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TRANSFORMATION OF δ-LACTONE IN γ-LACTONE IN THE COREY ROUTE FOR SYNTHESIS OF PROSTAGLANDINS

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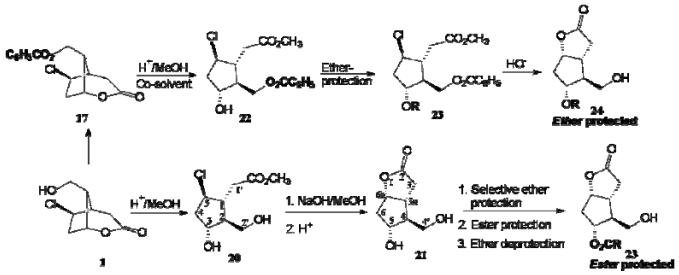
(Un)substituted benzoate ester protected δ-lactone alcohols are alcoholized in acid catalysis in almost quantitative yield to hydroxyl-halogenoesters. For alkylesters the yield drops to ~70%. After changing the protection between primary and secondary alcohols, the intermediate halogenoesters are transformed into the known γ-lactone alcohols protected as ether, silyl-ether or trityl at the secondary alcohol group. Unprotected δ-lactone alcohol **1** is also quantitatively transformed in chloroester **20**. After selective protection of the primary alcohol with bulky ether groups, this is finally transformed into the known Corey γ-lactone alcohol, protected as ester at the secondary alcohol.



INTRODUCTION

In the Corey total stereocontrolled synthesis of prostaglandins,[1] it is necessary to transform a δ-lactone alcohol **1**, or an intermediate with an ω-side chain **2** with the same δ-lactone structure, into a γ-lactone alcohol **3** or into the corresponding intermediate with an already built-in ω-side chain **4** (Scheme 1). (Scheme 1 exemplifies the process only for prostaglandin $F_{2\alpha}$ analogues, however all series of prostaglandins were obtained by this route).

This δ- to γ-lactone transformation must be done in good yield because the sequence behind δ-lactone-alcohol **1**, for racemic or optically active compounds, contains many steps (Scheme 2). In this sequence, the racemic carboxylic compound is separated in enantiomers at the level of compounds **6**[2] or **8**[3] by reaction with an optically active base: (S)-phenylethylamine[2] or ephedrine [this procedure was applied by us at a multimolar scale and the whole sequence at the level of hundreds of grams of final prostaglandin analogues], by separation of diastereoisomer salts by crystallization and finally by isolation of optically active acid of both enantiomers.

A few synthetic sequences were developed for the δ- to γ-lactone transformation. The first is Corey *et al.* procedure[4] [Scheme 3, route a): **1→11→12→13→3**], in which compound **1** was first protected as tetrahydropyranyl ether (4-methoxy-pyranyl and trimethylsilyl were also used as protecting groups) and the δ-lactone group was opened with LiOH in the presence of a great excess of 30% H_2O_2 (>10:1) (THF as solvent). The lithium salt of the intermediate acid closes the γ-lactone ring in an intramolecular SN2 reaction, resulting compound **12**. The following two steps are in the direction of PG synthesis and change the protection between the primary alcohol group to

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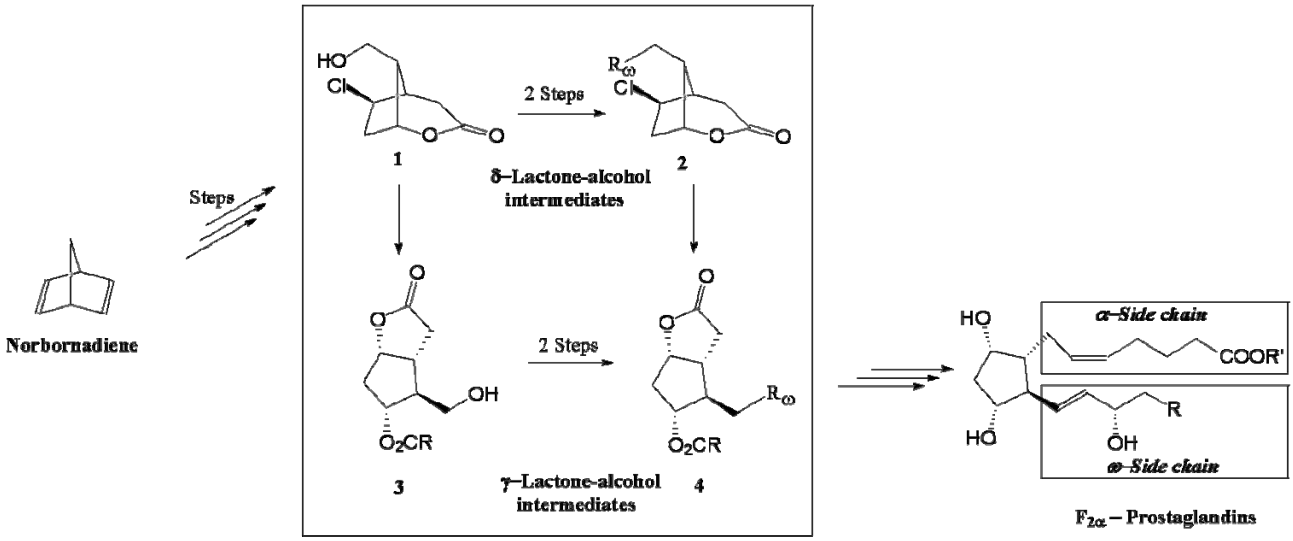
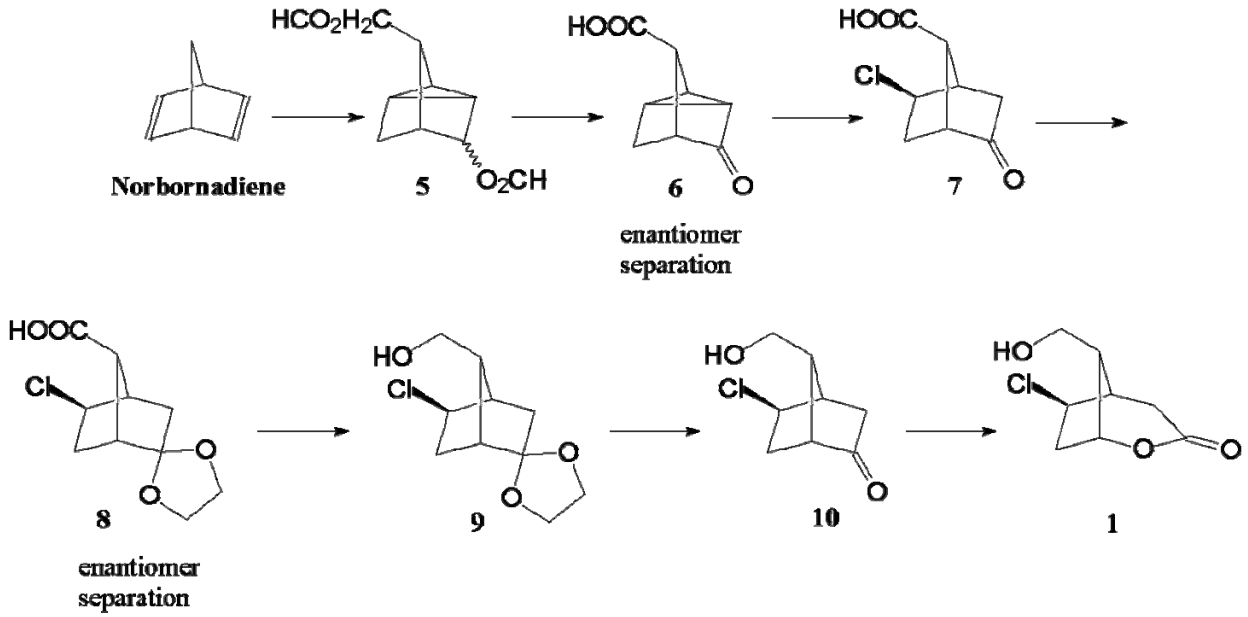
the **secondary alcohol group with an ester** (*p*-phenylbenzoate). Difficulties arise especially from the neutralization of excess peroxide and isolation of the compound.

