -lactone group, a primary and a secondary group, two primary and an alkene group and two primary and a secondary alcohol groups on scaffolds containing bicyclo[2.2.1]heptane, oxabicyclo[3.3.0]octane, bicyclo[2.2.1]heptane constrained with a cyclopropane ring and bicyclo[3.3.0]octane fragments. The esterification of all compounds was also quantitative in 24 to 72 h; this helped us to correct attribute the NMR signals to the protons and carbon atoms of the un-esterified compounds by comparison with those of the trifluoro acetylated compounds. A graphical presentation of ¹H- and ¹³C-NMR spectra of a few un-esterified and esterified compounds are presented in the paper.

Keywords: CF₃COOH, alcohols esterification, NMR tube trifluoroacetylation, bicyclo[2.2.1]heptane alcohols, oxabicyclo[3.3.0]octane, Corey lactol, bicyclo[3.3.0]octane, prostaglandin enone, prostaglandin diols

1. Introduction

A routine NMR characterization of a compound with a primary alcohol group needed to distinguish between two protons and after adding trifluoroacetic acid (TFA) in the tube we observed the appearance of signals which proved to be those of the trifluoro acetylated compound formed quantitatively after a day. Browsing the literature, we found that alcohols are even quantitative esterified with TFA [1, 2]. For example, synthesis of ethyl trifluoroacetate from ethyl alcohol and TFA is also mentioned in patents [3-6] and journals [7]. Methyl and isopropyl trifluoroacetate was also synthesized from TFA and methanol or isopropanol [8, 9]. The esterification of alcohols in TFA as solvent was performed and followed in NMR tube [10-12] to observe the transformation of alcohols into the corresponding trifluoroacetates, because the deshielding effect of the trifluoro acetyl group produces a considerable shift of the signal for the proton(s) linked to the hydroxyl group, by comparison with that of the corresponding protons in trifluoroacetate compound, which are moved to lower field. Though an esterification of hydroxyl groups were observed in CDCl₃ + TFA during NMR spectra registration, a paper on the trifluoroacetyl esterification during NMR studies was not found in the literature. And the paper is presented as a scholar theme exemplified for primary and secondary alcohol groups linked to different bicyclic and tricyclic scaffolds and in different configurations.

2. Materials and methods

The compounds were dissolved in CDCl₃, and ¹H, ¹³C, 2D-NMR spectra have been done. Then near 0.03 mL TFA were added and the NMR spectra were followed until the esterification approach the end in specified time of reaction. The same spectra have been done in DMSO-d₆ for a few of the compounds.

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^1H - and ^{13}C -NMR spectra were recorded on Bruker spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C), chemical shifts (δ) are given in ppm relative to TMS as internal standard. Complementary 2D-NMR spectra were done for correct assignment of NMR signals. The numbering of the atoms in the compounds is presented in Figure 1.

1. NMR spectra of the compound 1a and of the trifluoro acetylated compound 1b.

Compound 1a: ^1H -NMR-500 MHz (CDCl_3 , δ ppm, J Hz): 3.95 (dd, 1H, H-8, 7.6, 11.4), 3.93-3.92 (m, 2H, H-2, H-5), 3.92 (dd, 1H, H-8, 8.4, 11.4), 2.62 (dd, 1H, H-3, 8.0, 14.8), 2.51 (t, 1H, H-4, 4.3), 2.49 (d, 1H, H-1, 5.0), 2.13 (ddd, 1H, H-6, 5.0, 10.6, 13.8), 2.02 (t, 1H, H-7, 7.8), 2.00 (brt, 1H, H-3, 3.6, 14.8), 1.75 (s, 1H, OH), 1.05 (dd, 1H, H-6, 3.6, 13.8), ^{13}C -NMR-125 MHz (CDCl_3 , δ ppm, J Hz): 60.53 (C-5), 60.35 (C-8), 59.91 (C-2), 51.74 (C-7), 47.03 (C-1), 43.10 (C-4), 36.27 (C-6), 34.05 (C-3).

Compound 1b, formed after one day with TFA: ^1H -NMR-500 MHz (CDCl_3 + TFA, δ ppm, J Hz): 4.78 (dd, 1H, H-8, 9.3, 11.4), 4.68 (dd, 1H, H-8, 6.2, 11.4), 3.99 (m, 1H, H-5) from COSY, 3.95 (dd, 1H, H-2, 3.8, 8.0), 2.71 (dd, 1H, H-3, 8.0, 15.2), 2.60 (t, 1H, H-4, 4.2), 2.56 (d, 1H, H-1, 4.8), 2.20 (ddd, 1H, H-6, 5.0, 10.7, 14.0), 2.19 (m, 1H, H-7), 2.06 (brt, 1H, H-3, 3.5, 15.2), 1.11 (dd, 1H, H-6, 3.6, 14.0), ^{13}C -NMR-125 MHz (CDCl_3 + TFA, δ ppm, J Hz): 158.21 (q, COCF_3 , $J = 42.5$), 114.55 (q, COCF_3 , $J = 283.8$), 66.37 (C-8), 60.33 (C-5), 58.96 (C-2), 47.88 (C-7), 47.68 (C-1), 43.52 (C-4), 35.82 (C-6), 33.85 (C-3).

2. NMR spectra of the compound 2a and of the trifluoroacetylated compound 2b.

Compound 2a: ^1H -NMR-500 MHz (CDCl_3 , δ ppm, J Hz): 3.98 (dd, 1H, H-8, 7.9, 11.4), 3.91 (dd, 1H, H-8, 8.2, 11.4), 3.94 (dd, 1H, H-2, 3.8, 7.9), 3.49 (dd, 1H, H-5, 3.3, 7.6), 2.54 (d, 1H, H-1, 4.6), 2.40 (d, 1H, H-4, 4.5), 2.25 (t, 1H, H-7, 8.0), 2.14 (dd, 1H, H-3, 4.3, 15.0), 2.01 (dd, 1H, H-3, 8.0, 15.0), 1.69 (dd, 1H, H-6, 7.7, 14.0), 1.66 (s, 1H, OH), 1.59 (dt, 1H, H-6, 4.0, 14.0), ^{13}C -NMR-125 MHz (CDCl_3 , δ ppm, J Hz): 60.88 (C-5), 60.34 (C-8), 59.45 (C-2), 49.65 (C-7), 46.14 (C-1), 43.99 (C-4), 37.69 (C-6), 37.21 (C-3), (NMR spectra in CDCl_3 , [13-15]).

Compound 2b, formed after one day with TFA: ^1H -NMR-500 MHz (CDCl_3 + TFA, δ ppm, J Hz): 4.75 (dd, 1H, H-8, 8.8, 11.6), 4.73 (dd, 1H, H-8, 7.0, 11.6), 3.87 (dd, 1H, H-2, 4.0, 7.8) from COSY, 3.59 (dd, 1H, H-5, 3.2, 7.7), 2.61 (d, 1H, H-1, 4.4), 2.45 (d, 1H, H-4, 4.2), 2.40 (t, 1H, H-7, 7.9), 2.19 (dd, 1H, H-3, 4.3, 15.2), 2.11 (dd, 1H, H-3, 7.8, 15.2), 1.76 (dd, 1H, H-6, 7.7, 14.1), 1.65 (dt, 1H, H-6, 3.8, 14.1), ^{13}C -NMR-125 MHz (CDCl_3 + TFA, δ ppm, J Hz): 158.21 (q, COCF_3 , $J = 42.5$), 114.55 (q, COCF_3 , $J = 283.8$), 66.25 (C-8), 62.49 (C-5), 58.53 (C-2), 46.90 (C-1), 45.67 (C-7), 44.38 (C-4), 37.43 (C-6), 36.96 (C-3).

