Transeterification of the Intermediate Chloro-ester Compounds in the Sequence for Obtaining Corey Aldehyde Protected as Cyclic Acetals

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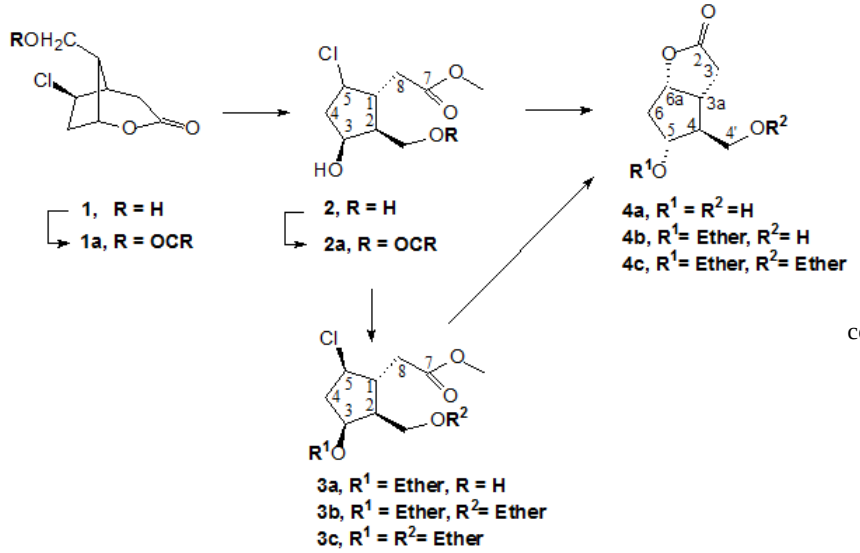
*Transesterification of the TBDMS-bis-protected compounds **10-1a** and **10-2a** with K_2CO_3 in methanol takes place with the cleavage of the secondary TBDMS group to compounds **13-1** and **13-2**. The same compounds were obtained as proof of the transesterification of the bis-benzoate compounds **10-1b** and **10-2b**. In case of bis-THP protected compounds **10-1c** and **10-2c**, the secondary THP group, stable in base conditions, was expected not to be removed in transesterification conditions, resulting the compounds rezultind compusii **13-1c** and **13-2c.***

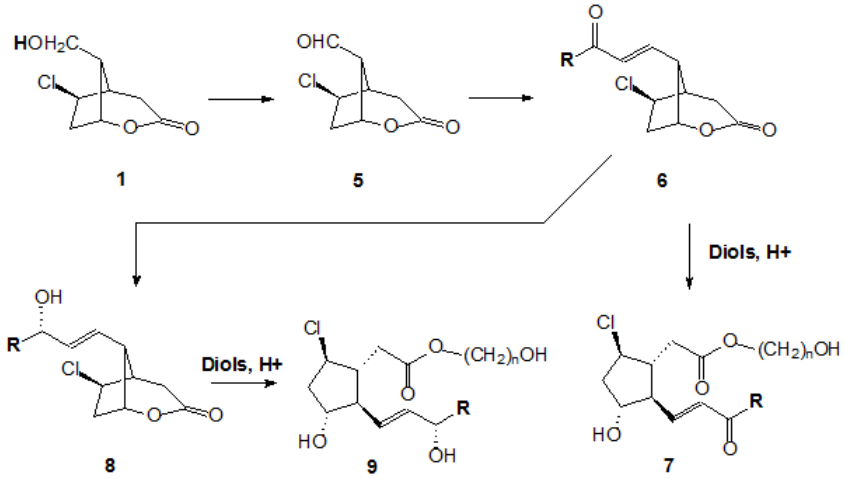
Keywords: transesterification, δ-lactone, TBDMS deprotection, 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl acetalization, ester methanolysis

In some previous papers [1, 2] we presented an efficient procedure for opening a δ-lactone starting from compound **1** to a chloroester intermediate **2** in an acid alcoholysis (MeOH, EtOH). By using the ester protected compound **1a**, for example with a benzoate group, the acid opening ($TsOH \cdot H_2O$) of the δ-lactone group with methanol in the presence of an inert solvent like CH_2Cl_2 was realized exclusively to the benzoate protected compound **2a**. It is to be mentioned that chloroesters **2a**, **3a**-**3c** are selectively protected to the hydroxyl groups (scheme 1), increasing the possibility for their use in other chemical fields. At the same time, the chloroesters are used in the direction of the synthesis of Corey intermediates **4** with the requested protection of the hydroxyl groups.