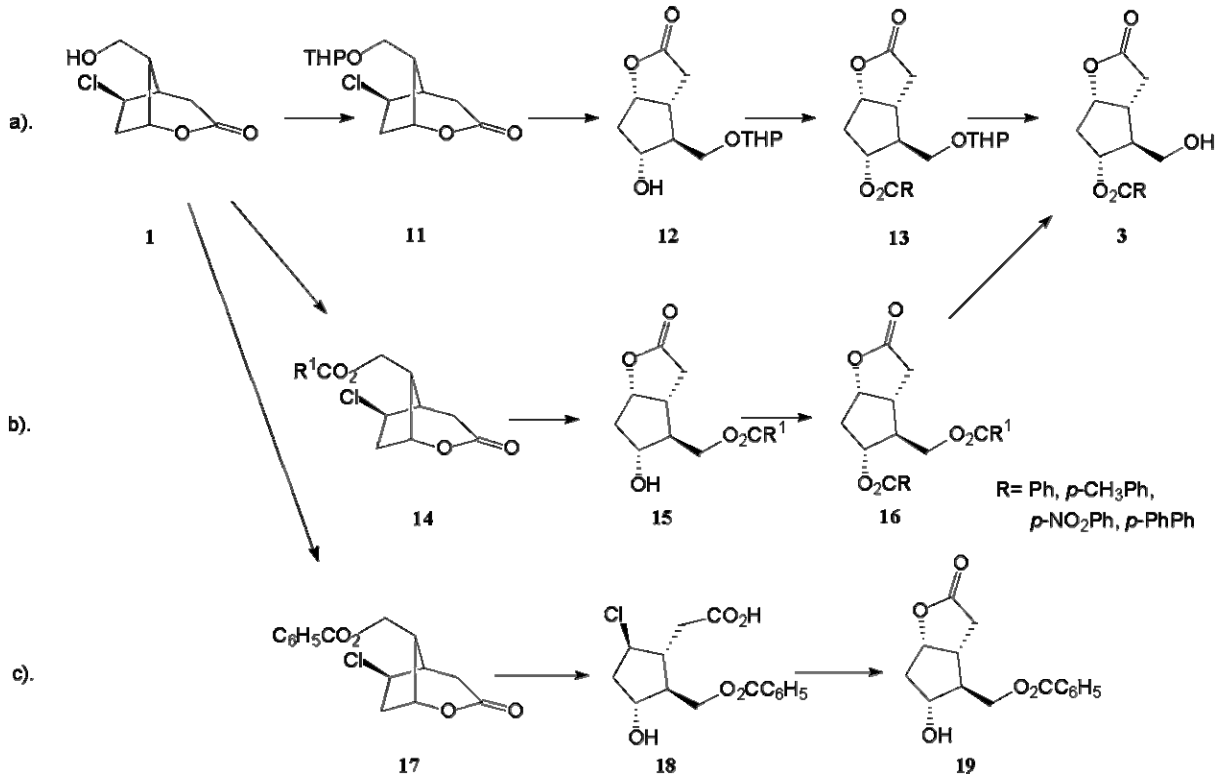
In the second procedure[5] [Scheme 3, route b): **1→14→15→16→3**], the alcohol is protected as alkyl ester ($R^1 = C_1$-C_3) instead of ether. δ-Lactone **14** is similarly opened with LiOH (or NaOH) as base, also in the presence of great excess of hydrogen peroxide. The resulting γ-lactonic compound **15** is then protected at the secondary alcohol as benzoate or *p*-substituted benzoate with methyl, nitro or phenyl groups. Then the alkyl-ester group is removed selectively in acid catalysis in methanol or ethanol. The difficulties encountered in the Corey procedure with excess peroxide neutralization remain and probably some difficulties also arise in the final step. It is to be mentioned that the last two steps are also in the direction of the prostaglandin synthesis of compound **3,** protected as benzoate or substituted benzoate.



