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A MILD PROCEDURE FOR THE SYNTHESIS OF ALLYL AND BENZYL α-HYDROXYESTERS USING *O*-ALLYL(BENZYL)-*N,N'*-DICYCLOHEXYLISOUREA

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ABSTRACT

Allyl protecting group and more commonly used benzyl protecting group were easily introduced in several (cyclo)alkyl α-hydroxycarboxylic acids through a modified Steglich esterification using *O*-allyl or *O*-benzyl-*N,N'*-dicyclohexylisoureas. Corresponding esters were prepared under mild conditions and short reaction times; high reaction yields and easy purification of final products favored this procedure. Complete unambiguous assignment for ^{1}H and ^{13}C-NMR data for prepared compounds is given.

Key words: Dicyclohexylcarbodiimide (DCC), O-allylisourea, α-hydroxyallylester, O-benzylisourea, α hydroxybenzylester

UN PROCEDIMIENTO "SUAVE" PARA LA SÍNTESIS DE DIVERSOS ALIL Y BENCIL α-HIDROXIÉSTERES EMPLEANDO *O*-ALIL(BENCIL)-*N,N'*-DICICLOHEXILISOUREA

RESUMEN

Los grupos protectores alilo y bencilo fueron facilmente adicionados sobre una serie de ácidos (ciclo)alquil α-hidroxicarboxílicos mediante una modificación a la esterificación de Steglich, utilizando *O*-alil y *O*-bencil-*N,N'*-diciclohexilisoureas. Los alil y bencil ésteres fueron preparados bajo condiciones suaves, en cortos tiempos de reacción; los rendimientos elevados y la alta pureza de los productos favorecen este procedimiento. Se presenta, además, la asignación completa de las señales de RMN para ^{1}H y ^{13}C de los compuestos sintetizados.

Palabras clave: Diciclohexilcarbodiimida (DCC), O-alilisourea, α-hidroxialiléster, O-bencilisourea, α-hidroxibenciléster

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INTRODUCTION

Esterification of carboxylic acids is a fundamental transformation in organic chemistry and several methods exist for that purpose.[1] Mild high yielding procedures for the formation of carboxylic acid esters are desirable and necessary for the synthesis of many highly functionalized and sensitive compounds of current chemical interest. In the field of peptide synthesis, for example, the nature of the N-terminus and side chain protecting groups precludes the use of many normal esterification procedures. With other complex organic compounds, degradation and side reactions with common procedures may reduce the yield and purity of the desired esters. Some reagents or procedures have inherent undesirable characteristics (*e.g.*, the danger of explosion with diazomethane) or form difficult-to-remove impurities (*e.g.*, the N-acylureas formed in the *one-pot* carbodiimide method).

Esterification of α-hydroxycarboxylic acids is a particular case due to the dual existence of reactive groups in the molecule. For this particular process potassium and caesium salts have proved useful. The CsF promoted esterification of α-hydroxycarboxylic acids described by Otera *et al.* is a good way to gain esters using alkyl bromides. The reaction is usually carried out under mild conditions and shows less racemization than the Mitsunobu esterification.[2,3] Correspondingly TCNE (tetracyanoethylene) can be used as a catalyst for the selective synthesis of α-hydroxyesters according to a procedure first described by Masaki *et al.*[4] Particularly an iron (III) acetylacetonate complex was used as catalyst for direct condensation of mandelic acid and benzhydrol.[5] An enzyme mimicking catalytic esterification of α-hydroxyacids by alcoholysis of their salicylaldehyde acetals was reported as a significant green alternative.[6]

In search of safety and optimal procedures for the preparation of allyl and benzyl α-hydroxyesters as synthons of more complex derivatives, here is presented the use of *O*-allyl and *O*-benzyl-*N,N'*-dicyclohexylisourea as mild esterification agents of α-hydroxycarboxylic acids, which molecular data has not been appropriately reported.[7,8] The use of this methodology, easy product purification and high reaction yields are important issues to consider when using allyl or benzyl protecting groups.

EXPERIMENTAL PART

NMR spectra were recorded on a *Bruker AM – 300* (300,13 MHz for ^{1}H-NMR and 75,48 MHz for ^{13}C – NMR) or a *Bruker Avance 400* (400,16 MHz for ^{1}H and 100,62 MHz for ^{13}C) spectrometers, with solutions in $CDCl_3$ or acetone-d^6 with TMS as internal standard (0 ppm). Unambiguous peak assignments were aided by DQF-COSY ^{1}H-^{1}H and GS-HSQC ^{1}H-^{13}C correlation experiments. All coupling constants (*J*) are quoted in Hertz (Hz).

IR spectra were recorded on a *Perkin – Elmer Spectrum One* spectrometer with an additional *ATR cell.* Intensities were automatically determined using ACD/SpecViewer v.4.53 (Advanced Chemistry Development Inc.) with relative intensity intervals (% of maximum

height) as Very Weak (VW) 0% - 10%, Weak (W) 10% - 30%, Medium (M) 30% - 60%, Strong (S) 60% - 90% and Very Strong (VS) 90% - 100%.

Mass spectra were recorded under EI conditions (70 eV) with previous gas chromatographic analysis on a *Finnigan MAT – 8500* spectrometer coupled with a *Hewlett Packard 5890 Series II* GC unit.

Melting points were recorded using an *Electrothermal 9100* apparatus.
Analytical gas chromatography was performed using a *Packard United Technologies Gas Chromatograph* Model 438S with DB – 5 silica column (30 m length and 0,32 mm diameter - J&W Scientific) 80 °C injection port, 3 °C / min to 280 °C coupled to a Shimadzu C-R3A as integrator.