3. NMR spectra of the compound **3a** and of the trifluoroacetylated compound **3b**.

Compound 3a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 4.05 (t, 1H, H-2, 6.2), 3.95 (d, 2H, H-8, 7.6), 2.86 (d, 1H, H-1, 4.8), 2.69 (s, 1H, H-4), 2.34 (s, 1H, OH), 2.23-2.28 (m, 3H, H-7, 2H-3), 2.23 (dd, 1H, H-6, 5.0, 18.2), 1.91 (d, 1H, H-6, 18.2), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 213.21 (C-5), 59.62 (C-8), 57.78 (C-2), 52.16 (C-4), 51.05 (C-7), 46.20 (C-1), 45.40 (C-6), 34.21 (C-3).

Compound 3b, formed after 3 days (over weekend) with TFA: $^1\text{H-NMR}$ -500 MHz (CDCl_3 + TFA, δ ppm, J Hz): 4.79 (dd, 1H, H-8, 9.3, 11.6), 4.70 (dd, 1H, H-8, 6.1, 11.6), 4.10 (dd, 1H, H-2, 4.6, 7.2), 2.96 (d, 1H, H-1, 4.6), 2.84 (brd, 1H, H-4, 2.7), 2.54 (brdd, 1H, H-7, 6.1, 9.3), 2.42-2.37 (m, 2H, H-3), 2.35 (dd, 1H, H-6, 5.0, 18.6), 2.07 (d, 1H, H-6, 18.6), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 + TFA, δ ppm, J Hz): 216.30 (C-5), 157.47 (q, COCF_3 , $J = 42.5$), 114.43 (q, COCF_3 , $J = 283.8$), 64.95 (C-8), 56.62 (C-2), 52.42 (C-4), 47.07 (C-7), 46.86 (C-1), 45.08 (C-6), 33.93 (C-3).

4. NMR spectra of the enantiomer compound **4a** and of the trifluoroacetylated compound **4b**.

Compound 4a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 4.03 (t, 1H, H-2, 6.2), 3.93 (d, 2H, H-8, 7.7), 2.84 (d, 1H, H-1, 4.7), 2.68 (s, 1H, H-4), 2.57 (s, 1H, OH), 2.29 (t, 1H, H-7, 9.0), 2.29-2.26 (m, 2H, 2H-3), 2.21 (dd, 1H, H-6, 4.9, 18.2), 1.99 (d, 1H, H-6, 18.2), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 213.31 (C-5), 59.53 (C-8), 57.74 (C-2), 52.14 (C-4), 51.04 (C-7), 46.17 (C-1), 45.37 (C-6), 34.14 (C-3). (See NMR spectra in DMSO, [16]).

Compound 4b, formed after 24 h with TFA: $^1\text{H-NMR}$ -500 MHz (CDCl_3 + TFA, δ ppm, J Hz): 4.79 (dd, 1H, H-8, 9.4, 11.5), 4.69 (dd, 1H, H-8, 6.1, 11.5), 4.10 (dd, 1H, H-2, 4.7, 7.1), 2.95 (d, 1H, H-1, 4.6), 2.82 (brd, 1H, H-4, 2.7), 2.53 (brt, 1H, H-7, 7.6), 2.44-2.36 (m, 2H, H-3), 2.34 (dd, 1H, H-6, 5.0, 18.7), 2.05 (d, 1H, H-6, 18.7), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 + TFA, δ ppm, J Hz): 216.06 (C-5), 157.45 (q, COCF_3 , $J = 42.5$), 114.39 (q, COCF_3 , $J = 282.5$), 64.96 (C-8), 56.65 (C-2), 52.40 (C-4), 47.03 (C-7), 46.84 (C-1), 45.04 (C-6), 33.91 (C-3).

5. NMR spectra of the enantiomer compound **5** and of the trifluoroacetylated compound **3b**.

Compound ($\pm$)-5a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 3.98 (dd, 1H, H-2, 3.7, 7.9), 3.93-3.85 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.80 (dd, 1H, 6.7, 12.0), 3.78 (dd, 1H, 6.6, 12.0), 2.50 (dd, 1H, H-3, 8.0, 13.9), 2.49 (d, 1H, H-1, 6.6), 2.30 (dd, 1H, H-7, 6.6, 6.7), 2.22 (d, 1H, H-4, 4.1), 1.96 (dt, 1H, H-6, 5.5, 13.9), 1.94 (m, 1H, H-3), 1.92 (s, 1H, H-OH), 1.48 (d, 1H, H-6, 13.9), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 113.84 (C-5), 64.51, 64.07 ($\text{OCH}_2\text{CH}_2\text{O}$), 60.50 (C-8), 59.92 (C-2), 51.51 (C-4), 46.40, 46.33 (C-7, C-1), 43.80 (C-6), 33.54 (C-3).

Compound (±)-5a with TFA for 24h gave 3b: $^1\text{H-NMR}$ -500 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 4.80 (dd, 1H, H-8, 9.3, 11.6), 4.71 (dd, 1H, H-8, 6.1, 11.6), 4.64 (s, 2H, CH_2OH), 4.48 (brt, 1H, $\text{HOCH}_2\text{CH}_2\text{O}_2\text{CCF}_3$, 4.5), 4.10 (dd, 1H, H-2, 4.6, 7.2), 4.02 (t, 1H, $\text{HOCH}_2\text{CH}_2\text{O}_2\text{CCF}_3$, 4.5), 2.96 (d, 1H, H-1, 4.6), 2.83 (brd, 1H, H-4, 2.7), 2.54 (brdd, 1H, H-7, 6.7, 8.3), 2.42-2.37 (m, 2H, H-3), 2.36 (dd, 1H, H-6, 4.8, 18.6), 2.06 (d, 1H, H-6, 18.6), $^{13}\text{C-NMR}$ -125 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 216.01 (C-5), 157.42 (q, COCF_3 , $J = 42.5$), 114.43 (q, COCF_3 , $J = 283.8$), 114.28 (q, COCF_3 , $J = 283.8$), 68.39 ($\text{HOCH}_2\text{CH}_2\text{O}_2\text{CCF}_3$), 64.98 (C-8), 64.24 ($\text{HOCH}_2\text{CH}_2\text{OH}$), 60.12 ($\text{HOCH}_2\text{CH}_2\text{O}_2\text{CCF}_3$), 56.66 (C-2), 52.44 (C-4), 47.09 (C-7), 46.89 (C-1), 45.10 (C-6), 33.96 (C-3).