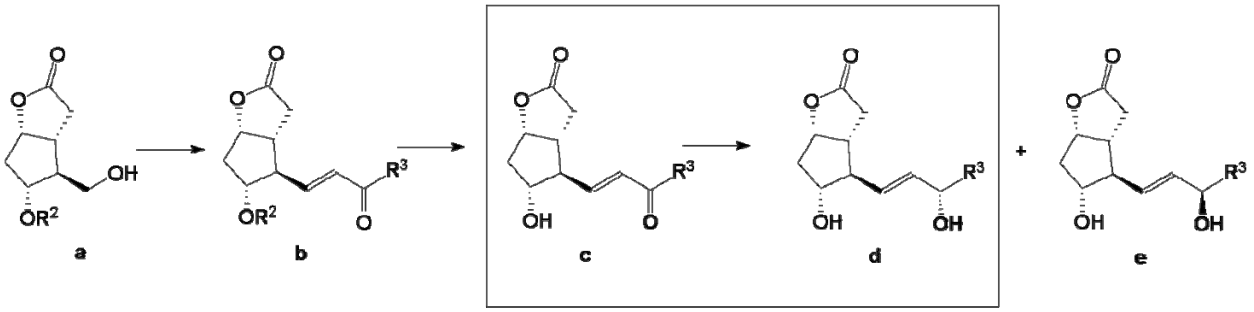
Scheme 1 – Corey synthesis of $F_{2\alpha}$- prostaglandins.



Scheme 2 – Corey procedure synthesis of intermediate **1** from norbornadiene[4] (Separation of enantiomers is realized on intermediates **6**; in our procedure the separation of enantiomers is performed on intermediate **8,** starting from norbornadiene to intermediate **1**).



Scheme 3 – Strategies for transforming δ-lactone **1** to γ-lactone **3**: a) Corey *et al.* procedure for transforming δ- to γ-lactone, b) Veselly et al. procedure for transforming δ-lactone **1** to γ-lactone **3**, c) Funfschilling *et al.* procedure for transforming δ-lactone **17** to γ-lactone **19**.



Scheme 4 – Steps from γ-lactone intermediate **a** to selectively reduced compound **d**.

The third procedure[6] is different from those mentioned above [Scheme 3, route c): **1→17→18→19**]. δ-Lactone alcohol **1** is protected as benzoate, then the lactone group is opened to the hydroxyacid **18** in acid catalysis (10% HCl, acetone-water, reflux, 14h). In the last step, the γ-lactone ring is closed by treating the acid with sodium hydroxide [i). 10% NaOH, r.t., 2h, ii). HCl]. The sodium salt of **18** substitutes the chlorine in an intramolecular SN2 reaction like in the previous two reactions. Some difficulties are also encountered in this sequence, especially at the second step where the benzoate group could also be deprotected.

The protection of γ-lactone-alcohol **a** is also very important, because the stereoselective reduction of intermediates **c** to **d** (Scheme 4) needs the alcohol group of **c** to be free in many reduction procedures: aluminium diisoborniloxyisopropoxide,[7] Yammamoto reagent,[8] etc. Basic deprotection of the ester group of compound **b** diminishes the yield of enone **c** and makes its separation difficult (sometimes the yield can be extremely low and a supplementary column chromatography purification is needed).

That is why a Corey intermediate protected at the secondary alcohol **as ether** instead of ester is desirable.

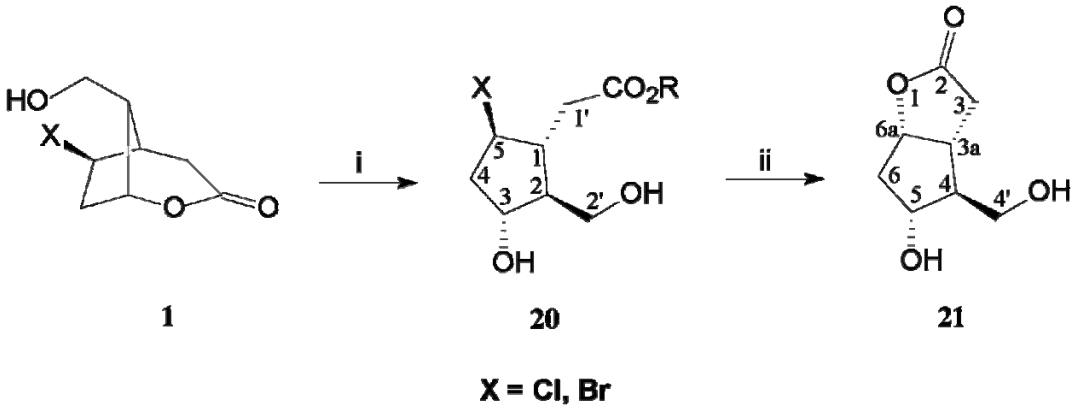
From the methods presented above, only the Funfschilling *et al.* procedure[6] results in the γ-lactone intermediate **19**, which can then be transformed in a Corey γ-lactone-alcohol substituted at the secondary alcohol with an ether protecting group, as needed for the following steps in prostaglandin synthesis, according to Scheme 4.

RESULTS AND DISCUSSION

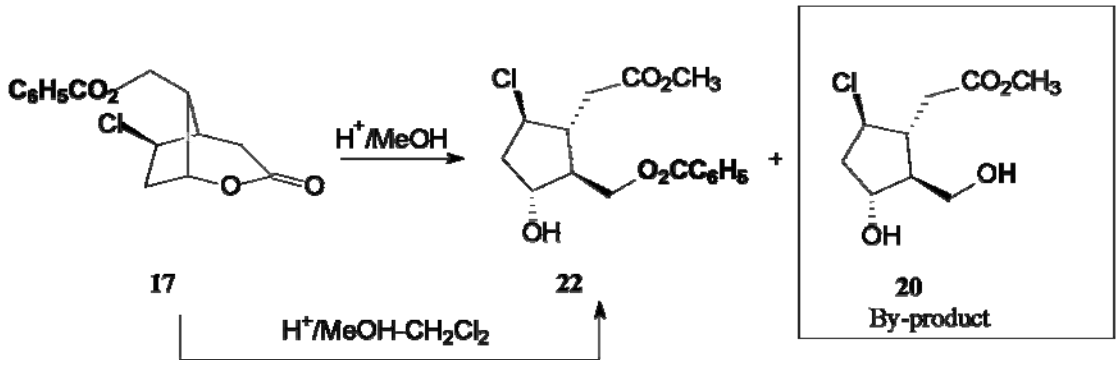
We have realized a new procedure for transforming δ-lactone intermediate **1** into the Corey γ-lactone intermediate **21** (Scheme 5),[9a] which consists of a two-reaction sequence: i). a clean ring opening of the δ-lactone ring of compound **1** to hydroxyester **20** in an acid catalyzed methanolysis, ii). Hydrolysis of the ester group followed by an intramolecular SN_2 reaction of halide (chloride, bromide,[9b] etc) by sodium carboxylate with closing of the γ-lactone ring.