We used then the opening of a δ-lactone group of different prostaglandin key intermediates **6** and **8**, in which the ω-side chain was already built. Now we replaced methanol or ethanol alcohols with diols from ethylene glycol to 1,6-hexane diol and also 1,4-butynediol in acid catalysis, obtaining new prostaglandin analogues [3, 4] also in efficient yield (scheme 2).



Scheme 1. The opening of δ-lactone starting compounds **1** and **1a** with methanol or ethanol alcohols in acid catalysis.



Scheme 2. The opening of the δ-lactone key intermediates **6** and **8** with diols in acid catalysis for obtaining new prostaglandin analogues

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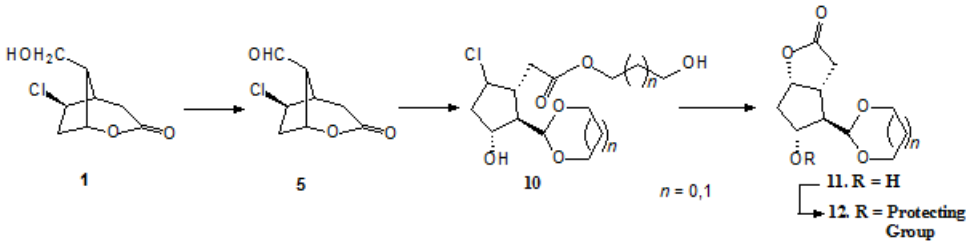
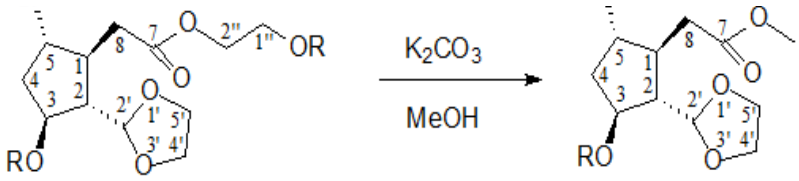


Scheme 3. The opening of the δ-lactone group of aldehyde compound **5** with ethylene glycol and 1,3-propanediol in acid catalysis, concomitant with cyclic acetalization of the aldehyde group.



10-1 a) R = TBDMS
b) R = Bz
c) R = THP

13-1, R = H
13-1c, R = THP

Scheme 4. Transesterification of the compounds **10-1** with 2.5 equiv. K_2CO_3 in methanol

Then a few diols (ethylene glycol and 1,3-propanediol) were used for the opening of the δ-lactone group of aldehyde **5**, generating the corresponding esters, concomitant with the cyclic acetalization of the aldehyde [5] to the intermediates **10**; finally, the base hydrolysis of the ester and subsequent SN2 substitution of the chlorine atom by the carboxylate ion, generate the formation of the γ-lactone Corey compound **11**, in which the cyclic acetalization to a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl is kept from the previous step [6].

Results and discussions

In the present paper, we report some transformations on the compounds **10**, obtained by opening of the δ-lactone group of aldehyde **5** simultaneously with the cyclic acetals of the aldehyde function by using ethylene glycol and 1,3-propanediol in acid catalyzed reaction.

Compounds **10** were protected at both primary hydroxyl group as well as at the secondary hydroxyl groups with TBDMS, THP and benzoate groups [6]. All compounds were synthesized by current procedures [5] and were obtained as oils after they were purified by pressure chromatography.

In the literature we observed that a compound, with a vicinal methyl acetate and a *cis* hydroxyl protected as benzoate, by transesterification of the benzoate group with K_2CO_3 in MeOH (60 h at r.t., N_2) gave a clean reaction for closing a γ-lactone ring in 85% yield [7]. The compounds **10-1** and **10-2**, presented in scheme 4 and 5, are similar behavior in the reaction with NaOH or KOH bases in methanol-water with closing γ-lactone ring 1, 2, 5]. We now wanted to observe the reaction of the compounds **10-1** and **10-2** with K_2CO_3 in MeOH in the conditions presented in literature [7].

In this direction we studied first the transesterification reaction of the bis-TBDMS protected compound **10-1a**, using 2.5 equivalents K_2CO_3 in methanol and, according to TLC, the reaction was clearly ended in 2.5 h. to a product. After isolation and purification, this compound did not present the signals of the protecting TBDMS group either in ^{1}H- or in ^{13}C-NMR. This means that in the reaction conditions, the secondary TBDMS protected hydroxyl was deprotected, concomitant with the transesterification of the 2-ethoxy-1-tert-butyldimethylsilyloxy fragment to the methyl ester.

