CHELIDONIC ACID AS PRECURSOR FOR 2,5-DESOXY-*C*-GLYCOSIDES

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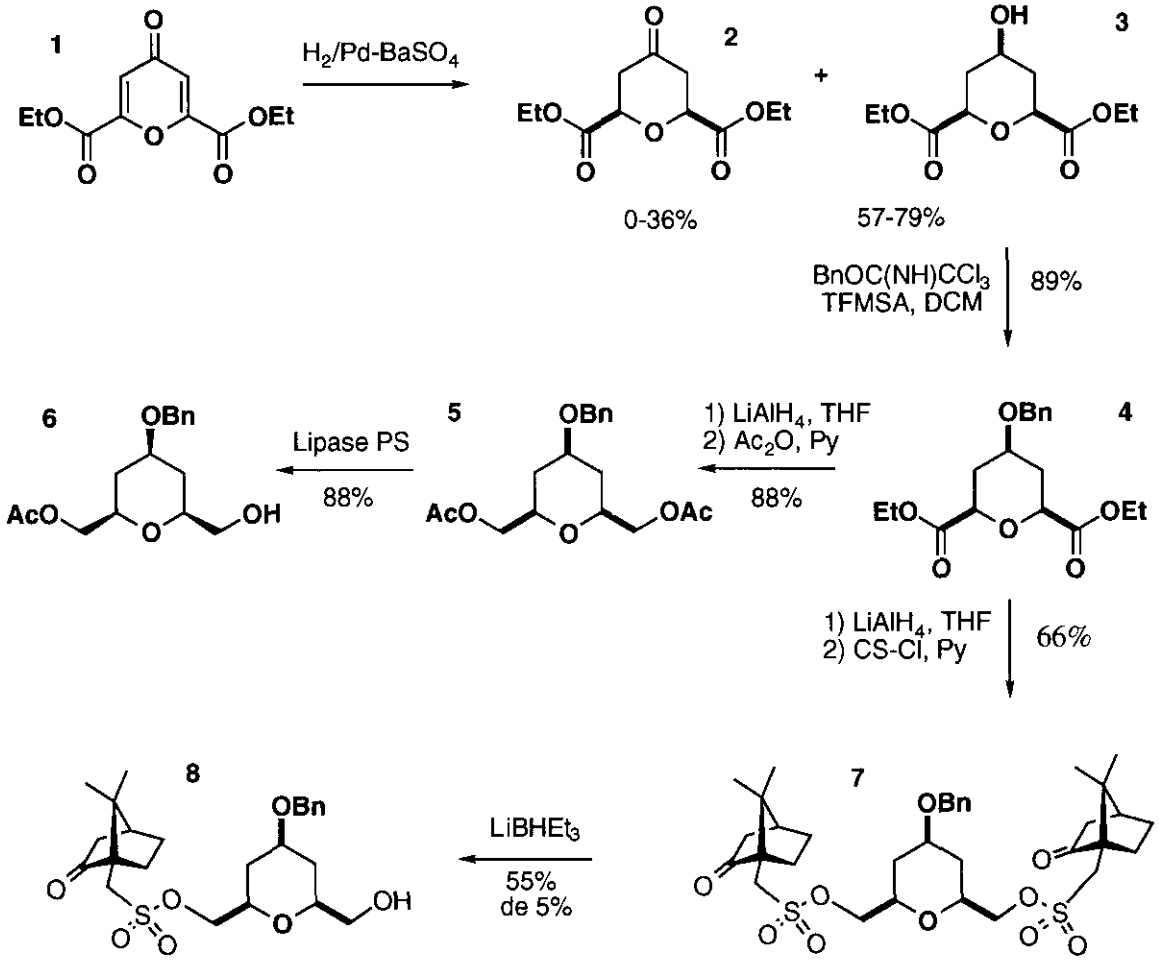
Abstract - Diethyl chelidonate (**1**) was converted by 5 convenient steps into the 2,4,6-trifunctionolized tetrahydropyran (**6**), which is a key intermediate for natural products and peptide turn mimetics. The important all *syn*-configuration was achieved by catalytic hydrogenation.