The whole sequence is realized in almost quantitative yield and the oily γ-lactone diol **21** can be further used without any purification. Using ethanol instead of methanol, the reaction time is longer, but the corresponding ethyl-ester **20** is obtained in quantitative yield (HPLC). This acid alcoholysis was also realized on δ-lactone compounds substituted with bromine instead of chlorine atom.[9]

However, compound **21** has both hydroxyl groups free and the next step requires discriminating between these two, for example by selective protection of one group. So for the first reaction we take into account the possibility of using the benzoate protected compound **17** used by Funfschilling et al. in their procedure for transforming δ- to γ-lactone (Scheme 5). We observed that compound **22** is also predominantly formed and the yield of the reaction is diminished by the formation of the by-product (unprotected) compound **20** by deprotection (7-10%) of the benzoate group (Scheme 6). Both compounds are oils and in order to obtain pure **22** it is necessary to separate it from the crude product by column chromatography purification.



Scheme 5 – Transformation of δ-lactone alcohol **1** in γ-lactone alcohol **21** in a two-step procedure through the haloester intermediate **20**: i).a) R = CH_3: MeOH, Amberlit IRC-50Wx2 (or TsOH), reflux, overnight, quantitative; b) R = C_2H_5: EtOH, reflux 48h, 83% purified by column chromatography; ii). NaOH, MeOH-H_2O, 4:1, 3h, >95%.

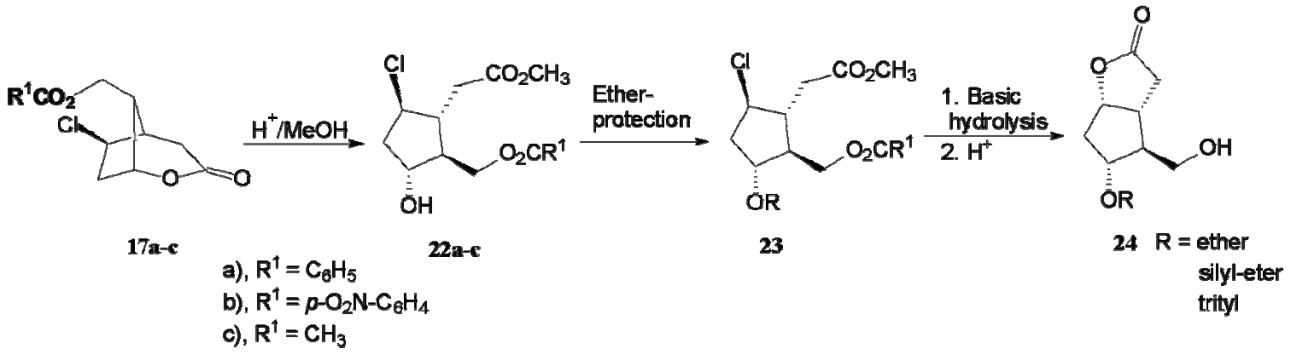


Scheme 6 – Acid catalyzed opening of δ-lactonealcohol benzoate in methanol.

We have then used an inert co-solvent (CH_2Cl_2) in acid catalyzed methanolysis and observed that the yield of hydroxyester **22** is quantitative without formation of by-product **20**. Other inert solvents (THF, $CHCl_3$, toluene, etc.) could be efficiently used in the reaction. Ethanol could also be used instead of methanol in the reaction presented in Scheme 6. Other substituted benzoate esters **17** could be used in the reaction, for example *p*-nitro-benzoate (94.5%), *p*-phenylbenzoate, etc.

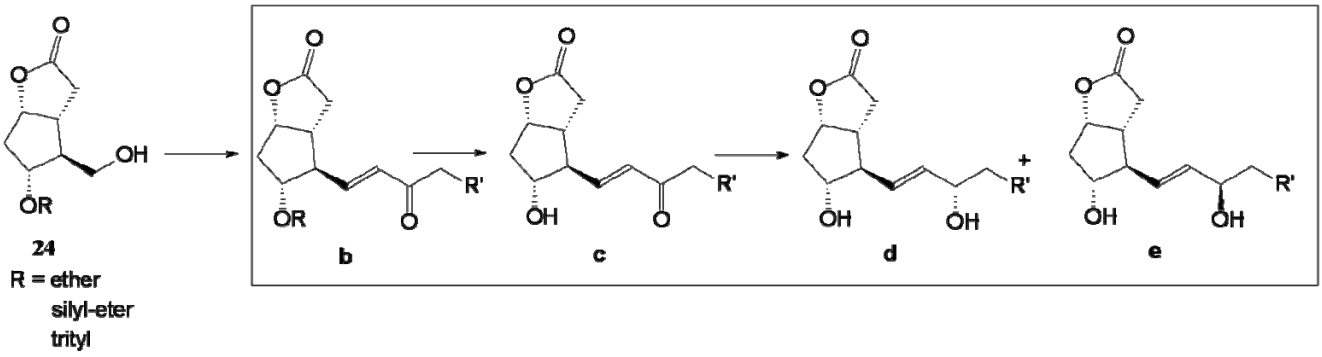
We also tried an alkyl ester protected compound **17** (acetate instead of benzoate) in the reaction, but observed that the deprotection of the acetate group takes place at a level of ~ 30% and the corresponding acetylated chloroester **22** is obtained pure after column chromatography purification in 68.6% yield.

We studied next the second reaction, *i.e.* the closing of the γ-lactone ring starting from chloroester **22** (Scheme 7):