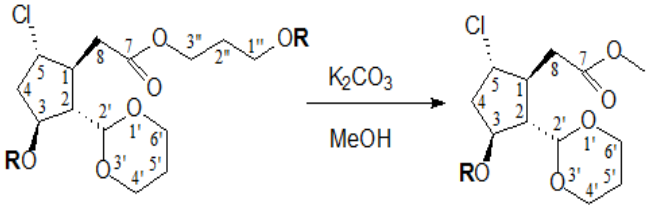
Afterwards, we performed the same reaction with the bis-benzoate protected compound **10-1b** and obtained the same compound **13-1**. In this case, in the transesterification reactions, we can clearly observe both the formation of the methyl ester as before as well as the deprotection of the secondary benzoate group.

When we used the bis-THP compound **10-1c** in the reaction, we obtained compound **13-1c**, in which the secondary THP group is preserved; in this case, the THP group is well known to be stable under base conditions (scheme 4). In the purification of the compounds by pressure chromatography, the usual product 2-tetrahydropyranyloxy-1-ethanol, from the trans-esterification of the (tetrahydro-2H-pyran-2-yl)oxy)ethyl fragment, was also isolated and characterized by ^{1}H- and ^{13}C-NMR.

In an experiment with a longer reaction (7 days), we observed that the compound **13-1c** remains in 40% isolated yield. But in the same time, about 51.5% of the initial compound was hydrolyzed and isolated as the Corey type compound **12** [5] (scheme 3, n = 1, R = THP), this behavior being similar with that presented in the literature [7].

In the case of compounds **10-2**, having a 1,3-dioxane protection of the aldehyde, we observed the same situation presented above for compounds **10-1**. The TBDMS group was deprotected in the same conditions of trans-esterification and the reaction product **13-2** was cleanly obtained as the only compound. The deprotection of the TBDMS group in base conditions is mentioned in the literature in a few cases, for deprotection of *tert*-butyldimethylsilyl-phenols [8] and also of alkyl alcohols [9]. We used in the transesterification reactions also Corey LAC bis-protected as TBDMS, but it was not unprotected in the reaction conditions presented above.

The bis-benzoate protected compound **10-2b** was also transformed to the compound **13-2** by a double transesterification of the secondary benzoate and of the alkyl ester benzoate. The bis-THP protected compound **10-2c** is transformed to the mono-THP methyl ester compound **13-2c** (scheme 5) (the THP group being expected not to be removed), similarly as realized for the compound **10-1c**.



10-2 a) R = TBDMS
b) R = Bz
c) R = THP

13-2, R = H
13-2c, R = THP

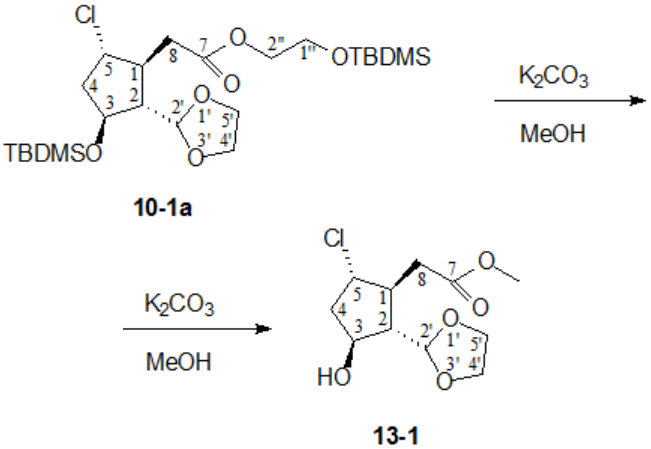
Scheme 5. Transesterification of the compounds 10-2 with 2.5 equiv. K_2CO_3 in methanol

It is to be mentioned that all compounds **10-1a,b** and **10-2a,b**, in reaction with 2.5 equivalents K_2CO_3 in methanol for only 2.5 h., gave cleanly the compounds **13-1** and **13-2**, with the deprotection of the secondary TBDMS or benzoate protecting groups. The protected THP group, in compounds **13-1c** and **13-2c**, is resistance in the corresponding transesterification conditions. The compounds **13-1** and **13-2** and **13-1c** and **13-2c** are new compounds.