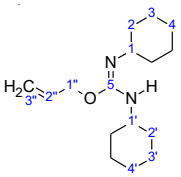
Column chromatography was realized using Merck silica gel 60, particle size 0,063-0,2 mm (70-230 mesh); thin layer chromatography (TLC in SiO2 plates: POLYGRAM® SIL G/ UV_{254}) was visualized with UV light (254 nm) and by heating after spraying with an aqueous developing solution (100 mL) of 1 g $CeSO_4$, 6 mL conc. H_2SO_4 and 2,5 g $12MoO_3$-H_3PO_4-H_2O.

DCC, benzyl and allyl alcohols as well as n-alkyl α-hydroxyacids were purchased from commercial sources (Aldrich, Merck); cycloalkyl α-hydroxyacids were prepared from the corresponding ketones by known procedures; solvents as THF, toluene, benzene and diethyl ether were purified by distillation after refluxing them over sodium under an argon atmosphere; for methylenchloride CaH_2 was used. For methanol and ethanol, Mg turnings (2,5 g in 500 mL) were used. Ethyl acetate was dried over P_2O_5.

Complete ^{1}H and ^{13}C-NMR data is given due to literature references lack of detailed information; numbers on structures are given in order to have a complete, unequivocal assignment and easier comparison between compounds and their ^{13}C NMR signals.

1. Synthesis of *O*-Alkyl-*N,N'*-dicyclohexylisoureas

O-Allyl-N,N'-dicyclohexylisourea ***(3a)***
General experimental procedure: In a round bottom flask 10,0 g (172 mmol) of allyl alcohol were added to 35,0 g (172 mmol) of DCC under argon; 0,04 g (0,29 mmol) of CuCl2 were added as catalyst. The mixture was stirred at 40 °C until the imide band (α = 2119 cm^{-1}) disappeared in IR (usually after 24 h). The crude product was pre-purified from the cupper salts and secondary compounds in an Al_2O_3 column chromatography using *n*-hexane / diethyl ether (9/1) as eluent. The product was then purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent. $R_f(SiO_2)$ = 0,42 (n-hexane : diethyl ether, 1 : 1, v : v). The pure product appears as colourless oil. Yield: 94% (42,7 g, 161 mmol). $R_f(SiO_2)$ = 0,42 (n-hexane : diethyl ether, 1 : 1, v : v).



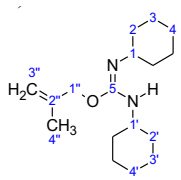
Molecular Formula = $C_{16}H_{28}N_2O$

Formula Weight = 264,406

IR (ATR) σ *(cm^{-1})* = 3447 (VW) [ν (N-H)], 2924 (S) [ν (-CH_2-)], 1662 (VS) [ν (C=N)], 1311 (S) [ν (C-O-C)], 1055 (M) [ν (C-O)], 919 (M) [ν (=C-H allyl)], 887 (M) [ν (=CH_2)], 710 (W) [ν (C-H allyl)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,95-1,38 (m, 10H, 2-H_{ax}, 2'-H_{ax}, 3-H_{ax}, 3'-H_{ax}, 4-H_{ax}, 4'-H_{ax}), 1,50-1,78 (m, 8H, 2'-H_{eq}, 3-H_{eq}, 3'-H_{eq}, 4-H_{eq}, 4'-H_{eq}), 1,83-1,97 (m, 2H, 2-H_{eq}), 2,70 (m, 1H, 1'-H_{ax}), 3,35 (m, 1H, 1-H_{ax}), 4,51 (dt, $^3J_{HH}$ = 5,35 Hz, $^4J_{HH}$ = 1,51 Hz, 2H, 1''-H), 5,11 (dq, $^3J_{HH}$ = 10,43 Hz, $^2J_{HH}$ = 1,65 Hz, $^4J_{HH}$ = 1,51 Hz, 1H, 3''-H_{cis}), 5,25 (dq, $^3J_{HH}$ = 17,29 Hz, $^2J_{HH}$ = 1,65 Hz, $^4J_{HH}$ = 1,51 Hz, 1H, 3''-H_{trans}), 5,91 (m, $^3J_{HH}$ = 5,35 Hz, $^3J_{HH}$ = 10,43 Hz, $^3J_{HH}$ = 17,29 Hz, 1H, 2''-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 25,67 (CH_2, 3'-C), 25,91 (CH_2, 3-C), 26,36 (CH_2, 4'-C), 26,65 (CH_2, 4-C), 34,37 (CH_2, 2-C), 34,43 (CH_2, 2'-C), 50,24 (CH, 1-C), 54,77 (CH, 1'-C), 65,51 (CH_2, 1''-C), 115,81 (CH_2, 3''-H), 134,11 (CH, 2''-C), 150,97 (C^q, 5-C); *MS (GC inlet, EI, 70 eV) m/z (%)* = 264 (7) [M^+], 221 (8) [M-C_3H_7]$^+$, 182 (27) [M-C_6H_{11}]$^+$, 167 (100) [M-$C_6H_{12}N$]$^+$, 139 (11) [M_{167}-CO]$^+$, 124 (11) [M_{182}-C_3H_5]$^+$, 98 (89) [$C_6H_{12}N^+$], 83 (37) [$C_6H_{11}^+$].

1,3-Dicyclohexyl-2-(2-methyl-allyl)-isourea ***(3b)***[9]

Colourless oil (4,86 g, 17,4 mmol, 90%) from 1,40 g (19,4 mmol) of 2-methyl-2-propen-1-ol and 4,0 g (19,4 mmol) of DCC; 0,04 g (0,29 mmol) of $CuCl_2$ were added as catalyst. The resulting mixture was stirred at room temperature for 1 day (controlled via IR). The product was purified by column chromatography on SiO_2 using n-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent. R_f (SiO_2) = 0,55 (*n*-hexane : diethyl ether, 2 : 3, v : v).