6. NMR spectra of the compound **6a** and of the trifluoroacetylated compound **6b**.

Compound 6a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 3.55 (dd, 1H, H-8, 6.6, 11.1), 3.50 (dd, 1H, H-8, 8.2, 11.1), 3.02 (br s, OH), 2.37 (t, 1H, H-7, 7.3), 2.08 (t, 1H, H-2, 4.8), 2.06 (t, 1H, H-1, 5.0), 1.93 (s, 1H, H-4), 1.87 (s, 2H, H-3), 1.38 (t, 1H, H-6, 5.4), $^1\text{H-NMR}$ -500 MHz ($\text{CDCl}_3 + \text{TFA}$, t_0 , δ ppm, J Hz): 3.73 (dd, 1H, H-8, 6.5, 11.4), 3.66 (dd, 1H, H-8, 7.4, 11.4), 2.53 (t, 1H, H-, 7.3), 2.27 (t, 1H, H-, 4.8), 2.21 (t, 1H, H-, 5.1), 2.09 (s, 1H, H-), 2.02 (d, 1H, H-, 11.5), 1.95 (d, 1H, H-, 11.5), 1.56 (t, 1H, H-5.3), 1.38 (t, 1H, H-, 5.4), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 213.20 (C-5), 61.37 (C-8), 44.85 (C-7), 39.93 (C-4), 27.46 (C-3), 21.90 (C-6), 20.47 (C-2), 19.87 (C-1).

Compound 6b, formed from 6a after 48 h with TFA: $^1\text{H-NMR}$ -500 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 4.32 (dd, 1H, H-8, 6.7, 11.2), 4.28 (dd, 1H, H-8, 8.4, 11.2), 2.66 (dd, 1H, H-7, 7.1, 7.8), 2.25 (t, 1H, H-2, 4.8), 2.19 (t, 1H, H-1, 5.2), 2.03 (d, 1H, H-3, 12.0), 2.02 (s, H, H-4), 1.96 (d, 1H, H-3, 12.0), 1.55 (t, 1H, H-6, 5.4), From 24 to 120 h, $^1\text{H-NMR}$ spectra remained unchanged, $^{13}\text{C-NMR}$ -125 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 213.69 (C-5), 157.37 (q, COCF_3 , $J = 42.5$), 114.37 (q, COCF_3 , $J = 283.7$), 66.21 (C-8), 40.91 (C-7), 39.92 (C-4), 27.64 (C-3), 22.06 (C-6), 20.47 (C-2), 20.26 (C-1).

7. NMR spectra of the enantiomer compound **7a** and of the trifluoroacetylated compound **7b**.

Compound 7a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 4.92 (brs, 1H, H-4), 4.27 (dd, 1H, H-2, 4.2, 8.1), 3.86 (dd, 1H, H-8, 8.8, 11.5), 3.84 (dd, 1H, H-8, 7.0, 11.5), 2.98 (dd, 1H, H-3, 8.1, 16.6), 2.85 (dd, 1H, H-6, 5.7, 18.9), 2.70 (m, 1H, H-1), 2.69 (d, 1H, H-6, 18.9), 2.49 (t, 1H, H-7, 8.0), 2.43 (dt, 1H, H-3, 4.4, 16.6), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 168.62 (C-5), 82.08 (C-4), 60.95 (C-8), 59.43 (C-2), 50.47 (C-7), 44.39 (C-1), 44.24 (C-3), 40.56 (C-6). (For esters of 7a see reference [17]).

The compound 7b, after 24 h with TFA of the compound 7b: $^1\text{H-NMR}$ -500 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 5.03 (brdd, 1H, H-4, 1.9, 4.1), 4.65 (dd, 1H, H-8, 6.6, 11.8), 4.61 (dd, 1H, H-8, 10.0, 11.8), 4.37 (dd, 1H, H-2, 4.0, 8.1), 3.13 (dd, 1H, H-3, 8.0, 17.2), 3.04 (dd, 1H, H-6, 5.6, 19.4), 2.86 (d, 1H, H-6, 19.4), 2.83 (m, 1H, H-1), 2.78 (t, 1H, H-7, 8.0), 2.57 (dt, 1H, H-3, 4.3, 17.2), $^{13}\text{C-NMR}$ -125 MHz ($\text{CDCl}_3 + \text{TFA}$, δ ppm, J Hz): 173.68 (C-5), 157.53 (q, COCF_3 , $J = 43.7$), 114.24 (q, COCF_3 , $J = 282.5$), 83.07 (C-4), 65.32 (C-8), 58.13 (C-2), 46.58 (C-7), 44.40 (C-1), 43.82 (C-3), 39.75 (C-6).

8. NMR spectra of the compound **8a** and of the trifluoroacetylated compound **8c**.

Compound 8a: $^1\text{H-NMR}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 4.23 (dt, 1H, H-5, 3.5, 9.9), 4.03 (dd, 1H, H-2, 3.6, 8.0), 3.96 (dd, 1H, H-8, 7.8, 11.4), 3.91 (dd, 1H, H-8, 6.5, 11.4), 2.79 (dd, 1H, H-3, 8.0, 14.6), 2.46 (d, 1H, H-1, 5.0), 2.39 (t, 1H, H-4, 4.1), 2.14 (ddd, 1H, H-6, 5.2, 9.9, 13.7), 2.00 (t, 1H, H-7, 7.9), 1.96 (brt, 1H, H-3, 3.6, 14.6), 1.59 (s, 2H, OH), 0.91 (dd, 1H, H-6, 3.0, 13.7), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 , δ ppm, J Hz): 70.25 (C-5), 60.78 (C-2), 60.69 (C-8), 51.38 (C-7), 47.68 (C-1), 44.88 (C-4), 39.50 (C-6), 32.48 (C-3). (See NMR spectra in DMSO- d_6 in ref. [15,18]).

Compound 8c, formed from 8a after 24 h with TFA: $^1\text{H-NMR}$ -500 MHz (CDCl_3 + TFA, δ ppm, J Hz): 5.20 (dt, 1H, H-5, 3.5, 10.0), 4.81 (dd, 1H, H-8, 9.3, 11.5), 4.70 (dd, 1H, H-8, 6.4, 11.5), 4.05 (dd, 1H, H-2, 3.9, 8.0), 2.83 (t, 1H, H-4, 4.1), 2.67 (dd, 1H, H-3, 8.1, 15.3), 2.64 (d, 1H, H-1, 4.8), 2.37 (ddd, 1H, H-6, 5.0, 10.1, 14.6), 2.25 (brt, 1H, H-7, 7.8), 2.13 (brdt, 1H, H-3, 3.8, 15.3), 1.26 (dd, 1H, H-6, 3.0, 14.6), $^{13}\text{C-NMR}$ -125 MHz (CDCl_3 + TFA, δ ppm, J Hz): 158.24 (q, COCF_3 in C_5 , $J = 43.7$), 157.80 (q, COCF_3 in C_8 , $J = 42.5$), 114.54 (q, COCF_3 in C_5 , $J = 282.5$), 114.41 (q, COCF_3 in C_8 , $J = 283.7$), 76.79 (C-5), 65.89 (C-8), 58.39 (C-2), 47.63 (C-1), 47.63 (C-7), 42.95 (C-4), 36.31 (C-6), 32.83 (C-3).