Experiemntal part

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}CNMR spectra are recorded on Varian Gemini 300 BB spectrometer (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 4 and 5. Progress of the reaction was monitored by TLC on Merck silica gel 60 plates (Merck) eluted with the solvent system presented for each compound. Spots were developed with sulfuric acid (15% in ethanol). In the present paper the pure enantiomer compounds were used.

Transesterification of compounds 10-1a with K_2CO_3 in methanol

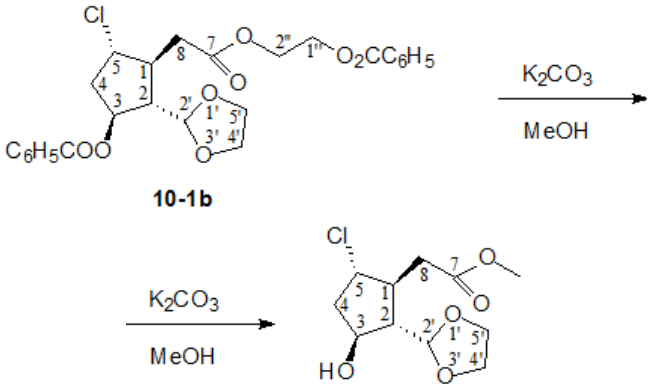


10-1a

13-1

To 330 mg (0.63 mmoles) compound **10-1a**, 2-((tert-butyldimethylsilyl)oxy)ethyl 2-((1S,2S,3S,5S)-3-((tert-butyldimethylsilyl)oxy)-5-chloro-2-(1,3-dioxolan-2-yl)cyclopentyl)acetate, in 7 mL methanol 225 mg (1.58 mmoles) K_2CO_3 were added and the mixture was stirred for 2.5 h monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ 10\text{-}1a}$ = 0.87, $R_{f\ 13\text{-}1}$ = 0.40). The mixture was diluted with 30 mL dichloromethane and 20 mL water, stirred 5 min., the phases were separated (aqueous phase extracted with 30 mL dichloromethane), organic phase washed with 20 mL brine, dried (Na_2SO_4), concentrated and the crude product was purified by pressure chromatography on silica gel (eluent: hexane-ethyl acetate, 3:2), resulting 155 mg (93.0 %) of pure product methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxolan-2-yl)-3-hydroxycyclopentyl)acetate **13-1** as oil, $[\alpha]_D$= +41,5° (c = 1% in $CHCl_3$), IR: 3455 br m, 2953m, 2891m, 1729vs, 1438m, 1397w, 1278s, 1228m, 1195m, 1178m, 1149s, 1086s, 1025s, 987m, 948m, ^{1}H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz):); 4.86 (d, 1H, H-2', 4.9), 4.25 (brq, 1H, H-3, 4.7), 4.17 (brq, 1H, H-5, 8.0), 3.96-3.77 (m, 4H, 2H-4', 2H-5'), 3.62 (s, 3H, CH_3O), 2.60 (dd, 1H, H-8, 6.0, 16.0), 2.54 (dd, 1H, H-8, 5.8, 16.0), 2.33 (ddt, 1H, H-1, 5.8, 6.0, 8.5), 2.19 (ddd, 1H, H-4, 4.7, 7.1, 13.7), 2.09 (ddd, 1H, H-4, 6.6, 8.2, 13.7), 1.92 (dt, 1H, H-2, 4.9, 8.5), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 172.77 (C-7), 104.99 (C-2'), 71.71 (C-3), 65.30, 65.03 (C-4', 5'), 60.72 (C-5), 55.13 (C-2), 51.82 (3H, CH_3O), 46.06 (C-1), 43.98 (CH_2, C-4), 35.97 (CH_2, C-8).