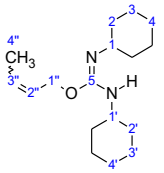
Molecular Formula = $C_{17}H_{30}N_2O$

Formula Weight = 278,432

IR (ATR) σ *(cm^{-1})* = 3443 (VW) [ν (N-H)], 3079 (VW) [ν (=C-H)], 2925 (S) [ν (-CH_2-)], 2852 (S) [ν (-CH_2-)], 1665 (VS) [ν (C=N)], 1449 (M) [ν (C-H)], 1316 (S) [ν (C-O-C)], 889 (S) [ν (=C-H)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 1,05 (m, 2H, 2-H_{ax}), 1,24 (m, 2H, 2'-H_{ax}), 1,10-1,35 (m, 6H, 3-H_{ax}, 3'-H_{ax}, 4-H_{ax}, 4'-H_{ax}), 1,70 (m, 2H, 2'-H_{eq}), 1,50-1,75 (m, 6H, 3-H_{eq}, 3'-H_{eq}, 4-H_{eq}, 4'-H_{eq}), 1,74 (s, 3H, 4''-H), 1,91 (m, 2H, 2-H_{eq}), 2,74 (br. s., 1H, 1'-H_{ax}), 3,41 (m, 1H, 1-H_{ax}), 3,47 (br. s., 1H, N-H), 4,42 (s, 2H, 1''-H), 4,82 (s, 1H, 3''-H_{cis}), 4,94 (s, 1H, 3''-H_{trans}); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 19,72 (CH_3, 4''-C), 25,01 (CH_2, 3'-C), 25,25 (CH_2, 3-C), 25,67 (CH_2, 4'-C), 25,95 (CH_2, 4-C), 34,44 (CH_2, 2'-C, 2-C), 50,43 (CH, 1'-C), 54,85 (CH, 1-C), 68,09 (CH_2, 1''-C), 110,83 (CH_2, 3''-C), 141,70 (C^q, 2''-C), 151,09 (C^q, 5-C); *MS (GC inlet, EI, 70 eV) m/z (%)* = 278 (4) [M^+], 263 (1) [M-CH_3]$^+$, 181 (88) [M-$C_6H_{12}N$]$^+$, 110 (39) [M_{181}-C_4H_7O]$^+$, 98 (100) [$C_6H_{10}NH_2^{+\cdot}$], 83 (54) [$C_6H_{11}^+$], 55 (92) [$C_4H_7^+$], 41 (48) [$C_3H_5^+$].

2-But-2-enyl-1,3-dicyclohexylisourea ***(3c)***

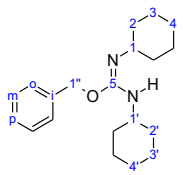
Yellowish oil (25,16 g, 90,3 mmol, 65%) from 10,0 g (139 mmol) of crotyl alcohol and 28,0 g (136 mmol) of DCC; 0,04 g (0,29 mmol) of $CuCl_2$ were added as catalyst. The resulting mixture was stirred at 40 °C for 2d (controlled via IR). The product was purified filtering the mixture in a small pad of Al_2O_3 using *n*-hexane / diethyl ether (2/3) mixture as eluent. The compound was unstable to be purified by column chromatography on SiO_2.



IR (ATR) σ *(cm^{-1})* = 3441 (W) [ν (N-H)], 2827 (S) [ν (-CH_2-)], 2853 (S) [ν (-CH_2-)], 1664 (VS) [ν (C=N)], 1448 (M) [ν (C-H)], 1318 (S) [ν (C-O-C)], 1034 (M) [ν (C-O)], 966 (W) [ν (=C-H)].

O-Benzyl-N,N'-dicyclohexylisourea ***(5)****10*

Colourless oil (10,39 g, 33 mmol, 87%) from 4,10 g (38 mmol) of benzyl alcohol and 7,82 g (38 mmol) of DCC; 0,04 g (0,29 mmol) of $CuCl_2$ were added as catalyst. The resulting mixture was stirred at 60 °C for 1d (controlled via IR). The product was purified by column chromatography on SiO_2 using n-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent. R_f (SiO_2) = 0,30 (n-hexane : diethyl ether, 10 : 1, v : v).

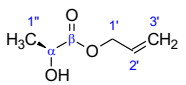


IR (ATR) σ *(cm^{-1})* = 3440 (VW) [ν (N-H)], 3032 (VW) [ν (=C-H)], 2928 (S) [ν (-CH_2-)], 2853 (M) [ν (-CH_2-)], 1665 (VS) [ν (C=N)], 1055 (M) [ν (C-O-C)], 734 (M) and 698 (S) [ν (C-H arom. monosubstituted)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 1,00-1,35 (m, 6H, 3-H_{ax}, 3'-H_{ax}, 4-H_{ax}, 4'-H_{ax}), 1,10 (m, 2H, 2-H_{ax}), 1,35 (m, 2H, 2'-H_{ax}), 1,80 (m, 2H, 2'-H_{eq}), 1,50-1,85 (m, 6H, 3-H_{eq}, 3'-H_{eq}, 4-H_{eq}, 4'-H_{eq}), 1,95 (m, 2H, 2-H_{eq}), 2,87 (br. s., 1H, 1'-H_{ax}), 3,47 (m, 1H, 1-H_{ax}), 3,58 (br. s., 1H, N-H), 5,16 (s, 2H, 1''-H), 7,20-7,35 (m, 5H, arom-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 25,05 (CH_2, 3'-C), 25,28 (CH_2, 3-C), 25,78 (CH_2, 4'-C), 26,15 (CH_2, 4-C), 34,53 (CH_2, 2-C), 34,60 (CH_2, 2'-C), 50,43 (CH, 1-C), 54,91 (CH, 1'-C), 66,54 (CH_2, 1''-C), 127,28 (CH, *para*-C), 127,52 (CH, *ortho*-C), 128,21 (CH, *meta*-C), 138,29 (C^q, *ipso*-C), 151,15 (C^q, 5-C); *MS (GC inlet, EI, 70 eV) m/z (%)* = 314 (11) [M^+], 223 (9) [M-C_7H_7]$^+$, 98 (100) [$C_6H_{10}NH_2^+$], 91 (94) [$C_7H_7^+$], 83 (21) [$C_6H_{11}^+$], 55 (29) [$C_4H_7^+$].