9. NMR spectra of the ent-Corey compound **9a** and of the bis-trifluoroacetylated compound **9c**.

Compound 9a: $^1\text{H-RMN}$ -500 MHz (CDCl_3 , δ ppm, J Hz): 4.93 (dt, 1H, H-6a, 2.7, 6.8), **4.19** (q, 1H, H-5, 6.3), **3.78** (dd, 1H, H-7, 5.3, 10.4), **3.66** (dd, 1H, H-7, 7.3, 10.4), 2.81 (dd, 1H, H-3, 9.9, 18.1), 2.62 (m, 1H, H-3a), 2.53 (dd, 1H, H-3, 2.0, 18.1), 2.46 (dt, 1H, H-6, 6.6, 14.9), 2.05-2.00 (m, 2H, H-4, H-6), $^{13}\text{C-RMN}$ -125 MHz (CDCl_3 , δ ppm): 180.63 (COO), 83.29 (C-6a), 75.65 (C-5), 63.73 (C-7), 55.02 (C-4), 40.81 (C-6), 39.44 (C-3a), 35.18 (C-3).

Compound 9c, formed from 9a after 72 h with TFA: $^1\text{H-RMN}$ -500 MHz (CDCl_3 + TFA, 72h, δ ppm, J Hz): **5.33** (dt, 1H, H-6a, 3.3, 5.9), 5.27 (brdt, 1H, H-5, 1.3, 6.7), **4.45** (dd, 1H, H-7, 5.4, 11.5), **4.39** (dd, 1H, H-7, 6.2, 11.5), **3.14** (dd, 1H, H-3, 10.2, 18.9), **2.96** (m, 1H, H-3a), 2.78 (dd, 1H, H-3, 2.0, 18.9), **2.66** (dt, 1H, H-4, 5.4, 10.0), 2.59 (dt, 1H, H-6, 6.1, 16.4), 2.47 (brdd, 1H, H-6, 3.1, 16.4), $^{13}\text{C-RMN}$ -125 MHz (CDCl_3 + TFA, 72h, δ ppm): 176.76 (COO), 157.41 (q, COCF_3 , $J = 49.5$), 114.26 (q, COCF_3 , $J = 282.8$), 157.10 (q, COCF_3 , $J = 42.4$), 114.61 (q, COCF_3 , $J = 283.4$), 85.83 (C-6a), 80.60 (C-5), 66.57 (C-7), 50.61 (C-4), 40.39 (C-3a), 37.59 (C-6), 35.93 (C-3).

10. NMR spectra of the ent-Corey compound **10a** and of the bis-trifluoroacetylated compound **10b**.

Compound 10a: ^1H -RMN-500 MHz (CDCl_3 , δ ppm, J Hz): 5.73 (m, 1H, H-6), 5.59 (dd, 1H, H-5, 2.4, 5.4), 3.67 (d, 2H, H-8, 7.4), 3.62 (dd, 1H, H-7, 7.6, 10.4), 3.57 (dd, 1H, H-7, 6.8, 10.4), 3.30 (brt, 1H, H-6a, 7.6), 2.90 (m, 1H, H-3a), 2.32 (dd, 1H, H-4, 9.7, 17.0), 2.25-2.17 (m, 3H, H-1, H-3, H-3a), 2.01 (brs, 2H, HO), 1.72 (dt, 1H, H-2, 5.4, 12.0), 0.85 (q, 1H, H-2, 12.0), ^{13}C -RMN-125 MHz (CDCl_3 , δ ppm): 132.32 (C-6), 129.73 (C-5), 64.38, 64.17 (C-7, C-8), 51.87 (C-6a), 45.96, 45.33 (C-1, C-3), 41.93 (C-3a), 33.03 (C-4), 30.80 (C-2). (NMR spectra in DMSO, ref. [19]).

Compound 10b: ^1H -RMN-500 MHz (CDCl_3 + TFA, 24 h, δ ppm, J Hz): 5.82 (brd, 1H, H-6, 3.5), 5.51 (brd, 1H, H-5, 3.7), 4.42 (2, 2H, H-8, 7.6), 4.33 (2, 2H, H-7, 7.6), 3.38 (brt, 1H, H-6a, 8.1), 2.99 (m, 1H, H-3a), 2.50-2.43 (m, 2H, H-1, H-3), 2.39 (dd, 1H, H-4, 9.7, 17.4), 2.19 (brd, 1H, H-4, 17.4), 1.82 (dt, 1H, H-2, 5.4, 12.3), 1.03 (q, 1H, H-2, 12.3), ^{13}C -RMN-125 MHz (CDCl_3 + TFA, 24 h, δ ppm): 158.06 (q, COCF_3 , $J = 42.1$), 158.04 (q, COCF_3 , $J = 42.1$), 133.51 (C-6), 128.30 (C-5), 114.52 (q, COCF_3 , $J = 282.5$), 69.67, 69.37 (C-7, C-8), 51.61 (C-6a), 42.17 (C-3a), 41.71, 41.14 (C-1, C-3), 33.29 (C-4), 30.68 (C-2).

11. NMR spectra of the optically active enone **13a** and of the trifluoroacetylated compound **13b**.

Compound 13a: ^1H -NMR-300 MHz (CDCl_3 , δ ppm, J Hz): 7.22 (t, 1H, H-22, 8.2), 7.00 (dd, 1H, H-21, 1.0, 8.2), 6.90 (d, 1H, H-19, 2.2), 6.85 (dd, 1H, H-13, 8.4, 15.7), 6.79 (dd, 1H, H-23, 2.4, 8.2), 6.54 (d, 1H, H-14, 15.7), 4.97 (dt, 1H, H-9, 2.7, 6.8), 4.68 (s, 2H, H-16), 4.16 (q, 1H, H-11, 6.6), 3.04 (dd, 1H, H-7, 9.9, 17.6), 2.95 (m, 1H, H-8), 2.69 (d + TFA, 1H, H-7, 17.6), 2.58 (dt + TFA, 1H, H-10, 6.8, 15.4), 2.60 (q, 1H, H-12, 7.3), 2.08 (ddd, 1H, H-10, 2.7, 6.6, 15.4), ^{13}C -NMR-75MHz (CDCl_3 , δ ppm): 194.59 (C-15), 176.28 (C-6), 158.51 (C-18), 146.68 (C-14), 135.11 (C-20), 130.50 (C-22), 126.51 (C-13), 122.11 (C-21), 115.15 (C-19), 113.02 (C-23), **82.59 (C-9)**, **76.55 (C-11)**, **72.21 (C-16)**, 56.35 (C-12), 42.39 (C-8), 40.39 (C-10), 34.44 (C-7).

Compound 13a with TFA, after 5 days:

^1H -NMR-300 MHz (CDCl_3 , δ ppm, J Hz): 7.24 (t, 1H, H-22, 8.3), 7.04 (brd, 1H, H-21, 8.3), 6.99 (dd, 1H, H-13, 8.1, 15.8), 6.90 (dd, 1H, H-19, 2.1, 2.4), 6.78 (dd, 1H, H-23, 2.4, 8.3), 6.64 (d, 1H, H-14, 15.8), 5.34-5.27 (m, 2H, H-9, H-11), 4.84 (s, 2H, H-16), 3.12-3.02 (m, 3H, H-7, H-8, H-12), 2.72 (1H, H-7, 17.0), 2.72 (dt, 1H, H-10, 6.4, 16.1), 2.41 (dd, 1H, H-10, 4.4, 16.1), ^{13}C -NMR-75MHz (CDCl_3 , δ ppm): 198.69 (C-15), 181.17.28 (C-6), 162.78 (q, COCF_3 , $J = 43.5$), 157.63 (C-18), 146.61 (C-14), 135.11 (C-20), 130.79 (C-22), 126.86 (C-13), 122.95 (C-21), 115.19 (C-19), 114.34 (q, COCF_3 , $J = 282.2$), 112.98 (C-23), **85.53 (C-9)**, **81.73 (C-11)**, **71.19 (C-16)**, 54.01 (C-12), 42.79 (C-8), 37.11 (C-10), 35.31 (C-7).