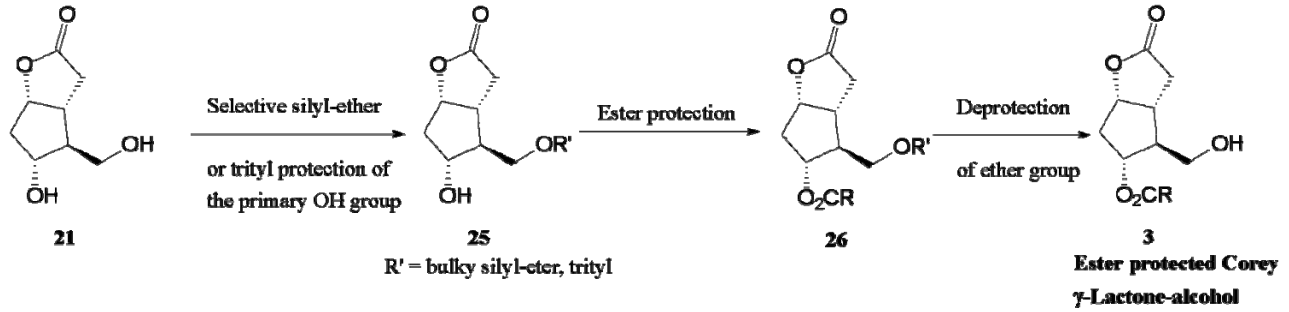


Scheme 7 – Transformation of δ-lactone-esters **17** to chloroester **22**, protection of secondary alcohol as ether and hydrolysis to γ-lactone-alcohol **24** protected at the secondary alcohol as ether:
22a). **17a**, MeOH-CH_2Cl_2, 1:1, TsOH, 2 days, quantitative; **22b**). **17b**, MeOH-CH_2Cl_2, 1:1, TsOH, 2 days, 94.5%, $[\alpha]_D$= +21.15° (c=1% in THF); **22c**). (±)-**17c**, MeOH-CH_2Cl_2, 1:1, TsOH, 2 days, 68.6%; **23a-TBDMS**). **22a**, TBDMSCl, imidazole, CH_2Cl_2, quantitative, $[\alpha]_D$ = +30.49° (c=1% in THF); **23a-THP**). **23a**, DHP, TsOH, CH_2Cl_2, quantitative; **23b-THP**). **23b**, DHP, TsOH, CH_2Cl_2, quantitative, $[\alpha]_D$= +18.10° (c=1% in THF); **24-TBDMS**). **23a-TBDMS**, 2.5 equiv. NaOH, MeOH-H_2O, then H^+, 92.9%*, mp 68.6-70.4°C, $[\alpha]_D$= +56.12° (c= 1% in THF); **24-THP**). **23a-THP**, the same conditions, 93.4%, $[\alpha]_D$= 36.20° (c=1% în THF); **24-THP**). **23b-THP**, the same conditions, 83.5%; * Purified product.

Taking into account the fact that we ultimately want to obtain Corey alcohol **24** protected at the secondary alcohol with an ether protecting group, we consider that it is most convenient at this stage to protect the secondary alcohol with an ether-, silyl-ether, trityl- or substituted trityl-ether group (it is worth mentioning that in this case almost all kinds of ether protecting groups could be used). Afterwards, basic hydrolysis of the methyl-ester group simultaneous with that of the benzoate group can be safely realized. These two reactions are realized as part of the reaction sequence for prostaglandin synthesis from intermediate **24** (Scheme 8):



Scheme 8 – Reaction sequence in prostaglandin synthesis from γ-lactone-alcohol **24** to the desired diol intermediate **d**.



Scheme 9 – Selective transformation of γ-lactone-diol **21** to Corey γ-lactone intermediate **3**.
25a). **21**, 1.1 equiv. TBDMS-Cl, imidazole, CH_2Cl_2, r.t. TLC monitoring, 94.5% **25a**; **25b**). **21**, 1.1 equiv. trityl chloride, Py- CH_2Cl_2, overnight, 93% **25b**; **26(R=C_6H_5, R^1=TBDMS)**). **25-TBDMS**, C_6H_5COCl, DMAP, Py-toluene, 92%*, mp 74.2-74.8°C, $[\alpha]_D$ = +80.95° (c=1% în THF); **3(R = C_6H_5)**). **26(R=C_6H_5, R^1=TBDMS)**, $CuCl_2.2H_2O$[12a] in acetone-water, 55°C, overnight, 92.4%*, 116.6-118.8°C, $[\alpha]_D$ = +107.30□°c=1% in THF); * Purified product.

Compounds **24** have the protection required for the following steps in the prostaglandin synthesis: ω-side-chain building, easy deprotection of the ether group in the presence of a keto-group and stereoselective reduction of the enone group (compound **c**) to the 15-α-OH group of compound **d**.

It is also very important that the intermediate chloro-esters **23** have the functional groups protected so that it is easy to realize a different reaction on each of the four functional groups of the molecule; the same is applicable to chloro-ester **22**. Therefore, these intermediates are valuable building block in fine organic synthesis, not only in prostaglandin synthesis, but also in other directions, like carbocyclic nucleoside or natural product synthesis.

An almost quantitative transformation of δ-lactone-alcohol **1** to γ-lactone-diol **21** was presented in Scheme 5. Due to this fact, it is **desirable** to use γ-lactone-diol **21** for obtaining the same ester protected γ-lactone-alcohol **3** (Scheme 9) as the one obtained by Corey[4] and Veselly.[5]

Three steps are required to achieve this goal, all "in the direction of" the sequence used in the prostaglandin synthesis. The first step is the most important because it needs a selective protection of the primary alcohol group with a bulky silyl-ether protecting group[9a,10] or a trityl group.[9a]

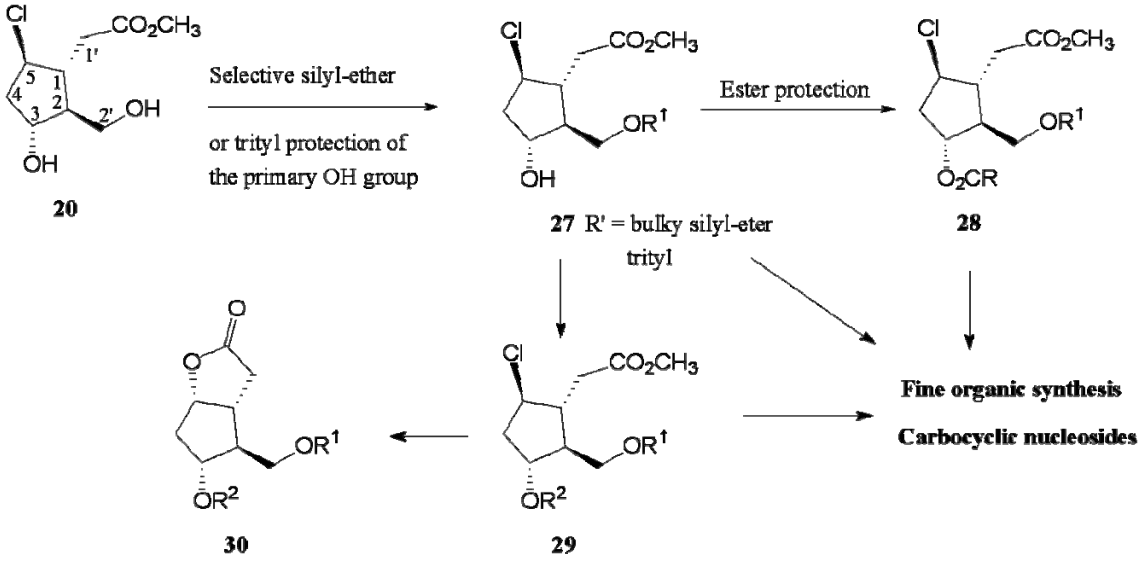
We realized for example, selective protection of the primary alcohol group with TBDMS Cl in 94.5% yield[9a] and with trityl chloride in 93% yield, similar to that reported in the literature.[10]