2. Synthesis of α-hydroxyallyl esters

Allyl lactate ***(7a)***[11]

General experimental procedure: In a 250 mL round bottom flask, 5,00 g (55 mmol) of lactic acid (commercial purchased acid contains about 20% water inside) were dissolved in 200 mL of benzene and 5 drops of concentrated sulphuric acid were added to the remaining solution as catalyst. A Dean – Stark apparatus was connected to trap the water by azeotropic distillation (5 hours). After the water was collected, 150 mL of benzene were distilled. The reaction mixture was cooled down to room temperature and 10,65 g (12,5 mL, 183 mmol) of allyl alcohol were added. Then the mixture was heated under reflux for 20 hours. The reaction flask was cooled to room temperature and the reaction mixture was extracted with diethyl ether from a $NaHCO_3$ solution (pH = 10) (4 x 50 mL) and the combined organic layers were dried over sodium sulphate. The solvent was removed by rotary evaporation and the resulting residue was purified by distillation under reduced pressure. The pure product appeared as a colourless oil. Yield: 50% (3,58 g, 27,5 mmol). R_f (SiO_2) = 0,46 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 60 °C / 8 mmHg – Kugelrohr.



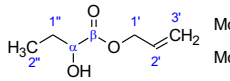
Molecular formula = $C_6H_{10}O_3$

Molecular Weight = 130,142

IR (ATR) σ *(cm*$^{-1}$*)* = 3440 (W) [ν (O-H)], 2987 (W) [ν (-CH_2-)], 2942 (W) [ν (-CH_2-)], 1735 (S) [ν (C=O)], 1201 (S), 1123 (VS) [ν (C-O)], 1043 (M) [ν (C-O-C)], 924 (S) [ν (C-H)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 1,34 (dd, $^3J_{HH}$ = 6,86 Hz, 3H, 1''-H), 4,23 (q, $^3J_{HH}$ = 6,86 Hz, 1H, H-α), 4,57 (dt, $^3J_{HH}$ = 5,77 Hz, $^4J_{HH}$ = 1,24 Hz, 2H, 1'-H), 5,17 (dq, $^3J_{HH}$ = 10,56 Hz, $^4J_{HH}$ = 1,24 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{cis}), 5,24 (dq, $^3J_{HH}$ = 17,16 Hz, $^4J_{HH}$ = 1,24 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{trans}), 5,85 (ddt, $^3J_{HH}$ = 5,77 Hz, $^3J_{HH}$ = 10,56 Hz, $^3J_{HH}$ = 17,16 Hz, 1H, 2'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 20,16 (CH_3, 1''-C), 65,79 (CH_2, 1'-C), 66,62 (CH, C-α), 118,60 (CH_2, 3'-C), 131,39 (CH, 2'-C), 175,17 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 131 (2) $[M+H]^+$, 130 (2) $[M^+]$, 115 (29) $[M-CH_3]^+$, 112 (13) $[M-H_2O]^+$, 86 (20) $[M-C_2H_5O]^+$, 57 (46) $[C_3H_5O^+]$, 45 (100) $[C_2H_5O^+]$, 43 (39) $[C_3H_7^+]$.

2-Hydroxybutanoic acid allyl ester ***(7b)***

General experimental procedure when using isoureas: A solution of 2-hydroxybutanoic acid (10,66 g, 101,3 mmol) and O-allyl isourea **3a** (26,79 g, 101,3 mmol) in 400 mL dry THF was stirred in a Schlenk round bottom flask for 16 hours at 60 °C under argon atmosphere. The *N,N'*-dicyclohexylurea formed during the reaction was separated out by filtration and the product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (9/1) as eluent. Afterwards the product was distilled at 80 °C and 7 mmHg. The product appeared as a colourless oil. Yield: 73% (10,22 g, 70,9 mmol). R_f (SiO_2) = 0.46 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 80 °C / 7 mmHg – Kugelrohr.



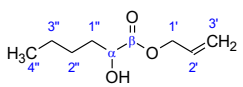
Molecular formula = $C_7H_{12}O_3$

Molecular Weight = 144,168

IR (ATR) σ *(cm^{-1})* = 3474 (W) [ν (O-H)], 2969 (W) [ν (-CH_2-)], 2939 (W) [ν (-CH_2-)], 1732 (VS) [ν (C=O)], 1198 (S) [ν (C-O-C)], 1128 (VS) [ν (C-O)], 991 (S) [ν (=C-H)], 932 (S) [ν (C-H allyl)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,91 (t, $^3J_{HH}$ = 7,48 Hz, 3H, 2''-H), 1,56-1,74 (m, 1H, 1''-H), 1,70-1,88 (m, 1H, 1''-H), 2,96 (br. s., 1H, O-H), 4,13 (dd, $^3J_{HH}$ = 6,68 Hz, $^3J_{HH}$ = 4,60 Hz, 1H, H-α), 4,62 (d, $^3J_{HH}$ = 5,77 Hz, 2H, 1'-H), 5,21 (dt, $^3J_{HH}$ = 10,43 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{cis}), 5,28 (dd, $^3J_{HH}$ = 17,25 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{trans}), 5,87 (ddt, $^3J_{HH}$ = 5,77 Hz, $^3J_{HH}$ = 10,43 Hz, $^3J_{HH}$ = 17,15 Hz, 1H, 2'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 8,82 (CH_3, 2''-C), 27,39 (CH_2, 1''-C), 65,90 (CH_2, 1'-C), 71,35 (CH, C-α), 118,85 (CH_2, 3'-C), 131,42 (CH, 2'-C), 174,78 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 145 (5) $[M+H]^+$, 126 (2) $[M-H_2O]^+$, 115 (8) $[M-C_2H_5]^+$, 86 (3) $[M-C_3H_7O]^+$, 70 (21) $[M_{126}-C_3H_5O]^+$, 59 (100) $[C_3H_7O^+]$, 57 (41) $[C_3H_5O^+]$, 41 (95) $[C_3H_7^+]$.