12. NMR spectra of the optically active diol compound **14a** and of the bis-trifluoroacetylated compound **14c**.

Compound 14a: ^1H -NMR-300 MHz (CDCl_3 , δ ppm, J Hz): 7.40 (t, 1H, H-22, 8.0), 7.24 (d, 1H, H-21, 8.0), 7.14 (brs, 1H, H-19), 7.09 (brd, 1H, H-23, 8.0), 5.77-5.67 (m, 2H, H-13, H-14), **4.92 (td, 1H, H-9, 6.9, 3.1)**, **4.54 (dt, 1H, H-15, 3.5, 7.1)**, **4.03 (dd, 1H, H-16, 3.3, 9.4)**, **4.00 (dd, 1H, H-11, 7.1, 9.4)**, 3.93 (dd, 1H, H-16, 7.6, 9.4), 2.75 (dd, 1H, H-7, 9.5, 17.7), 2.63 (brq, 1H, H-8, 8.4), 2.54 (dd, 1H, H-10, 7.1, 14.6), 2.45 (d, 1H, H-7, 17.7), 2.35 (m, 1H, H-12), 1.98 (ddd, 1H, H-10, 2.8, 7.4, 14.6), ^{13}C -

NMR-75MHz (CDCl_3 , δ ppm): 176.68 (C-6), 158.42 (C-18), 132.64 (C-14 or 13), 130.98 C-13 or 14), 130.16 (C-22), 118.06 (C-19), 111.37 (C-23), **82.42 (C-9)**, **76.52 (C-11)**, **71.81 (C-16)**, **70.50 (C-15)**, 56.35 (C-12), 42.49 (C-8), 39.85 (C-10), 34.22 (C-7).

Compound 14a with TFA, after 4 days: ^1H -NMR-300 MHz (CDCl_3 + TFA 3 days, δ ppm, J Hz): 7.42 (t, 1H, H-22, 8.0), 7.28 (d, 1H, H-21, 8.0), 7.11 (brt, 1H, H-19, 2.1), 7.07 (dd, 1H, H-23, 2.1, 8.0), 5.87-5.73 (m, 3H, H-13, H-14, H-15), 5.28-5.22 (m, 2H, H-11, H-9), 4.21 (d, 2H, H-16, 4.7), 3.07 (dd, 1H, H-7, 9.8, 18.5), 2.95 (m, 1H, H-8, 9.8), 2.85 (q, 1H, H-12, 6.3), 2.68 (d, 1H, H-7, 18.6), 2.66 (dt, 1H, H-10, 6.5, 16.0), 2.34 (dd, 1H, H-10, 4.2, 16.0), ^{13}C -NMR-75MHz (CDCl_3 , δ ppm): 181.62 (C-6), 157.97 (C-18), 134.58 (C-14), 130.42 C-13), 126.71 (C-22), 118.92 (C-21), 118.36 (C-19), 111.45 (C-23), **85.42 (C-9)**, **81.74 (C-11)**, **76.39 (C-15)**, 68.47 (C-16), 53.79 (C-12), 42.56 (C-8), 36.66 (C-10), 35.16 (C-7). In this experiment, the amount of **14a** was small and the time acquisition of the ^{13}C -NMR spectra was short to put in evidence the carbon atoms C_{20} , C_{21} and CF_3 for the compound **14a**, and the carbon atoms C_{20} , CF_3 and the carbon atoms of the trifluoroacetyl groups for the compound **14c**.

13.NMR spectra of the optically active diol compound 15a and of the bis-trifluoroacetylated compound 15c.

Compound 15a: ^1H -NMR-300 MHz (CDCl_3 , δ ppm, J Hz): 7.20 (t, 1H, H-22, 8.2), 6.96 (dd, 1H, H-21, 2.4, 8.2), 6.91 (t, 1H, H-19, 2.3), 6.79 (dd, 1H, H-23, 2.4, 8.2), 5.71 (dd, 1H, H-13, 4.8, 16.5), 5.67 (dd, 1H, H-14, 4.8, 16.5), 4.91 (td, 1H, H-9, 7.0, 3.1), 4.50 (dt, 1H, H-15, 3.6, 7.4), 4.00 (t, 1H, H-11, 7.6), 3.99 (dd, 1H, H-16, 3.8, 9.5), 3.87 (dd, 1H, H-16, 7.7, 9.5), 2.74 (dd, 1H, H-7, 9.5, 18.9), 2.62 (brq, 1H, H-8, 9.0), 2.53 (dd, 1H, H-10, 7.0, 14.7), 2.43 (dd, 1H, H-7, 1.2, 18.9), 2.34 (m, 1H, H-12), 1.96 (ddd, 1H, H-10, 3.1, 7.6, 14.6), ^{13}C -NMR-75MHz (CDCl_3 , δ ppm): 176.74 (C-6), 159.02 (C-18), 134.97 (C-20), 132.69 (C-14 or 13), 130.06 C-13 or 14), 130.38 (C-22), 121.57 (C-21), 115.06 (C-19), 113.06 (C-23), 82.41 (C-9), 76.42 (C-11), 71.74 (C-16), 70.50 (C-15), 56.32 (C-12), 42.43 (C-8), 39.77 (C-10), 34.18 (C-7).

Compound 15a with TFA, after 4 days: ^1H -NMR-300 MHz (CDCl_3 + TFA 4 days, δ ppm, J Hz): 7.23 (t, 1H, H-22, 8.2), 7.01 (brd, 1H, H-21, 7.4), 6.89 (t, 1H, H-19, 2.1), 6.78 (dd, 1H, H-23, 2.3, 8.2), 5.91-5.72 (m, 3H, H-13, H-14, H-15), 5.27-5.22 (m, 2H, H-19, H-11), 4.17 (d, 2H, H-16, 4.7), 3.07 (dd, 1H, H-7, 9.9, 18.6), 2.95 (m, 1H, H-8), 2.84 (q, 1H, H-12, 6.3), 2.68 (d, 1H, H-7, 18.6), 2.64 (dt, 1H, H-10, 6.6, 16.0), 2.34 (brdd, 1H, H-10, 4.2, 16.0), ^{13}C -NMR-75MHz (CDCl_3 , δ ppm): 181.61 (C-6), 161.58 (q, CF_3CO , $J_{\text{CF}} = 43.5$), 158.46 (C-18), 135.28 (C-20), 134.55 (C-14), 130.62 C-13), 126.70 (C-22), 122.44 (C-21), 115.31 (C-19), 114.34 (q, CF_3CO , $J_{\text{CF}} = 282.8$), 113.23 (C-23), 85.44 (C-9), 81.79 (C-11), 76.37 (C-15), 68.43 (C-16), 53.79 (C-12), 42.53 (C-8), 36.67 (C-10), 35.20 (C-7).

14.NMR spectra of the compound 12a and of the bis-trifluoroacetylated compound 12c.