The next two steps, **25→26→3**, are cleanly performed by the procedure mentioned in the literature: a) ester protection of the secondary hydroxyl group[11] and b) deprotection of the silyl-ether[12] or ether group.[13]

It is worth mentioning that the same steps are also used in the Corey or Vessely procedures for obtaining γ-lactone alcohol **3**, but ether- or alkyl-ester protection of the primary alcohol was realized on the δ-lactone alcohol **1**; the last two steps, in which the protection is changed from the primary alcohol to the secondary alcohol, are the same for the Corey procedure and they are similar in the Veselly procedure (in the latter procedure the alkylester protected primary alcohol is changed for an aromatic acid secondary ester protecting group) (Scheme 9).

As in the case of γ-lactone **21**, it is challenging to deal with chloroester **20**, because it is necessary to discriminate between the primary and secondary hydroxyl groups; the problem was resolved in the same way: protection of the primary hydroxyl group with a bulky silyl-ether protecting group,[9a,10] (very good results were obtained with the cheapest TBDMS group) or a trityl group.[9a] (Scheme 10).

By silylation with TBDMS chloride, the bis-hydroxy-chloroester **20** was selectively silylated to the primary hydroxyl group, the mono-silylated **27a** being obtained in 94% yield after column chromatography purification. Compound **29a**, with greater mobility on the elution, was also isolated in ~ 5% yield; this was formed by later silylation of the secondary hydroxyl group of compound **27a**. The same mono-protection of the primary hydroxyl group of **20** was realized with trityl chloride: 85% isolated yield of mono-trityl-compound **27b** and 6.5% isolated yield of bis-triyl protected derivative **29b**. Mono-protected silyl- or trityl derivatives **29** could easily be afterwards protected with an ester group, as in **28** (for ex. with benzoate) or with an ether [like THP, **30c** (R^1 = TBDMS, R^2 = THP)], trityl [like **30d** (R^1 = TBDMS, R^2 = Tr)] or with a silyl-ether protecting group, the same or different from that existing in **29**, to compounds **30**. Of course, the protection of both hydroxyl group with the same protecting group could be easy realized in the same step with excess reagent.



Scheme 10 – Selective functionalization of of primary and seconday hydroxyl groups.
27a and **29a**). **20**, 1.1 equiv. TBDMS-Cl, imidazole, CH_2Cl_2, r.t. TLC monitoring, 94% **27a**, $[\alpha]_D$ = +22.26° (c=1% in THF), ~5% **29a**; **27b** and **29b**). **20**, 1.1 equiv. trityl chloride, Py- CH_2Cl_2, overnight, 85% **27b**, $[\alpha]_D$ = +14.63° (c=1% in THF), 6.5% **29b** $[\alpha]_D$ = +21.67° (c=1% in THF); **29c** (R^1 = TBDMS, R^2 = THP)). **27a**, DHP, TsOH.Py, CH_2Cl_2, overnight, 82%*, $[\alpha]_D$= + 27.79° (c=1% in THF); **29d** (R^1 = TBDMS, R^2 = trityl)). **27a**, trityl chloride, Py-CH_2Cl_2, overnight, 96%*, $[\alpha]_D$= +20.96° (c=1% in THF).

Bis-ether-, silyl-ether or trityl protected compounds **29** are easily transformed in the corresponding Corey γ-lactone alcohol **30**.

Through the procedures presented in this article we have obtained a series of chlorooesters, **22**, **23**, **27** and **28**, as racemic and also as enantiomeric pure compounds, with specific and different functionalization of the four groups attached to the cyclopentane skeleton. The chlorooesters are useful as synthons in natural product synthesis, carbocyclic nucleosides synthesis and in fine organic synthesis.

EXPERIMENTAL

IR spectra were recorded on a FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequencies are expressed in cm^{-1}, with the following abbreviations: w = weak, m = medium, s = strong, v = very, br = broad. ^{1}H-NMR and ^{13}C-NMR spectra are recorded on Varian Gemini 300 BB spectrometers (300 MHz for ^{1}H and 75 MHz for ^{13}C), chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling were done for correct assignment of NMR signals. The numbering of the atoms in compounds is presented in Schemes 7 and 12. Progress of the reaction was monitored by TLC on Merck silica gel 60 or $60F_{254}$ plates (Merck) eluted with the solvent system presented for each compound. Spots were developed with sulfuric acid (15% in ethanol). The numbering of atoms is given in Schemes. In Schemes, the structure is given for natural (or racemic) compounds, though the examples presented below were chosen for the enantiomer serie. A few examples for synthesis of the compounds are given below.[9a]

Methyl (5-Chloro-3-hydroxy-2-hydroxymethyl-cyclopentyl)-acetate, **(20)**.

106.75 g (0.56 M) enantiomer-**1** were dissolved in 450 mL methanol, 7.5 g Amberlit IRC-50Wx2 (H form) cation exchange resin added and refluxed until the disappearance of the starting compound on TLC (ethyl acetate-hexane-acetic acid, 5:1:0.1, $R_{f\ in}$ = 0.52, $R_{f\ fin}$ = 0.42). The resin was filtered off, washed with 2x50 mL methanol, 2 mL pyridine were added to the filtrate and methanol was distilled under vacuum. The residue was taken in 500 mL CH_2Cl_2, the solution was washed with 100 mL sat. sol. $NaHCO_3$, dried and concentrated, resulting 125.7 g product (in quantitative yield). 1g Product was purified by pressure chromatography on silica gel, resulting 0.96 g pure product ***ent*-20** (X = Cl) as oil, $[\alpha]_D$ = +45.50º(c=1% in THF), $[\alpha]_D$ = +44.63º(c=1% in MeOH), ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 4.29 (dt, 1H, H-3, 5.0, 6.6); 4.13 (q, 1H, H-5, 8.0); 3.77 (dd, 1H, H-2', 4.9, 11.0); 3.71 (s, 3H, CH_3); 3.63 (dd, 1H, H-2', 6.6, 11.0); 2.76 (dd, 1H, H-1', 4.4, 16.5); 2.49 (dd, 1H, H-1', 8.0, 16.5); 2.27 (dd, 1H, H-4, 5.0, 13.7); 2.21 (m, 1H, H-1); 2.17 (ddd, 1H, H-4, 6.6, 8.0, 13.7); 1.76 (m, 1H, H-2, 6.6), ^{13}C-NMR ($CDCl_3$, δ ppm): 173.59 (COO), 73.34 (C-3); 63.24 (C-2'); 60.82 (C-5); 52.01 (C-2); 52.14 (*C*H_3); 46.48 (C-1); 43.95 (C-4); 36.20 (C-1').