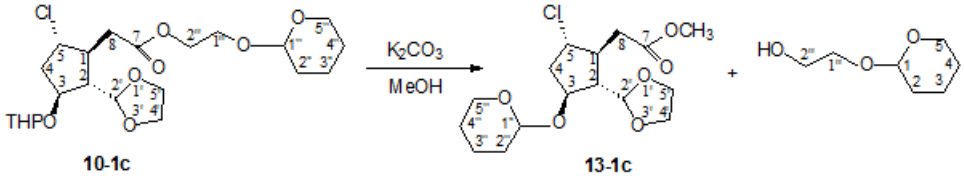
Transesterification of compounds 10-1b with K_2CO_3 in methanol



10-1b

13-1

850 mg (1.7 mmoles) 2-(2-((1S,2S,3S,5S)-3-(benzoyloxy)-5-chloro-2-(1,3-dioxolan-2-yl)cyclopentyl)acetoxy)ethyl benzoate **10-1b** were dissolved in 13 mL anh. methanol, 586.5 mg (4.25 mmoles) K_2CO_3 were added and the mixture was stirred at r.t. for 2.5 h, monitoring the reaction by TLC (silica gel, ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ 10\text{-}1b}$ = 0.85, $R_{f\ 13\text{-}1}$ = 0.39). Then 50 mL dichloromethane and 30 mL water were added, phases separated (aqueous phase was extracted with 50 mL dichloromethane), organic phase washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure by rotavapor and the crude product (794 mg) was purified by pressure chromatography (silica gel, eluent: hexane-ethyl acetate, 3:2), resulting a pure fraction of 315.3 mg (70.07 %) pure compound methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxolan-2-yl)-3-hydroxycyclopentyl)acetate, **13-1**, as oil (a slightly impure fraction of 75 mg was also obtained), $[\alpha]_D$= +41.0° (c = 1% în $CHCl_3$), IR: 3478br vs, 2987m, 2955m, 2892s, 1733vs, 1439m, 1410m, 1332m, 1303m, 1271m, 1227m, 1195m, 1178m, 1087m, 1028m, 985w, 953m, ^{1}H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz):); 4.86 (d, 1H, H-2', 4.9), 4.25 (dt, 1H, H-3, 4.7, 6.6), 4.17 (brq, 1H, H-5, 7.7), 3.96-3.80 (m, 4H, 2H-4', 2H-5'), 3.63 (s, 3H, CH_3O), 2.60 (dd, 1H, H-8, 6.0, 16.0), 2.54 (dd, 1H, H-8, 5.8, 16.0), 2.33 (ddt, 1H, H-1, 5.8, 6.0, 8.5), 2.20 (ddd, 1H, H-4, 4.7, 7.1, 13.7), 2.10 (ddd, 1H, H-4, 6.6, 8.2, 13.7), 1.92 (dt, 1H, H-2, 4.9, 8.5), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 172.79 (C-7), 105.04 (C-2'), 71.75 (C-3), 65.33, 65.06 (C-4', 5'), 60.74 (C-5), 55.18 (C-2), 51.83 (CH_3O), 46.12 (C-1), 44.00 (CH_2, C-4), 36.00 (CH_2, C-8).



10-1c **13-1c**

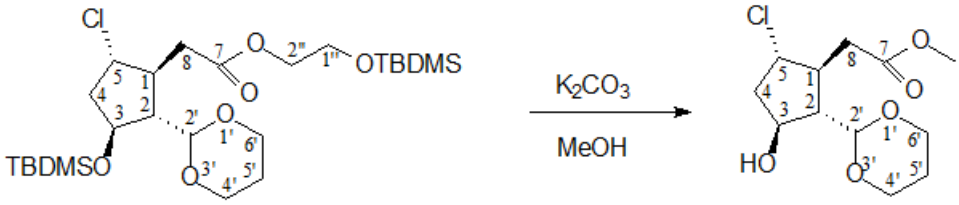
Transesterification of compounds 10-1c with K_2CO_3 in methanol