Compound 12a: ^1H -NMR (DMSO- d_6 , δ ppm, J Hz): 3.97 (d, 2H, H-8, 7.6), 3.77 (q, 1H, H-6, 7.1) (t + TFA, 10.8), 3.62 (dd with THF, 1H, H-7, 6.7, 10.8), 2.57 (dt + TFA, 1H, H-3a, 6.2, 9.0), 2.20 (dt, 1H, 6a, 6.3, 8.8), 2.08-1.99 (m, 2H, H-1, H-3), 1.98 (s, 3H, CH_3), 1.67 (m, 1H, H-5), 1.61 (dt, 1H, H-2, 5.4, 12.4), 1.49 (m, 1H, H-4), 1.28 (m, 1H, H-5), 1.14 (m, 1H, H-4), 0.86 (q, 1H, H-2, 12.4), ^{13}C -NMR

(DMSO-d₆, δ ppm): 170.37 (COO), 72.69 (C-6), 64.66 (C-7), 61.90 (C-8), 51.80 (C-6a), 43.82 (C-3), 42.48 (C-1), 40.46 (C-3a) 35.39 (C-5), 31.02 (C-2), 23.03 (C-4), 20.72 (CH₃) (NMR spectra in DMSO, [20]).

NMR spectra of the compound **12a** + TFA, after 7 days, are presented below:

The un-symmetric triol **12** was esterified with trifluoroacetic anhydride in TFA (in NMR tube) and the complete esterification proceeded in 4 h. The signals of the bis-trifluoroacetylated compound **12c** are described below: $^1\text{H-NMR}$ (TFA + $(\text{CF}_3\text{CO})_2\text{O}$, δ ppm, J Hz): 5.18 (dt, 1H, H-6, 5.5, 6.6), 4.54 (dd, 1H, H-7, 6.6, 11.3), 4.45 (dd, 1H, H-7, 8.0, 11.3), 4.26-4.20 (m, 2H, H-8), 2.92 (qv, 1H, H-3a, 8.2), 2.83 (td, 1H, H-6a, 14.7, 9.1), 2.48 (hp, 1H, H-1, 6.1), 2.36 (m, 1H, H-3), 2.18 (s, 3H, CH_3), 2.13 (m, 1H, H-5), 1.91-1.68 (m, 3H, H-2, H-4, H-5), 1.42 (m, 1H, H-4), 1.11 (q, 1H, H-2, 12.6), $^{13}\text{C-NMR}$ (TFA + $(\text{CF}_3\text{CO})_2\text{O}$, δ ppm): 176.05 (COO), 157.96 ($J_{\text{C-F}} = 42.8$), 157.87 (COCF_3 , $J_{\text{C-F}} = 42.8$), 114.44 (COCF_3 , $J_{\text{C-F}} = 282.0$), 80.72 (C-6), 67.70 (C-7), 66.49 (C-8), 49.45 (C-6a), 43.16 (C-3a), 40.31 (C-1), 39.92 (C-3), 32.65 (C-5), 30.81 (C-2), 23.74 (C-4), 20.82 (CH_3) (NMR spectra in DMSO, [20]).

15. NMR spectra of the *ent*-Corey compound **11a** and of the bis-trifluoroacetylated compound **11c**.

Compound 11a: $^1\text{H-NMR}$ (DMSO- d_6 , δ ppm, J Hz): 4.26 (t, 2H, HO-C_{7,8}, 5.0, deuterable), 4.16 (d, 1H, HO-C₅, 2.8, deuterable), 4.09 (bs, 1H, H-5), 3.36 (d, 2H, H-8, 11.6), 3.33 (brd, 2H, H-7, 7.3), 2.63 (hext, 2H, H-6a, H-3a, 8.5), 1.95 (hept, 2H, H-1, H-3, 7.2), 1.55 (dt, 1H, H-2, 5.3, 12.4), 1.51-1.47 (m, 2H, H-4, H-6), 1.27-1.20 (m, 2H, H-4, H-6), 0.71 (q, 1H, H-2, 12.4), $^1\text{H-NMR}$ (DMSO- d_6 + TFA, t_0 , δ ppm, J Hz): 4.10 (brs, 1H, H-5), 3.34 (d, 4H, 2H-7, 2H-8, 7.3, 11.0), 2.64 (hex, 2H, H-6a, H-3a, 8.5), 1.95 (hept, 2H, H-1, H-3,), 1.55 (dt, 1H, H-2, 5.2, 12.4), 1.51-1.47 (m, 2H, H-4, H-6), 1.28-1.20 (m, 2H, H-4, H-6), 0.71 (q, 1H, H-2, 12.4), $^{13}\text{C-NMR}$ (DMSO- d_6 , δ ppm): 72.90, 72.78 (C-5), 61.95, 61.83 (C-7, C-8), 44.32, 44.27 (C-1, C-3), 41.98 (C-3a, C-6a), 35.30, 35.25 (C-4, C-6), 30.63 (C-2). (NMR spectra in DMSO, [20]).

The compound **11a** was not completely esterified, even after 10 days and with a significant excess of TFA. No proton and carbon NMR spectra couldn't be decipherable, as in the case of **10a** + TFA.

The symmetric triol **11** was esterified with trifluoroacetic anhydride in TFA (in NMR tube) and the complete esterification proceeded in 4 h. The signals of the tri-esterified compound **11c** are described below: $^1\text{H-NMR}$ (TFA + $(\text{CF}_3\text{CO})_2\text{O}$, δ ppm, J Hz): 5.53 (t, 1H, H-5, 3.7), 4.43 (dd, 2H, H-7, H-8, 7.3, 11.1), 4.35 (dd, 2H, H-7, H-8, 3.0, 11.1), 3.04-2.91 (m, 2H, H-3a, H-6a), 2.58-2.44 (m, 2H, H-1, H-3), 2.05 (brd, 1H, H-4 or H-h, 4.2), 2.02 (brd, 1H, H-6 or H-4, 7.1), 1.89 (dt, 1H, H-2, 11.5, 5.3), 1.61-1.55 (m, 2H, H-4, H-6), 1.16 (q, 1H, H-2, 11.5), $^{13}\text{C-NMR}$ (TFA + $(\text{CF}_3\text{CO})_2\text{O}$, δ ppm): 158.13 (COCF_3 in C₇ and C₈, $J_{\text{C-F}} = 42.8$), 157.90 (COCF_3 in C_c, $J_{\text{C-F}} = 42.8$), 114.49 (COCF_3 , in C₇ and C₈, $J_{\text{C-F}} = 283.5$), 114.43 (COCF_3 , in C₅, $J_{\text{C-F}} = 283.5$), 83.50 (C-5), 68.41 (C-7, C-8), 42.17 (C-3a, C-6a), 40.01 (C-1, C-3), 32.74 (C-4, C-6), 29.51 (C-2).

The influence of the solvent showed the uselessness of this esterification effort, because the NMR signals were of no help to find these signals in the NMR spectra in DMSO- d_6 .

3. Results and discussions

TFA is usual used in NMR of alcohols, amines or thiols, whose signals overlap over those of the protons linked to vicinal carbon atoms and made difficult to calculate the coupling constants and to assign the signals to the corrected protons. Due to its acidity, it moved the labile protons (OH, NH, SH) to lower field, and also suppress their coupling with the protons linked to the carbon atoms vicinal to oxygen, nitrogen or sulfur. In this paper, NMR spectra of the compounds **1-10** and **13-15** have been done in CDCl_3 as solvent and for the compounds **11** and **12** (insoluble in CDCl_3) in DMSO, followed by addition of TFA in NMR tube.