2-Hydroxyhexanoic acid allyl ester ***(7c)***

Colourless oil (6,95 g, 40,4 mmol, 97%) from 5,50 g (41,6 mmol) of 2-hydroxyhexanoic acid and 11,00 g (41,6 mmol) of *O*-allyl isourea **3a** dissolved in 250 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (95/5) mixture as eluent. R_f (SiO_2) = 0,77 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 80 °C / 7 mmHg – Kugelrohr.



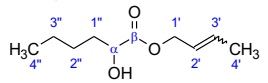
Molecular formula = $C_9H_{16}O_3$

Molecular Weight = 172.222

IR (KBr) σ *(cm^{-1})* = 3471 (M) [ν (O-H)], 2958 (S) [ν (-CH_2-)], 2869 (S) [ν (-CH_2-)], 1743 (VS) [ν (C=O)], 1133 (S) [ν (C-O-C)], 1084 (S) [ν (C-O)], 988 (S) [ν (=C-H)], 932 (M) [ν (C-H allyl)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,89 (t, $^3J_{HH}$ = 7,08 Hz, 3H, 4''-H), 1,25-1,50 (m, 4H, 2''-H and 3''-H), 1,55-1,70 (m, 1H, 1''-H), 1,70-1,87 (m, 1H, 1''-H), 2,62 (br. s., 1H, O-H), 4,19 (dd, $^3J_{HH}$ = 5,08 Hz, $^3J_{HH}$ = 4,25 Hz, 1H, H-α), 4,67 (d, $^3J_{HH}$ = 5,81 Hz, 2H, 1'-H), 5,28 (dt, $^3J_{HH}$ = 10,39 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{cis}), 5,35 (dd, $^3J_{HH}$ = 17,25 Hz, $^2J_{HH}$ = 1,51 Hz, 1H, 3'-H_{trans}), 5,93 (ddt, $^3J_{HH}$ = 5,81 Hz, $^3J_{HH}$ = 10,39 Hz, $^3J_{HH}$ = 17,25 Hz, 1H, 2'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 13,89 (CH_3, 4''-C), 22,37 (CH_2, 3''-C), 26,84 (CH_2, 2''-C), 34,11 (CH_2, 1''-C), 66,08 (CH_2, 1'-C), 70,46 (CH, C-α), 119,01 (CH_2, 3'-C), 131,47 (CH, 2'-C), 175,13 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 173 (8) $[M+H]^+$, 154 (3) $[M-H_2O]^+$, 127 (14) $[M-C_2H_3]^+$, 115 (3) $[M-C_4H_9]^+$, 87 (88) $[M_{115}-CO]^+$, 69 (100) $[M_{127}-C_4H_9]^+$, 57 (28) $[C_4H_9^+]$, 43 (34) $[C_3H_7^+]$.

(2E,Z)-But-2-enyl 2-hydroxyhexanoate ***(7d)***

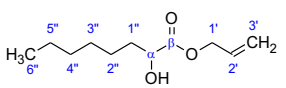
Colourless oil (16,70 g, 89,6 mmol, 98%) from 11,89 g (90 mmol) of 2-hydroxyhexanoic acid and 25,00 g (90 mmol) of *O*-(2-butenyl) isourea **3c** dissolved in 250 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (gradient from mixture 95/5 to only diethyl ether) as eluent. R_f (SiO_2) = 0,76 (*n*-hexane : diethyl ether, 2 : 3, v : v).



IR (KBr) σ *(cm^{-1})* = 3484 (M) [ν (O-H)], 2954 (S) [ν (-CH_2-)], 2865 (S) [ν (-CH_2-)], 1735 (VS) [ν (C=O)], 1454 (M), 1202 (S), 1134 (M) [ν (C-O-C)], 1083 (S) [ν (C-O)], 968 (S) [ν (=C-H)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,79 (t, $^3J_{HH}$ = 7,14 Hz, 3H, 4''-H), 1,15-1,38 (m, 4H, 2''-H and 3''-H), 1,45-1,75 (m, 2H, 1''-H), 1,65 (d, $^3J_{HH}$ = 6,48 Hz, 3H, 4'-H), 3,11 (br. s., 1H, O-H), 4,07 (dd, $^3J_{HH}$ = 6,70 Hz, $^3J_{HH}$ = 4,39 Hz, 1H, H-α), 4,49 (d, $^3J_{HH}$ = 6,55 Hz, 2H, 1'-H), 5,41-5,53 (m, 1H, 2'-H), 5,63-5,77 (m, 1H, 3'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 13,63 (CH_3, 4''-C), 17,43 (CH_3, 4'-C), 22,15 (CH_2, 3''-C), 26,68 (CH_2, 2''-C), 33,84 (CH_2, 1''-C), 65,77 (CH_2, 1'-C), 70,29 (CH, C-α), 124,38 (CH, 2'-C), 131,79 (CH, 3'-C), 174,93 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 186 (4) [M^+], 168 (3) [M-H_2O]$^+$, 114 (9) [M-C_4H_7O]$^+$, 87 (77) [$C_5H_7O^+$], 69 (100) [M_{87}-H_2O]$^+$, 57 (34) [$C_4H_9^+$], 55 (81) [$C_4H_7^+$], 43 (37) [$C_3H_7^+$].

2-Hydroxyoctanoic acid allyl ester ***(7e)***

Colourless oil (5,10 g, 25,4 mmol, 82%) from 5,00 g (31,2 mmol) of 2-hydroxyoctanoic acid and 8,25 g (31,2 mmol) of *O*-allyl isourea **3a** dissolved in 200 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (4 / 1) mixture as eluent. R_f (SiO_2) = 0,30 (*n*-hexane : diethyl ether, 4 : 1, v : v).