510 mg (1.1 mmoles) Compound **10-1c**, 2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxolan-2-yl)-3-((tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl)acetate were dissolved in 20 mL anh. methanol, 380 mg (2.75 mmoles) K_2CO_3 were added and the mixture was stirred at r.t. for 2.5 monitoring the reaction by TLC (eluent: ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ 10\text{-}1c}$ = 0.66, $R_{f\ 13\text{-}1c}$ = 0.73). The mixture was diluted with 100 mL dichloromethane and 20 mL water, stirred 5 min., phases were separated (aqueous phase was extracted with 2×60 mL dichloromethane), organic phase washed with 20 mL brine, dried (Na_2SO_4), concentrated and the crude product was purified by pressure chromatography on silica gel (eluent: hexane-ethyl acetate, 3:2), resulting 317 mg (83.0 %) pure compound **13-1c**, methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxolan-2-yl)-3-((tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl)acetate, **13-1c**, as oil, ^{1}H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz) (due to the tetrahydropyranyl group, a chiral atom is introduced and this makes possible to have a mixture of two compounds): 4.96 (d, 0.5H, H-2', 3.0), 4.86 (d, 0.5H, H-2', 3.6), 4.57 (dt, 1H, H-1-THP, 3.0, 6.6), 4.14 (dt, 1H, H-3, 5.8, 6.3), 4.03 (m, 1H, H-5), 3.96-3.72 (m, 5H, 2H-4', 2H-5', H-5''), 3.61 (s, 3H, OCH_3), 3.42 (m, 1H, H-5''), 2.60 (dd, 1H, H-8, 5.8, 14.8), 2.48 (dt, 1H, H-8, 6.7, 14.8), 2.33 (m, 1H, H-1), 2.04 (m, 1H, H-2), 1.98 (ddd, 1H, H-4, 6.3, 10.7, 13.2), 1.85 (ddd, 1H, H-4, 5.8, 11.0, 13.5), ^{13}C-NMR-75MHz ($CDCl_3$, δppm): 172.57, 172.46 (C-7), 103.98, 103.86 (C-2'), 97.39, 96.39 (C-1-THP), 75.59, 74.47 (C-3), 65.30, 65.10 ($2CH_2$, C-4', C-5'), 62.72. 61.98 (C-5''), 61.62, 61.53 (C-5), 53.53, 53.35 (C-2), 51.60, 51.58 (CH_3O), 45.57, 44.89 (C-1), 43.52, 41.51 (C-4), 37.34, 37.28 (C-8), 30.95, 30.75 (CH_2, C-4''), 25.44, 25.41 (CH_2, C-3''), 19.70, 19.19 (CH_2, C-2'').

A pure fraction of the secondary product, ethylene glycol mono-tetrahydropyranyl ether, (R_f = 0.39) was obtained as oil with the same NMR spectrum: ^{1}H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz): 4.51 (m, 1H, H-2', 2.4), 3.86 (m, 1H, H-5'), 3.75-3.61 (m, 4H, 2H-1, 2H-2), 3.47 (m, 1H, H-5'), 1.73 (m, 2H, H-2', H-4'), 1.55-1.44 (m, 4H, H-2', 2H-3', H-4'), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 100.13 (C-2'), 70.68 (C-5'), 63.25, 62.20 (C-1, C-2''), 30.79 (CH_2, C-4'), 25.47 (CH_2, C-3'), 19.99 (CH_2, C-2').

In an experiment with the same quantities, but increasing the time to 7 days, we observed that in the organic phase, after column chromatography purification, were isolated 153 mg (40.0 %) pure compound **13-1c**. The aqueous phases were acidified with 1N HCl to *p*H 4.5-5.5, saturated with solid ammonium sulfate, multiple extracted with dichloromethane (TLC monitoring), organic phases washed with 20 mL brine, dried (Na_2SO_4), concentrated and the crude product (162 mg) was purified by pressure chromatography on silica gel (eluent: hexane-ethyl acetate, 3:2), resulting 155 mg (47.2%) pure Corey type compound **12** [5] (scheme 3, n = 1, R = THP) as oil.

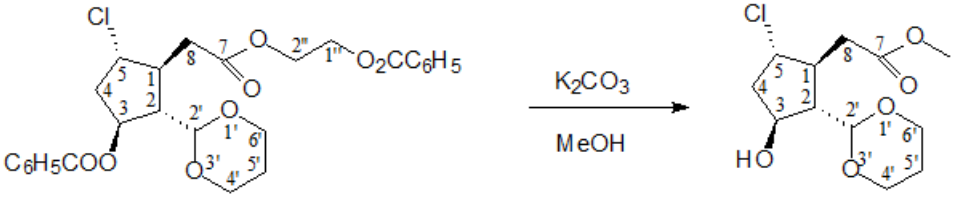
Transesterification of compounds 10-2a with K_2CO_3 in methanol