This paper started from this idea that for the correct assignment of the signals for the protons H₂ and H₅ of the *endo*-azide **1a** (Figure 1), TFA was added; but in spectrum began to appear signals at lower field suggesting that here started the esterification reaction of the compound with TFA. The *endo*-azide **1a** was completely esterified in 24 h to the trifluoroacetate **1b**, and this can be observed in both ¹H and ¹³C-NMR. In ¹H-NMR, the methylene protons of primary alcohol are deshielded from 3.95 to 4.78ppm, respectively 3.92 to 4.68 ppm. In ¹³C-NMR, the chemical shift of carbon atom C₈ is deshielded from 60.35 ppm to 66.37 ppm, and the vicinal carbon atom C₇ is shielded from 51,74 to 47.88 ppm. And the signals for trifluoroacetate group are present in the spectrum at: 158.21 (COCF₃) and 114.55 (COCF₃) ppm. A comparison of ¹H and ¹³C-NMR spectra of the starting compound **1a** and the esterified compound **1b** is presented in Figure 2.

Figure 1. Compounds studied in NMR tube, in CDCl₃ (**1-10, 13-15**) and DMSO (**11** and **12**) as solvents without and with TFA; in the paper the compounds with R = H, are numbered **xa** (for example **1a**) and the compounds with R = CF₃CO, are numbered **xb** (or **xc**) (for example **1b**)

Figure 2. ^1H and ^{13}C -NMR spectra in CDCl_3 of *endo*-azide **1a** and that of the esterified compound **1b**, formed in 24 h by addition of TFA

Starting from this observation, the *exo*-azide compound **2a** was similarly studied by addition of TFA in NMR tube, and the esterification to **2b** was also finished in 24 h (Figure 3 and Experimental, 2):

Figure 3. ^1H and ^{13}C -NMR spectra in CDCl_3 of *endo*-azide **2a** and that of the esterified compound **2b**, formed in 24 h by addition of TFA

Then the study was extended to other compounds with primary alcohol groups (**3a-7a**), with primary and secondary alcohol groups (**8a-12a**), a secondary alcohol group alone (**13**) and a secondary alcohol group in the presence of a secondary allylic alcohol (**14-15**), in racemic: **5a**, **10a-12a**, or optically active form: **1a-4a**, **6a-9a**, **13-15**, usually used in our laboratory, presented in Figure 1, which contain:

- a 5-keto group in the bicyclo[2.2.1]heptane skeleton (compounds **3a** and **4a**) or protected with an ethylene ketal group as in the compound **5a**, or in a more constrained structure containing a cyclopropane ring (compound **6a**).
- a δ -lactone (compound **7a**).
- a primary and a secondary alcohol group in a bicyclo[2.2.1]heptane (compound **8a**) or oxabicyclo[3.3.0]octane (*ent*-Cotey lactone **9a**) skeleton.
- a double bond in a bicyclo[3.3.0]octane diol with two primary alcohol groups (compound **10a**).
- a bicyclo[3.3.0]octane triol containing two primary alcohol groups and a secondary alcohol group linked to C_5 carbon atom (compounds **11a**) or to C_6 carbon atom (**12a**, with a primary alcohol protected as acetate).

- an enone (**13**) and two diols (**14,15**) in prostaglandin intermediate, containing a double bond.

The 5-keto compounds **3a** and **4a** were cleanly esterified with TFA in 24 h to the compounds **3b** and **4b**, and the deshielding of the H₈ protons from $\delta = 4.05$ to 4.79 and $\delta = 3.95$ ppm to 4.70 ppm and of the carbon atom C₈ from $\delta = 59.62$ ppm to 64.95 ppm by trifluoro acetyl esterification is observed in NMR spectra, as previously. After 3 days (over weekend), the compound **3b** was obtained pure (Figure 4 and Experimental, 3).

Figure 4. ¹H and ¹³C-NMR spectra in CDCl₃ of compound **3a** and that of the esterified compound **3b**, formed in 3 days by addition of TFA

In the case of the ethylene-ketal protected compound ($\pm$)-**5a**, trifluoroacetic acid esterified the primary alcohol, but in the same time it deprotected the ethylene ketal group giving the compound **3b**, as can be observed in ¹³C-NMR spectrum where the ketal C₅ carbon atom ($\delta = 113.84$ ppm) no more appear in the spectrum, but appear the C₅-ketone carbon atom at 216.01 ppm (Figure 5). The ethylene ketal seems to be transformed into ethylene glycol and ethylene glycol mono-trifluoroacetate in a ratio of 1:1, as can be observed in ¹H-NMR and ¹³C-NMR (Experimental 5, were the signals of ethylene glycol and of the mono-trifluoroacetate are evidenced in red color).

Figure 5. ¹H and ¹³C-NMR spectra in CDCl₃ of compound **5a** and that of the esterified compound **3b**, formed in 24 h by addition of TFA

The compound **6a**, a tricyclic ketone what behaves like an α,β -unsaturated ketone, was also quantitatively trifluoroacetylated in 48 h (Experimental, 6).

For the compound **7a**, the δ -lactone resists during its quantitative TFA-esterification to the trifluoroacetylated compound **7b** in 24h (Experimental, 7).

The diol **8a** was esterified with TFA to both the primary alcohol and the secondary alcohol (Figure 6a) and this was observed even after two hours (Figure 6b), but it was not observed that the esterification of the primary alcohol to **8b** proceeded selectively before begins the esterification of the secondary one; in 24 h the reaction proceeded quantitatively and gave the compound **8c** (Experimental 8), which is clearly observed in ¹H- and ¹³C-NMR (Experimental, 8). In ¹H-NMR, H₅ was deshielded from $\delta = 4.23$ ppm to $\delta = 5.20$ ppm, and the H₈-protons were deshielded from $\delta = 3.96$ to 5.20 ppm, respectively 3.91 to 4.81 ppm. Both trifluoro acetyl groups appear in ¹³C-NMR spectra, at 158.24 and 114.54 ppm for COCF₃ and COCF₃ linked to OC₅, respectively 157.80 and 114.41 ppm for COCF₃ and COCF₃ linked

to OC₈. The signals for C₅ and C₈ are deshielded from 70.25, respectively 60.69 ppm to 76.79, respectively 65.89 ppm; even the vicinal carbon atoms to C₅ and C₈, the carbon atoms C₇, respectively C₄ and C₆ are shielded from 51.38, 44.88 and 39.50 ppm to 47.63, 42.95 and 36.31 ppm.

Figure 6a. Trifluoroacetylation of the diol **8a** to the diester **8c** with TFA in CDCl₃

Figure 6b. ¹H and ¹³C-NMR spectra in CDCl₃ of the compound **8a** and that of the esterified compound **8c**, formed in 24 h after addition of TFA

Corey lactone **9a**, with an oxabicyclo[3.3.0]octane fragment, was esterified to both primary and secondary alcohols group, without the observation of the selective trifluoro acetylation of the primary alcohol before begins the trifluoroacetylation of the secondary alcohols (Experimental, 9). In ^{13}C -NMR, both trifluoro acetyl groups appear in NMR spectra, at 157.41 and 114.26 ppm for COCF_3 and COCF_3 of the primary alcohol ester, respectively 157.10 and 114.61 ppm for COCF_3 and COCF_3 for the secondary alcohol ester. The deshieldings of the H_5 and H_7 - protons from 5.27, 4.19 and 3.78 ppm to 5.27, 4.45 and 4.39 ppm and the deshieldings of the corresponding carbon atoms C_5 and C_7 from 75.65 to 80.60 ppm and 63.73 to 66.57 ppm are clearly observed as previously for **8a** to **8c**. The same shieldings of the vicinal carbon atoms to C_7 and C_5 , C_4 and C_6 from 55.02 and 40.81 ppm to 50.61 and 37.59 ppm are also observed, as can be seen in Figure 7.