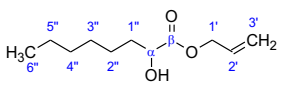


IR (ATR) σ *(cm^{-1})* = 3482 (W) [ν (O-H)], 2955 (M) [ν (-CH_2-)], 2927 (M) [ν (-CH_2-)], 2859 (M) [ν (-CH_2-)], 1734 (VS) [ν (C=O)], 1457 (M), 1130 (S) [ν (C-O-C)], 1088 (S) [ν (C-O)], 985 (S) [ν (=C-H)], 932 (S) [ν (C-H allyl)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,82 (t, $^3J_{HH}$ = 7,00 Hz, 3H, 6''-H), 1,15-1,30 (m, 6H, 3''-H and 4''-H and 5''-H), 1,25-1,50 (m, 2H, 2''-H), 1,51-1,66 (m, 1H, 1''-H), 1,66-1,81 (m, 1H, 1''-H), 2,92 (d, $^3J_{HH}$ = 5,90 Hz, 1H, O-H), 4,16 (ddd, 1H, H-α), 4,61 (ddt, $^3J_{HH}$ = 5,76 Hz, $^4J_{HH}$ = 1,65 Hz, $^4J_{HH}$ = 1,51 Hz, 2H, 1'-H), 5,21 (dt, $^3J_{HH}$ = 10,43 Hz, $^4J_{HH}$ = 1,51 Hz, $^2J_{HH}$ = 1,23 Hz, 1H, 3'-H_{cis}), 5,28 (dt, $^3J_{HH}$ = 17,29 Hz, $^4J_{HH}$ = 1,51 Hz, $^2J_{HH}$ = 1,23 Hz, 1H, 3'-H_{trans}), 5,87 (ddt, 1H, $^3J_{HH}$ = 5,76 Hz, $^3J_{HH}$ = 10,43 Hz, $^3J_{HH}$ = 17,29 Hz, 2'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 13,91 (CH_3, 6''-C), 22,43 (CH_2, 5''-C), 24,59 (CH_2, 4''-C), 28,86 (CH_2, 3''-C), 31,54 (CH_2, 2''-C), 34,32 (CH_2, 1''-C), 65,88 (CH_2, 1'-C), 70,41 (CH, C-α), 118,79 (CH_2, 3'-C), 131,45 (CH, 2'-C), 174,99 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 200 (2) [M+H]$^+$, 182 (1) [M-H_2O]$^+$, 171 (7) [M-C_2H_5]$^+$, 115 (30) [M-$C_2H_5O_2$]$^+$, 97 (86) [M_{115}-H_2O]$^+$, 69 (25) [M_{97}-C_2H_4]$^+$, 55 (100) [$C_4H_7^+$], 43 (40) [$C_3H_7^+$].

3. Synthesis of α-hydroxybenzyl esters

2-Hydroxypropanoic acid benzyl ester ***(9a)***

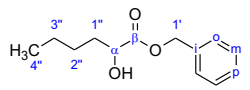
Colourless oil (2,26 g, 12,59 mmol, 94%) from 1,20 g (13,40 mmol) of lactic acid previously dried over Na_2SO_4 and 4,33 g (13.40 mmol) of *O*-benzyl isourea **5** dissolved in 100 mL of dry toluene, stirring and refluxing for 24 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using petroleum ether / ethyl acetate (4 / 1) mixture as eluent. R_f (SiO_2) = 0,47 (petroleum ether : ethyl acetate, 4 : 1, v : v).



IR (ATR) σ *(cm^{-1})* = 3482 (W) [ν (O-H)], 2955 (M) [ν (-CH_2-)], 2927 (M) [ν (-CH_2-)], 2859 (M) [ν (-CH_2-)], 1734 (VS) [ν (C=O)], 1457 (M), 1130 (S) [ν (C-O-C)], 1088 (S) [ν (C-O)], 985 (S) [ν (=C-H)], 932 (S) [ν (C-H allyl)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 0,82 (t, $^3J_{HH}$ = 7,00 Hz, 3H, 6''-H), 1,15-1,30 (m, 6H, 3''-H and 4''-H and 5''-H), 1,25-1,50 (m, 2H, 2''-H), 1,51-1,66 (m, 1H, 1''-H), 1,66-1,81 (m, 1H, 1''-H), 2,92 (d, $^3J_{HH}$ = 5,90 Hz, 1H, O-H), 4,16 (ddd, 1H, H-α), 4,61 (ddt, $^3J_{HH}$ = 5,76 Hz, $^4J_{HH}$ = 1,65 Hz, $^4J_{HH}$ = 1,51 Hz, 2H, 1'-H), 5,21 (dt, $^3J_{HH}$ = 10,43 Hz, $^4J_{HH}$ = 1,51 Hz, $^2J_{HH}$ = 1,23 Hz, 1H, 3'-H_{cis}), 5,28 (dt, $^3J_{HH}$ = 17,29 Hz, $^4J_{HH}$ = 1,51 Hz, $^2J_{HH}$ = 1,23 Hz, 1H, 3'-H_{trans}), 5,87 (ddt, 1H, $^3J_{HH}$ = 5,76 Hz, $^3J_{HH}$ = 10,43 Hz, $^3J_{HH}$ = 17,29 Hz, 2'-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int})* δ *(ppm)* = 13,91 (CH_3, 6''-C), 22,43 (CH_2, 5''-C), 24,59 (CH_2, 4''-C), 28,86 (CH_2, 3''-C), 31,54 (CH_2, 2''-C), 34,32 (CH_2, 1''-C), 65,88 (CH_2, 1'-C), 70,41 (CH, C-α), 118,79 (CH_2, 3'-C), 131,45 (CH, 2'-C), 174,99 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 200 (2) $[M+H]^+$, 182 (1) $[M-H_2O]^+$, 171 (7) $[M-C_2H_5]^+$, 115 (30) $[M-C_2H_5O_2]^+$, 97 (86) $[M_{115}-H_2O]^+$, 69 (25) $[M_{97}-C_2H_4]^+$, 55 (100) $[C_4H_7^+]$, 43 (40) $[C_3H_7^+]$.