The potential of glycosides and *C*-glycosides as precursors for peptide turn mimetics[1] and natural products stimulates the demand for enantiopure tetrahydropyran subunits. To this end a synthesis of deoxygenated carbohydrates has been developed by Hoffmann *et al.*[2] Key step in their reaction is the desymmetrisation of a *meso*-configurated diacetate (**5**). However, the total synthesis requires 8 reagents in 7 steps and demands laborious chromatography and is requires a highly exothermic debromination, which disfavours upscaling. The need for a save, inexpensive protocol initiated this investigation. Commercial chelidonic acid was converted to diethyl chelidonate (**1**) and to pyranol (**3**) as lined out by Attenburrow.[3] The catalytic hydrogenation to the pyranone (**2**) and pyranol (**3**) crucially depends on the catalyst, the amount of hydrogen and the purification procedure. Using H_2 at 1 bar and palladium on $BaSO_4$ provided the ketone in 0-36% and the alcohol in 57-79 % yield depending on the hydrogen consumption. The partial reduction allowed isolation of the versatile ketone (**2**) by chromatography. However, the prolonged reduction provided the alcohol sufficiently pure after removal of the catalyst and crystallisation from the same solvent. The 2,6-*syn*-stereochemistry of **3** was assigned by the symmetry of the NMR spectrum and the 2,4 *syn*-stereochemistry by 12 Hz couplings for hydrogens bound to positions 2, 3 and 4, which rule out boat and chair conformation of a 2,4-*anti*-configuration. This was later confirmed by conversion into the known diacetate (**5**). The protection of the hydroxy function by nucleophilic substitution of benzyl derivatives was unsuccessful and lead to decomposition of the starting material by base catalysis. Therefore the benzyl group was introduced by benzyl trichloroacetimidate in 89% yield. The reduction by $LiAlH_4$ and treatment of the crude product with camphorsulfonyl chloride rendered the enantiopure disulfonate (**7**). However, diastereoselective deprotection by hydrolysis was unsuccessful. Neither direct hydrolysis, nor reduction of the ketones by complex hydrides (e.g. DIBAL, L-Selectride™) followed by anchimerically assisted cleavage provided significant diastereomeric excess for **8**. The encouraging absence of signal doublets in the ^1H NMR spectra was thwarted by 5 signal doublets in the ^{13}C NMR. The

difficult separation of the diastereomeric mixtures and the insufficient atom economy of this process stimulated the synthesis of the known intermediate diacetate (**5**), which is easily synthesised by reduction with $LiAlH_4$ and treatment of the crude product by acetic anhydride in 88%. Finally the enantioselective hydrolysis by Lipase PS[2] gave the monoacetate (**6**) in high yield and with high enantiopurity (ee> 98%).



EXPERIMENTAL

General – ^1H and ^{13}C NMR spectra: Bruker WP 200, Bruker AM 400 at 200 (50.3) MHz and 400 (100.6) MHz. Chemical shifts are reported as δ values (ppm) downfield from Me_4Si – IR spectra: Perkin Elmer 1710 FT, Bruker IFS 25, recorded in $\nu_{max.}(cm^{-1})$ – MS: Finnigan MAT 312, VG Autospec (FAB, HRMS) – Elemental analysis: Heraeus Elementaranalysator CHN Rapid – Optical activity: Perkin Elmer 241, λ = 589 nm. Column chromatography: Baker silica gel 60 (40-60 μm), E (ether), EA (ethyl acetate), PE (light petroleum, bp 40-60°C). TLC: silica gel 60 F_{254} (0.2 mm, E. Merck).