Figure 7. ^1H and ^{13}C -NMR spectra in CDCl_3 of the compound **9a** and that of the esterified compound **9c**, formed in 72 h after addition of TFA

The double bond of the diol-alkene **10a** was not affected during trifluoroacetylation of the primary double bonds to **10b**. In 4 h, near half esterification of the hydroxyl groups had been done and both hydroxyl groups were esterified after 24 h (Figure 8, Experimental, 10).

Figure 8. ^1H and ^{13}C -NMR spectra in CDCl_3 of the compound **10a** and that of the esterified compound **10b**, formed in 24 h after addition of TFA

The enone group of the prostaglandin intermediate **13a** remained unmodified during 5 days in the presence of TFA. The deshielding of the proton H_{11} from 4.39 to the multiplet centered at 5.30 ppm (where it appears together with H_9 proton) and of the corresponding carbon atom C_{11} from 76.55 ppm to 81.73 ppm is also observed (Figure 9). Deshielding of the vicinal carbon atoms C_{10} and C_{12} from 40.39, respectively 56.35 ppm to 37.10 respectively 54.01 is also observed (experimental, 11).

Figure 9. ^1H and ^{13}C -NMR spectra in CDCl_3 of the compound **13a** and that of the esterified compound **13b**, formed after 5 days after addition of TFA

The prostaglandin diol intermediate **14a**, containing a secondary (11-OH) and an allylic secondary (15-OH) alcohol groups was esterified with TFA over weekend (4 days; in 24 h the bis-trifluoroacetylation did not ended), without concluding that the 15-OH allylic alcohol is selectively esterified than the 9-secondary alcohol (Figure 10 and Experimental 12). The deshielding of the protons H₁₁ and H₁₅ from 4.00 and 4.54 ppm to the multiplets centered at 5.25 and 5.85 ppm and of the corresponding carbon atoms C₁₁ and C₁₅ from 76.52 and 70.50 ppm to 81.74 and 76.39 ppm is clearly observed (Figure 10). The shielding of the vicinal carbon atoms, C₁₀, C₁₂ and C₁₆ from 39.85, 56.35, respectively 71.81 ppm to 36.66, 53.79, respectively 68.47 is also observed on this diol.

Figure 10. ¹H and ¹³C-NMR spectra in CDCl₃ of the compound **14a** and that of the esterified compound **14c**, formed in 4 days after addition of TFA

210303-SC5-33-CF3 1 1 D:\CCO\TCaprol\data\ICON-NMR-Lab\nmr
Scale : 0.50
210303-SC5-33-CF3 1 1 D:\CCO\TCaprol\data\ICON-NMR-Lab\nmr

Compound 15a

15 9 16 7 12 10 10 13 11 16 13 14 9 15 16 11 7 8 7 12 10

8 7 6 5 4 3 2 (ppm)

210303-SC5-33-CF3 3 1 D:\CCO\TCaprol\data\ICON-NMR-Lab\nmr
Scale : 0.50
210303-SC5-33-CF3 3 1 D:\CCO\TCaprol\data\ICON-NMR-Lab\nmr

Compound 15a

9 11 15 16 12 8 10 7 9 11 15 16 12 8 10 7

80 60 40 (ppm)

<https://doi.org/10.37358/RC.21.2.8428>

(Experimental, 14, for compound **12a** with TFA). The esterification with trifluoroacetic anhydride in TFA proceeded cleanly to the esterified compounds **12c** and **11c**, and both compounds were fully characterized; unfortunately, because of the different solvents in NMR experiments, the signals of the trifluoroacetylated compounds couldn't be useful to identify them between the compounds formed in DMSO-d₆ + TFA (Experimental 14 and 15). In conclusion, the use of TFA to clarify the NMR spectra of the alcohol compounds in DMSO-d₆ at shorter times (even until hours) is beneficial, because the secondary trifluoroacetylated compounds are not formed in amounts to complicate the NMR spectrum.

So, the transformation of the alcohol compounds **1a-10a** and **13a-15a** into the corresponding trifluoroacetates in CDCl₃ + TFA in NMR tubes helped us to correctly attribute or to confirm the NMR signals of some protons and carbon atoms in the molecules, otherwise difficult. Some observations should be mentioned. The *primary alcohol groups* of the compounds **1a-7a** and **10a** were quantitatively transformed with TFA into the trifluoroacetylated compounds **1b-4b**, **6b-7b**, **10b** in short time (mainly 24 h). Only the ethylene ketal group of the compound **5a** was deprotected during the esterification of primary alcohol, giving the trifluoro acetylated compound **3b**. The *secondary alcohol groups* of the compounds **8a** and **9a** were concomitant esterified with TFA with the primary alcohol groups (to the compounds **8c** and **9c**), without the observation that the esterification of the secondary alcohols begins after the primary hydroxyl groups were esterified. For compounds **14a** and **15a**, the esterification of the secondary 15-allylic alcohols proceeded not selectively against the 11-secondary alcohols; at longer time (3-4 days) both alcohols groups were esterified. It is worth mentioned that the trifluoroacetylation proceeded faster than that in DMSO-d₆, where also an additional amount of TFA did not lead to completion of the esterification reaction. The results are to be taken into consideration when TFA is added in NMR tube, because not only the shifting of the couplings of the deuterable protons could help us to simplify the NMR spectrum, but also trifluoro acetylation could help us to more precisely attribute the signals in ¹H- and ¹³C-NMR spectra to the protons and carbon atoms in the molecule.

4. Conclusions

TFA added to the solutions of the compounds **1a-10a** and **13a-15a** in CDCl₃ esterified the primary and the secondary alcohols to the corresponding trifluoro acetylated compounds **1b-7b**, **8c-10c** and **13b-15c** in 24 to 72 h in quantitative yield. Ethylene ketal group of the compound **5a** was deprotected to the ketone group of the compound **3b**, concomitant with the esterification of the primary alcohol. The δ -lactone group of the compound **7a** and γ -lactone group of the *ent*-Corey lactone **9a** were not opened during esterification of the alcohol groups. The esterification of the secondary 15-allylic alcohols of the compounds **14a** and **15a** proceeded not selectively against the 11-secondary alcohols, so at longer time (3-4 days) both alcohols groups were esterified.

In DMSO-d₆, the esterification of the secondary and primary alcohol groups of the triols **11a** and **12a** is much slower and didn't went to complete even after 7 days, though the amount of TFA was greater.

In conclusion, TFA added in NMR tube, not only shifts the deuterable protons and simplify the NMR spectrum, but by trifluoroacetylation of the alcohol groups cloud make easier and more precisely attribution of the signals in ¹H- and ¹³C-NMR spectra to the protons and carbon atoms in the molecule.

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