2-Hydroxyhexanoic acid benzyl ester ***(9b)****12*

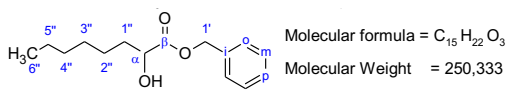
Colourless oil (1,38 g, 6,2 mmol, 87%) from 0,94 g (7,1 mmol) of 2-hydroxyhexanoic acid and 2,24 g (7,1 mmol) of *O*-benzyl isourea **5** dissolved in 50 mL of dry THF, stirring and refluxing for 19 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (1 / 1) mixture as eluent. R_f (SiO_2) = 0,56 (*n*-hexane : diethyl ether, 1 : 1, v : v).



IR (ATR) σ (cm^{-1}) = 3478 (W) [ν (O-H)], 2957 (M) [ν (-CH_2-)], 1731 (S) [ν (C=O)], 1193 (S) [ν (C-O-C)], 1129 (S) [ν (C-O)], 1083 (S) [ν (C-O)], 749 (S) and 696 (VS) [ν (C-H arom. monosubstituted)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 0,87 (t, $^3J_{HH}$ = 7,35 Hz, 3H, 4''-H), 1,20-1,49 (m, 4H, 3''-H and 2''-H), 1,57-1,72 (m, 1H, 1''-H), 1,73-1,86 (m, 1H, 1''-H), 2,95 (d, $^3J_{HH}$ = 5,90 Hz, 1H, O-H), 4,21 (ddd, $^3J_{HH}$ = 7,27 Hz, $^3J_{HH}$ = 5,90 Hz, $^3J_{HH}$ = 4,25 Hz, 1H, H-α), 5,17 (d, $^2J_{HH}$ = 12,21 Hz, 1H, 1'-H), 5,22 (d, $^2J_{HH}$ = 12,21 Hz, 1H, 1'-H), 7,30-7,37 (m, 5H, arom-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 13,79 (CH_3, 4''-C), 22,28 (CH_2, 3''-C), 26,71 (CH_2, 2''-C), 33,98 (CH_2, 1''-C), 67,09 (CH_2, 1'-C), 70,44 (CH, C-α), 128,52 (CH, *ortho*-C), 128,22 (CH, *para*-C), 128,41 (CH, *meta*-C), 135,21 (C^q, *ipso*-C), 175,16 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 223 (2) $[M+H]^+$, 204 (1) $[M-H_2O]^+$, 91 (100) $[C_7H_7^+]$, 87 (38) $[C_5H_{11}O^+]$, 77 (6) $[C_6H_5^+]$, 69 (87) $[C_5H_9^+]$, 65 (13) $[C_5H_5^+]$, 41 (29) $[C_3H_5^+]$.

2-Hydroxyoctanoic acid benzyl ester ***(9c)***

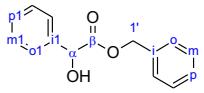
Colourless oil (3,76 g, 15,0 mmol, 94%) from 2,55 g (15,9 mmol) of 2-hydroxyoctanoic acid and 5,00 g (15,9 mmol) of *O*-benzyl isourea **5** dissolved in 150 mL of dry THF, stirring and refluxing for 19 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / diethyl ether (2 / 3) mixture as eluent. R_f (SiO_2) = 0,56 (*n*-hexane : diethyl ether, 1 : 1, v : v).



IR (ATR) σ (cm^{-1}) = 3483 (W) [ν (O-H)], 2927 (M) [ν (-CH_2-)], 2958 (W) [ν (-CH_2-)], 1732 (S) [ν (C=O)], 1187 (S) [ν (C-O)], 1130 (S) [ν (C-O)], 749 (S) and 696 (VS) [ν (C-H arom. monosubstituted)]; *^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 0,86 (t, $^3J_{HH}$ = 7,13 Hz, 3H, 6''-H), 1,15-1,50 (m, 8H, 5''-4''-3'' and 2''-H), 1,56-1,71 (m, 1H, 1''-H), 1,71-1,86 (m, 1H, 1''-H), 2,86 (d, $^3J_{HH}$ = 5,76 Hz, 1H, O-H), 4,21 (ddd, $^3J_{HH}$ = 7,13 Hz, $^3J_{HH}$ = 5,76 Hz, $^3J_{HH}$ = 4,40 Hz, 1H, H-α), 5,17 (d, $^2J_{HH}$ = 12,21 Hz, 1H, 1'-H), 5,22 (d, $^2J_{HH}$ = 12,21 Hz, 1H, 1'-H), 7,32-7,37 (m, 5H, arom-H); *^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 13,97 (CH_3, 6''-C), 22,45 (CH_2, 5''-C), 24,55 (CH_2, 4''-C), 28,88 (CH_2, 3''-C), 31,57 (CH_2, 2''-C), 34,33 (CH_2, 1''-C), 67,15 (CH_2, 1'-C), 70,48 (CH, C-α), 128,27 (CH, *meta*-C), 128,46 (CH, *ortho*-C), 128,57 (CH, *para*-C), 135,22 (C^q, *ipso*-C), 175,21 (C^q, C=O); *MS (GC inlet, EI, 70 eV) m/z (%)* = 250 (2) $[M^+]$, 115 (22) $[C_7H_{15}O^+]$, 97 (59) $[C_7H_{13}^+]$, 91 (100) $[C_7H_7^+]$, 77 (4) $[C_6H_5^+]$, 55 (90) $[C_4H_7^+]$, 43 (20) $[C_3H_7^+]$.