(2S,6R*)-cis*-2,6-Bis(ethoxycarbonyl)-γ-tetrahydropyranol (**3**), *(2S*,6R*)-cis*-2,6-Bis(ethoxycarbonyl)-γ-tetrahydropyranon (**2**). The diethyl esters (**2**) and (**3**) were synthesized by a modified literature[3] procedure. Chelidonic acid monohydrate (5.1 g, 25.8 mmol) is suspended in 100 mL of HCl saturated EtOH and stirred for 24 h. Filtration, concentration and filtration through 25 g of silica gel (EA/PE 1:1) and final concentration leaves diethyl chelidonate (**1**) (5.45 g, 88%) as colorless needles (mp 60°C). ^{1}H NMR δ 1.42 (t, J = 7, 6H, CH_3), 4.45 (q, J = 7, 4H, CH_2), 7.16 (s, 2H, 3). IR ($CHCl_3$) ν 1748s, 1660s. MS *m/z* 241 (5), 241 (M^+, 39), 212 (M^+-C_2H_5, 17), 69 (100). The diethyl chelidonate is dissolved in 80 mL of EtOH in the presence of 10% Pd/$BaSO_4$ (1 g), and hydrogenated at 1000 hPa until hydrogen uptake seizes. The mixture is filtered, concentrated to leave a grey mass, which was purified by LC through 50 g of silica gel (EA/PE 1:1) to give varying amounts of **3** (57-79%) and **2** (up to 36%).[4] *(2S*,6R*)-cis*-2,6-Bis(ethoxycarbonyl)-γ-tetrahydropyranol (**3**): mp 48°C (lit.,[3] 48-50°C), ^{1}H NMR δ 1.30 (t, J = 7, 6H, 2'), 1.56 (dd, J = 11.1, J = 12, 2H, 3a,5a), 2.3-2.5 (m, 3H, 3b, OH), 3.85-4.0 (m, 1H, 4), 4.03 (dd, J = 12, J = 2, 2H, 2, 6), 4.25 (q, J = 7, 4H, 1'). IR ($CHCl_3$) 1752, 1228, 1164, 1024. MS *m/z* 173 (M^+-CO_2Et, 24), 155 (M^+-H_2O, -CO_2Et, 94), 127 (100). *(2S*,6R*)-cis*-2,6-Bis(ethoxycarbonyl)-γ-tetrahydropyranon (**2**): mp 80°C (lit.,[3] 80-82°C), ^{1}H NMR δ 1.32 (t, J = 7, 6H, 2'), 2.6-2.75 (m, 4H, 3, 5), 4.2-4.4 (m, 6H, 1', 2, 6). IR ($CHCl_3$) 1750, 1732, 1276. MS *m/z* 244 (M^+, 1), 171 (M^+-CO_2Et, 100).

(2S,6R*)-cis*-2,6-Bis(ethoxycarbonyl)-4-benzyloxytetrahydropyran (**4**) - A solution of all *syn*-2,6-bis(ethoxycarbonyl)-γ-tetrahydropyranol (**3**) (1.170 g, 4.8 mmol), benzyl trichloracetimidate (0.98 mL, 5.1 mmol), in dry DCM (10 mL) and cyclohexane (10 mL) is treated with TFMSA (50 µL) for 22 h. The precipitate is filtered off. Concentration of the filtrate leaves a yellow oil, which is purified by LC (EA/PE 1:1) to give **4** (1.434 g, 89%) as a colorless oil (R_f 0.61 EA/PE 1:1). ^{1}H NMR (400 MHz) δ 1.30 (t, J = 7.2, 6H, CH_3), 1.60 (dd, J = 12.7, ^{2}J = 24, 2H, 3_α), 2.43 (dm, ^{2}J = 24, 2H, 3_β), 3.7-3.75 (m, 1H, 4), 4.01 (dd, J = 12.7, J = 2, 2H, 2), 4.25 (q, J = 7, 4H, $C\underline{H}_2CH_3$), 4.61 (s, 2H, $PhCH_2$), 7.15-7.4 (m, $5H_{arom.}$). ^{13}C NMR (100.6 MHz) δ 14.12 (q, 2C, CH_3), 34.47 (t, 2C, 3), 61.63 (t, $Ph\underline{C}H_2$), 69.90 (t, 2C, $\underline{C}H_2CH_3$), 73.34 + 74.72 (2x d, 3C, 2, 4), 127.59 + 127.83 + 128.53 (d, $5C_{arom.}$), 137.92 (s, $1C_{arom.}$), 169.86 (s, $\underline{C}O$). IR ($CHCl_3$) 1732, 1530, 1192. MS *m/z* 230 (10), 202 (5), 91 (100). Anal. Calcd for $C_{18}H_{24}O_6$; C 64.27, H 7.19. Found C 64.41, H 7.05.

(2S,6R*)-cis*-2,6-Bis(acetoxymethyl)-4-benzyloxytetrahydropyran (**5**) - A suspension of the diester (**4**) (284 mg, 845 µmol) and $LiAlH_4$ (300 mg, 8 mmol) in THF (10 mL) is heated to reflux for 18 h, quenched by addition of ethyl acetate (30 mL) and 2 N HCl (10 mL). The aqueous phase is extracted by 4x 50 mL of EA. The combined extracts are dried ($MgSO_4$) and concentrated. The resulting oil is dissolved in dry pyridine (2 mL) and treated with Ac_2O (0.4 mL, 4.2 mmol) for 18 h. Solvent removal gives a brown oil, which is dissolved in 20 mL of Et_2O, washed by 4x 2 mL of sat. $NaHCO_3$, dried ($MgSO_4$), concentrated and the residue is purified by chromatography (EA/PE 1:1, R_f 0.61) to give pure diacetate (**5**) (249 mg, 88%). All spectra are identical with literature data.[2,5]

(-)-*(2R,6S)-cis*-2-Acetoxymethyl-4-benzyloxy-6-hydroxymethyltetrahydropyran (**6**) was prepared according to literature[2] using lipase PS (generous gift from U. Bornscheuer) in 62% yield, $[\alpha_D]^{25°C}$ = -2.4° ± 0.2° (*c* = 1.0, MeOH) [lit.,[2] 88%, $[\alpha_D]^{25°C}$ = -4.7° (*c* = 1.0, MeOH), 98% ee].