3-Cloro-5-hydroxy-2-methoxycarbonylmethyl-cyclopentylmethyl benzoate, **(22)**.

136.45 g (0.46295 M) enantiomer-**17** (X = Cl) were dissolved in 580 mL CH_2Cl_2 and 580 mL methanol, 2.8g TsOH were added and the solution was stirred for 2 days at r.t. monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1; $R_{f\ in}$ = 0.72, $R_{f\ fin}$ = 0.62; twice eluted: $R_{f\ in}$= 0.80, $R_{f\ fin}$= 0.72). The acid was neutralized with 4 g solid $NaHCO_3$, the reactiom mixture was concentrated under vacuum, the concentrate was taken in 600 mL CH_2Cl_2, the solution was washed with sat. sol. $NaHCO_3$ (2x200mL), brine (100mL), dried (Na_2SO_4 anh.), filtered and concentrated. (Aqueous phases were extracted with 2x200 mL CH_2Cl_2). 151.5 g Crude oily product was obtained, ***ent*-22** (X = Cl) (in almost

quantitative yield); 1 g of crude product was purified by pressure chromatography on silica gel (eluent: hexane-ethyl acetate, 5:2), resulting 0.994 g pure product, ***ent*-22** (X = Cl), as oil, $[\alpha]_D$ = +24.16º(c=1% in THF), IR: 3464brm, 2953m, 1716vs, 1473m, 1442m, 1439m, 1379w, 1315w, 1269vs, 1197m, 1176m, 1113s, 1069m, 1026m, 710s, ^{1}H-NMR-300MHz($CDCl_3$, δ ppm, *J* Hz): 8.04(dd, 2H, H-*o*, 1.4, 7.4); 7.59(tt, 1H, H-*p*, 1.4, 7.4); 7.46(t, 2H, H-*m*, 7.4); 4.49(dd, 1H, H-2', 5.2, 11.3); 4.33(dd, 1H, H-2', 6.0, 11.3); 4.31-4.24(m, 2H, H-3,5); 3.69(s, 3H, CH_3); 2.72(dd, 1H, H-1', 5.8, 16.2); 2.65(dd, 1H, H-1', 6.3, 16.2); 2.39-2.10(m, 4H, 2H-4, H-1, H-2), ^{13}C-NMR-75MHz($CDCl_3$, δ ppm): 172.52(COO), 166.71(PhCO); 133.39(C-*p*); 129.90(C-*q*); 129.75(C-*o*); 128.65(C-*m*); 73.32(C-3); 65.03(C-2'); 60.37(C-5); 52.01(C-2); 51.90(CH_3); 47.44(C-1); 44.38(C-4); 35.87(C-1').

5-hydroxy-4-hydroxymethyl-hexahydro-cyclopenta[b]furan-2-one, **(21)**.

50 mmoles enantiomer Chloroester **20** dissolved in 135 mL methanol were treated with a solution of 2.5 equivalents (5.0 g, 125 mmoles) NaOH in 32 mL water, monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1; $R_{f\ in}$ = 0.62, $R_{f\ fin}$ = 0.00). After all starting compound **20** reacted, methanol was removed at reduced pressure, the aqueous solution was acidulated with conc. HCl to pH ~4, stirred for 2 hours, concentrated to remove water, co-evaporated with ethanol and the product was extracted with hot ethanol. Crude product (9.2 g) was crystallized from ethanol and had physical characteristics identical with those published:[3,14] m.p. 118-121°C (acetone), $[\alpha]_D$ = +43.5º(c=1% in MeOH), [lit.[3]: m.p.115-117.5°C, $[\alpha]_D$ = +43.6º(c=1% in MeOH)], $[\alpha]_D$ = +51.6º(c=1% in THF), IR: 3356vs, 2938m, 2888w, 1733s, 1408w, 1371m, 1354w, 1325w, 1300w, 1202ms, 1095w, 1071w, 1055w, 1033m, 1016w, 993w, 966m, ^{1}H-RMN (DMSO-d_6 δ ppm, *J* Hz): 4.86 (dt, 1H, H-5a, 2.2, 6.9); 3.90 (q, 1H, H-5, 5.5); from HETCOR, 3.38 (dd, 1H, H-4', 5.8, 11.0); 3.27 (dd, 1H, H-4', 6.6, 11.0); 2.78 (dd, 1H, H-3, 10.4, 17.9); 2.62 (dddd, 1H, H-3a, 2.7, 4.1, 6.6, 10.4); 2.37 (dd, 1H, H-3, 2.7, 17.9); 2.15 (ddd, 1H, H-6, 6.6, 12.6, 14.6); 1.80-1.70 (m, 2H, H-4, H-6); ^{13}C-RMN (DMSO-d_6 δ ppm): 177.38 (C-2); 83.88 (C-6a); 72.81 (C-5); 61.18 (C-4'); 56.11 (C-4); 40.24 (C-3a); 39.36 (C-6); 35.48 (C-3).

Methyl [2-(tert-Butyl-dimethyl-silanyloxymethyl)-5-chloro-3-(tetrahydro-pyran-2-yloxy)-cyclopentyl]-acetate, **(29c)**.