10-2a **13-2**

420 mg (0.76 mmoles) Compound **10-2a**, 3-((tert-butyldimethylsilyl)oxy)propyl 2-((1S,2S,3S,5S)-3-((tert-butyldimethylsilyl)oxy)-5-chloro-2-(1,3-dioxan-2-yl)cyclopentyl)acetate in 7 mL methanol was treated with 265 mg (1.9 mmoles) K_2CO_3 for 2.5 h as for compound **10-1a**, monitoring the reaction by TLC (ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ 10\text{-}2a}$ = 0.89, $R_{f\ 13\text{-}2}$ = 0.38). After similar work-up and purification of the crude product by pressure chromatography on a silica gel column (eluent: hexane-ethyl acetate, 3:2), 220 mg (84.5%) pure product **13-2** (R = H), methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxan-2-yl)-3-hydroxycyclopentyl)acetate, were obtained as oil, $[\alpha]_D$ = +30,1° (c = 1% in $CHCl_3$), IR: 3463br s, 2968s, 2929m, 2854s, 2732w, 1733vs, 1436m, 1477m, 1387m, 1331m, 1282s, 1194m, 1145s, 1096s, 1046m, 996s, 942w, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 4.54 (d, 1H, H-2', 5.8), 4.29 (dt, 1H, H-3, 5.8, 6.9), 4.10 (q, 1H, H-5, 7.4), 4.04-3.97 (m, 2H, H-4', H-6'), 3.70 (dt, 2H, H-4', H-6', 2.5, 12.4), 3.62 (s, 3H, CH_3O), 2.57 (m, 2H, H-8, 6.0), 2.36 (m, 1H, H-1, 5.8, 6.0), 2.17 (dd, 1H, H-4, 5.8, 13.7), 2.08 (dd, 1H, H-4, 6.9, 13.7), 2.01 (m, 1H, H-5'), 1.77 (dt, 1H, H-2, 5.8, 9.3), 1.28 (br hept, 1H, H-5', 1.4, 13.5), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 172.81 (C-7), 103.28 (C-2'), 71.81 (C-3), 67.01, 66.82 (C-4', 6'), 60.75 (C-5), 56.23 (C-2), 51.76 (CH_3O), 46.27 (C-1), 43.38 (CH_2, C-4), 36.31 (CH_2, C-8), 25.77 (C-5').

Transesterification of compounds 10-2b with K_2CO_3 in methanol

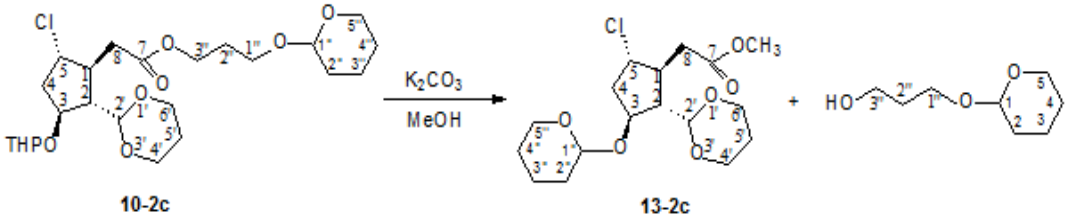


10-2b **13-2**

320 mg (0.607 mmoles) 3-(Benzoyloxy)propyl 2-((1S,2S,3S,5S)-3-(benzoyloxy)-5-chloro-2-(1,3-dioxan-2-yl)cyclopentyl)acetate in 5 mL anh. methanol was treated with 212 mg (1.53 mmoles) K_2CO_3 for 2.5 h as for compound **10-1b**, monitoring the reaction by TLC (silica gel, ethyl acetate-hexane-acetic acid, 5:4:0.1, $R_{f\ 10\text{-}2b}$ = 0.73, $R_{f\ 13\text{-}2}$ = 0.38). After similar work-up and purification of the crude product by pressure chromatography on a silica gel column (eluent: hexane-ethyl acetate, 3:2), a fraction of 127.5 mg (75.4 %) pure product **13-2** (R = H), methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxan-2-yl)-3-hydroxycyclopentyl)acetate were obtained as oil, $[\alpha]_D$ = +29.0° (c = 1% in $CHCl_3$), IR: 3445br m, 2954m, 2929m, 2854m, 2732w, 1733vs, 1436m, 1378m, 1331w, 1281m, 1240m, 1195m, 1144s, 1095s, 1043m, 996s,