(2S,6R)-cis-2,6-Bis-((1S)-(+)-camphor-10-sulfonyloxymethyl)-4-benzyloxytetrahydropyran (**7**) was prepared as **5** by replacement of Ac_2O by *(1S)*-(+)-camphor-10-sulfonyl chloride and purified by chromatography (EA/PE 1:1, R_f 0.4) to give a colorless wax - ^{1}H NMR (400 MHz), $CDCl_3$ 0.94 (s, 6H, CH_3), 1.36 (s, 6H, CH_3), 1.3-1.55 (m, 4H), 1.65-1.75 (m, 2H), 2.00 (dd, ^{2}J = 18.6, J = 2.2, 2H), 2.05-2.2 (m, 6H), 2.4-2.55 (m, 4H), 3.11 (dd, ^{2}J = 15.8, J = 1.6, 2H), 3.65-3.8 (m, 5H), 4.3-4.4 (m, 4H), 4.63 (s, 2H, PhC$\underline{H}_2$O), 7.2-7.45 (m, 5H) ^{13}C NMR (100.6 MHz) $CDCl_3$ 19.68 (Me), 24.91 (Me), 26.83, 26.85, 33.50, 42.48, 42.80, 47.03, 47.96, 58.00, 69.85, 71.69, 73.37, 76.76, 127.58, 127.76, 128.50, 138.08, 214.49 (C=O). FAB 681 (M^+, 12), 574 (M^+-C_7H_7O, 3). IR 1744, 1364 (SO_2O), 1172 (SO_2O). Anal. Calcd for $C_{34}H_{48}O_{10}S_2$; C 59.98, H 7.11. Found C 59.30, H 7.28. $[\alpha_D]^{25°C}$ = 31.5° ±0.3° (*c*=1.70, $CHCl_3$)

(2S,6R*)*-2-((1S)-(+)-Camphor-10-sulfonyloxymethyl)-4-benzyloxytetrahydropyran (**8**) - **7** (798 mg, 1.47 mmol) was dissolved in THF (10 mL), cooled to -78°C under inert argon and treated with 1.0 M L-Selectride solution in THF (1.2 mL). The mixture immediately turned cloudy and was warmed to rt, concentrated, dissolved in EA (20 mL) and washed by saturated $NaHCO_3$ solution to leave the crude product after drying ($MgSO_4$) and concentration. Chromatography (EA/PE 1:1) provided the diastereomeric alcohols as colorless oil (685 mg, 55%). $C_{24}H_{34}O_7S$:MW 466.59. ^{1}H NMR (400 MHz), $CDCl_3$ 0.89 (s, 3H, Me), 1.13 (s, 3H, Me), 1.2-1.5 (m, 3H), 1.6-1.7 (m, 1H), 1.9-2.2 (m, 6H), 2.3-2.6 (m, 2H), 3.07 (dd, J = 15.3, J = 2.4, 1H), 3.45-3.75 (m, 5H), 3.73 (dd, J = 15.3, J = 2.2, 1H), 4.25-4.35 (m, 2H), 4.58 (s, 2H, $PhCH_2$), 7.3-7.45 (m, 5H). ^{13}C NMR (100.6 MHz) $CDCl_3$ 19.67 + 19.86 (Me), 24.97, 26.81, 33.43, 33.54 (33.56), 42.53, 42.86 (42.89), 47.42, 47.92, 58.18, 65.72, 69.78, 72.20 (72.22), 73.37 (73.39), 73.82, 76.60 (76.62), 127.58, 128.48, 138.27, 140.69, 215.27 (C=O). IR 3592, 3524, 1744, 1360 (SO_2O), 1172 (SO_2O), 980. FAB 360 (3), 329 (2). $[\alpha_D]^{25°C}$= 24.0° (*c* = 1.00, $CHCl_3$).

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