To a solution of 3.51 g (10 mM) *ent*-**27a** in 40 mL CH_2Cl_2, 100 mg TsOH.Py were added and then 1.06 mL dihydropyran were added dropwise. The solution was stirred overnight, monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ in}$ - 0.65, $R_{f\ fin}$= 0.82). 40 mL Sat. soln. $NaHCO_3$ were added, phases were separated, organic phase was washed with water (50 mL), dried, concentrated and crude product (4.44 g) was purified by pressure chromatography (eluent: hexane-ethyl acetate, 5:1). 3.57 g (82.07%) Pure product **29c** resulted as oil, $[\alpha]_D$= + 27.79° (c=1% in THF), IR: 2950vs, 2900m, 2857s, 1739vs,1469w, 1438m, 1386w, 1351w, 1254s, 1200m, 1179m, 1154m, 1116s, 1077vs, 1034s, 1029s, 970m, 868w, 833vs, 813m, 776s, ^{1}H-RMN-400MHz ($CDCl_3$, δ ppm, *J* Hz): 4.60 (m, 1H, H-1"); 4.18-4.06 (m, 2H, H-3, H-5); 3.84 (m, 1H, H-5"); 3.75 (dd, 0.5H, H-2', 4.5, 10.2); 3.69 (dd, 0.5H, H-2', 4.5, 10.2); 3.68 (s, 3H, CH_3); 3.60 (dd, 0.5H, H-2', 4.7, 10.2); 3.52 (dd, 0.5H, H-2', 6.2, 10.2); 3.48 (m, 1H, H-5"); 2.64 (dd, 0.5H, H-1', 5.9, 15.0); 2.63 (dd, 0.5H, H-1', 6.0, 14.8); 2.53 (dd, 0.5H, H-1', 6.8, 14.8); 2.48 (dd, 0.5H, H-1', 7.4, 15.0); 2.40-1.83 (m, 4H, 2H-4, H-1, H-2); 1.82-1.64 (2m, 2H, H-2"-4"); 1.63-1.45 (m, 4H, 2H-3", H-2", 4"); 0.90 (s, 9H, CH_3C); 0.06; 0.05(2s, 6H, CH_3Si); ^{13}C-RMN-100MHz ($CDCl_3$, δ ppm): 172.56; 172.50 (COO); 98.38, 96.77 (C-1''); 78.14, 76.21 (C-3); 63.45, 63.04 (C-5''); 62.92, 62.25 (C-2'); 61.67, 61.53 (C-5); 53.14, 52.85 (C-2); 51.58; 51.54 (CH_3); 46.48, 46.34 (C-1); 43.06, 41.49 (C-4); 37.10, 36.72 (C-1'); 31.14, 30.92 (C-4"); 25.89 (CH_3C); 25.45, 25.43 (C-3"); 20.00, 19.41 (C-2"); 18.26 (CCH_3); -5.50, -5.53 ($2CH_3$Si).

Methyl [2-(tert-Butyl-dimethyl-silanyloxymethyl)-5-chloro-3-trityloxy-cyclopentyl]-acetate, **(29d)**.

To a solution of 3.581 g (10.86 mM) *ent*-**27a** and 117 mg DMAP in 80 mL CH_2Cl_2 and 10 mL pyridine, 5.35 g 95% trityl chloride were added in portions. The solution was stirred overnight, monitoring the reaction by TLC (hexane-ethyl acetate-acetic acid, 5:2:0.1, $R_{f\ in}$ - 0.27, $R_{f\ fin}$= 0.69). The reaction mixture was poured on 50 mL sat. soln. $NaHCO_3$ and ice, stirred 1 h, phases were separated, organic phase was dried, concentrated, co-evaporated with toluene and the crude product (9.16 g) was taken in hot heptane and cooled on ice-water bath. Trityl alcohol was filtered, filtrate was concentrated, resulting 6.43 g oily product which was similarly purified by pressure chromatography (eluent: hexane-ethyl acetate, 5:1). 6.04 g (96%) Pure product **29d** resulted as oil, $[\alpha]_D$= + 20.96° (c=1% in THF), IR: 3087w, 3060w, 3026w, 2952s, 2930s, 2886m, 2856s, 1738vs, 1491 w, 1469w, 1446m, 1360w, 1252s, 1179m, 1152m, 1117m, 1080s, 1025s, 984w, 910w, 833s, 811w, 774s, 762s, 746m, 700vs, 631m, ^{1}H-RMN-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.49-7.26 (m, 15H, H-Tr); 4.19 (dt, 1H, H-3, 6.7, 9.8); 4.01 (m, 1H, H-5); 3.72 (s, 3H, CH_3); 3.46 (dd, 1H, H-2', 3.6, 9.9); 3.41 (dd, 1H, H-2', 4.7, 9.9); 2.73 (dd, 1H, H-1', 5.8, 14.8); 2.60 (dd, 1H, H-1', 7.4, 14.8); 2.26 (m, 1H, H-4,); 2.04 (m 1H, H-1); 1.44 (dd, 1H, H-4, 4.9, 10.4); 0.96 (m, 1H, H-2); 0.85 (s, 9H, CH_3C); -0.11; -0.07 (2s, 6H, CH_3Si), ^{13}C-RMN-75MHz ($CDCl_3$, δ ppm): 172.74 (COO); 144.82 (C-*q*); 129.04 (C-*m*); 127.95 (C-*o*); 127.26 (C-*p*); 87.48 (C-tritil); 75.75 (C-3); 63.22 (C-2'); 62.12 (C-5); 54.05 (C-2); 51.64 (CH_3); 46.48 (C-1); 43.60 (C-4); 37.28 (C-1'); 25.93 (CH_3C); 18.27 (CCH_3); -5.49; -5.56 ($2CH_3$Si).

CONCLUSIONS

We have realized an efficient two-step procedure for transforming the protected (especially as benzoate or substituted benzoate group) δ-lactone alcohol **17** in γ-lactonalcohol Corey **24**, substituted as ether at the secondary alcohol group. An efficient procedure for transforming protected (especially as benzoate or substituted benzoate group) δ-lactone alcohol **17** in γ-lactonalcohol Corey **24**, substituted as ether at the secondary alcohol group was realized in two steps. By the same procedure, δ-lactone alcohol **1** was transformed in γ-lactonalcohol Corey **21**.

Unprotected chloroester **20**, like γ-lactonalcohol Corey **21** was selectively protected with bulky silylether or trityl group at the primary alcohol group and transformed into the known Corey γ-lactone alcohol **3**, protected with an aromatic ester group at the secondary alcohol.

Chloroester intermediates **22**, **23**, **27**, **28** and **29** have different substitutions on the functional groups, so individual reactions can be carried out efficiently on every one of the four groups.

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