942w, [1]H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz): 4.54 (d, 1H, H-2', 6.0), 4.29 (dt, 1H, H-3, 5.8, 6.9), 4.10 (q, 1H, H-5, 7.4), 4.08-3.97 (m, 2H, H-4', H-6'), 3.70 (dt, 2H, H-4', H-6', 2.5, 12.4), 3.62 (s, 3H, CH_3O), 2.57 (d, 2H, H-8, 5.8), 2.36 (m, 1H, H-1), 2.16 (dd, 1H, H-4, 5.8, 13.7), 2.10 (dd, 1H, H-4, 6.9, 13.7), 2.01 (m, 1H, H-5'), 1.77 (dt, 1H, H-2, 6.0, 9.0), 1.29 (br hept, 1H, H-5', 1.4, 13.5), [13]C-NMR-75MHz ($CDCl_3$, δ ppm): 172.80 (C-7), 103.26 (C-2'), 71.77 (C-3), 66.98, 66.79 (C-4', 6'), 60.72 (C-5), 56.19 (C-2), 51.74 (3H, CH_3O), 46.23 (C-1), 43.33 (CH_2, C-4), 36.28 (CH_2, C-8), 25.73 (C-5').

Transesterification of compounds 10-2c with K_2CO_3 in methanol



295 mg (0.6 mmoles) 3-((tetrahydro-2H-pyran-2-yl)oxy)propyl 2-((1S,2S,3S,5S)-3-(tetrahydro-2H-pyran-2-yl)oxy-5-chloro-2-(1,3-dioxan-2-yl)cyclopentyl)acetate, **10-2c**, in 11 mL anh. methanol was treated with 210 mg (1.52 mmoles) K_2CO_3 for 2.5 h as for compound **10-1c**, monitoring the reaction by TLC (silica gel, ethyl acetate-hexane-acetic acid, 5:2:0.1, $R_{f\ 13\text{-}2c}$ = 0.31; ethyl acetate-hexane-acetic acid, 5:2:0.1 twice eluted: $R_{f\ 13\text{-}2c}$ = 0.62). After similar work-up and purification of the crude product by pressure chromatography on a silica gel column (eluent: hexane-ethyl acetate, 3:2), a fraction of 157 mg (72 %) pure product **13-2c** (R = THP), methyl 2-((1S,2S,3S,5S)-5-chloro-2-(1,3-dioxan-2-yl)-3-hydroxycyclopentyl)acetate were obtained as oil, $[\alpha]_D$ = +20.1 ° (c=1% in $CHCl_3$), IR: 2947s, 2853m, 1737vs, 1437w, 1379w, 1351w, 1281w, 1258w, 1240w, 1199w, 1151m, 1132m, 1116m, 1097m, 1075m, 1033m, 1017s, 1001s, 969w, 943w, 869w, 810w, [1]H-NMR 300 MHz ($CDCl_3$, δ ppm, *J* Hz) (due to the tetrahydropyranyl group, a chiral atom is introduced and this makes possible to have a mixture of two compounds): 4.62-4.18 (m, 4H, H-2', H-1'', H-3, H-5), 4.10-3.38 (m, 6H, 2H-4', 2H-6', 2H-5''), 3.61 (s, 3H, CH_3O), 2.59 (dd, 1H, H-8, 5.5, 14.3), 2.54 (dd, 1H, H-8, 5.0, 14.3), 2.46-1.40 (m, 11H, 2H-2'', 2H-3'', 2H-4'', H-5', H-1, H-2, 2H-4, H-5'), 1.22 (m, 1H, H-5'), [13]C-NMR-75MHz ($CDCl_3$, δ ppm): 172.86 (C-7), 101.85, 101.72 (C-2'), 97.46, 96.19 (C-1"), 75.99, 74.52 (C-3), 67.01, 66.79 (C-4', 6'), 62.75. 61.98 (C-5"), 61.81, 61.61 (C-5), 55.34, 54.80 (CH, C-2), 51.65 (CH_3O), 45.63, 45.05 (C-1), 43.72, 41.58 (CH_2, C-4), 37.37, 37.29 (CH_2, C-8), 31.09, 30.88 (CH_2, C-4'), 25.78, 25.57 ($2CH_2$, C-3'', C-5'), 19.77, 19.23 (CH_2, C-2'').

Conclusions

Transesterification of the TBDMS-bis-protected compounds **10-1a** and **10-2a** with 2.5 K_2CO_3 equivalents in methanol takes place with the clean cleavage of the secondary TBDMS group concomitant with the formation of the methyl ester group in 2.5 h. Bis-benzoate protected compounds **10-1b** and **10-2b** are transformed in high yields in the same unprotected compounds **13-1** and **13-2**, obtained previously. In the bis-THP protected compounds **10-1c** and **10-2c**, the group being stable in base conditions, the trans-esterification of the alkyloxy tetrahydropyranyl fragment takes place with the formation of the corresponding methyl ester.

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