2-Hydroxy-2-phenylacetic acid benzyl ester ***(9d)***[8]

White solid (3,11 g, 12,8 mmol, 94%) from 2,08 g (13,7 mmol) of mandelic acid and 4,33 g (13,7 mmol) of *O*-benzyl isourea **5** dissolved in 60 mL of dry toluene, stirring and refluxing for 19 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using petroleum ether / ethyl acetate (4 / 1) mixture as eluent. R_f (SiO_2) = 0,56 (petroleum ether : ethyl acetate, 4 : 1, v : v). m. p. = 92 ºC.

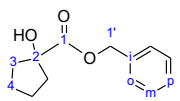


Molecular Formula = $C_{15}H_{14}O_3$
Formula Weight = 242,26986

IR (KBr) σ (cm^{-1}) = 3447 (W) [ν (O-H)], 1729 (S) [ν (C=O)], 1210 (S) [ν (C-O-C)], 1182 (S) [ν (C-O)], 1098 (S) [ν (C-O)], 727 (S) and 693 (VS) [ν (C-H aromatic mono substituted)]; *^{1}H-NMR (400 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 3,47 (d, $^3J_{HH}$ = 5,74 Hz, 1H, OH), 5,13 (d, $^2J_{HH}$ = 12,21, 1H, 1"-H), 5,24 (d, $^2J_{HH}$ = 12,21, 1H, 1"-H), 5,21 (s, 1H, H-α), 7,33-7,45 (m, 10H, aromatic H); *^{13}C-NMR (100 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 67,68 (CH_2, C-1"), 72,72 (CH, C-α), 126,57 (CH, C-*ortho1*), 127,93 (CH, C-*meta1*), 128,44 (CH, C-*para1*), 128,49 (CH, C-*ortho*) 128,55 (CH, C-*meta*), 128,59 (CH, C-*para*), 134,92 (C_q, C-*ipso*), 138,11 (C_q, C-*ipso1*), 173,51 (C_q, C=O); *MS (CG inlet, EI, 70 eV) m/z (%)* = 107 (100) [$C_7H_7O^+$], 91 (50) [$C_7H_7^+$], 79 (50) [$C_6H_5^+$].

1-Hydroxy-1-cyclopentancarboxylic acid benzyl ester ***(9e)***

Colourless oil (2,11 g, 9,22 mmol, 95%) from 1,20 g (9,23 mmol) of 1-hydroxycyclopentanecarboxylic acid and 3,01 g (9,57 mmol) of O-benzyl isourea **5** dissolved in 50 mL of dry THF, stirring and heating at 50 ºC for 15 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using *n*-hexane / ethyl acetate (5 / 1) mixture as eluent. R_f (SiO_2) = 0,50 (*n*-hexane : ethyl acetate, 5 : 1, v : v).

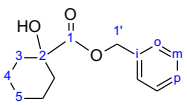


Molecular Formula = $C_{13}H_{16}O_3$
Formula Weight = 220,26434

IR (KBr) σ (cm^{-1}) = 3486 (S) [ν(OH)], 3070 (M), 3039 (M), 2962 (S), 2869 (S), 1727 (VS) [ν(C=O)], 1604 (W), 1542 (W), 1496 (M), 1450 (S), 1373 (S), 1265 (VS) [ν(-O-C(O)-C)]; *^{1}H-NMR (400 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 1,70-2,15 (m, 8H, cycloalkane-H), 3,29 (s, 1H, O-H), 5,19 (s, 2H, CH_2Ph), 7,32 (t, 1H, *para*-H), 7,34 (td, 2H, *meta*-H), 7,36 (d, 2H, *ortho*-H); *^{13}C-NMR (100 MHz, $CDCl_3$, TMS_{int}) δ (ppm)* = 24,92 (3-C, x2), 39,65 (4-C, x2), 67,25 (CH_2-Ph), 81,81 (2-C), 128,06 (*ortho*-C, x2), 128,43 (*para*-C), 128,66 (*meta*-C, x2), 135,55 (*ipso*-C), 177,27 (C=O); *MS (CG inlet, EI, 70 eV) m/z (%)* = 220 (1) [M^+], 202 (2) [M^+-H_2O], 107 (3) [M^+-$C_6H_9O_2$], 91 (71) [M^+-$C_6H_9O_3$], 85 (100) [M^+-$C_8H_7O_2$], 77 (10) [M^+-$C_7H_{11}O_3$], 67 (35) [85-H_2O], 65 (15) [67-H_2].

1-Hydroxy-1-cyclohexancarboxylic acid benzyl ester ***(9f)***

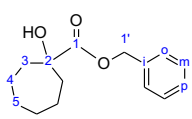
White solid (3,74 g, 16,0 mmol, 85%) from 2,71 g (18,81 mmol) of 1-hydroxycyclohexanecarboxylic acid and 6,00 g (19,08 mmol) of *O*-benzyl isourea **5** dissolved in 50 mL of dry THF, stirring and heating at 50 ºC for 15 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using n-hexane / ethyl acetate (10 / 1) mixture as eluent. R_f (SiO_2) = 0,60 (*n*-hexane : ethyl acetate, 10 : 1, v : v). m. p. = 54 ºC.



IR (KBr) σ (cm^{-1}) = 3502 (S) [ν(OH)], 2931 (S), 2854 (M), 1712 (VS) [ν(C=O)], 1450 (M) [ν(COOH)], 1388 (M), 1280 (S), 1218 (S); *^{1}H-NMR (400 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm)* = 1,21-1,87 (m, 10H, cycloalkane-H), 2,91 (s, 1H, O-H), 5,19 (s, 2H, CH_2Ph), 7,32 (t, 1H, *para*-H), 7,34 (td, 2H, *meta*-H), 7,36 (d, 2H, *ortho*-H); *^{13}C-NMR (100 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm)* = 21,13 (3-C, x2), 25,18 (5-C), 34,67 (4-C, x2), 67,25 (CH_2-Ph), 73,67 (2-C), 128,03 (*ortho*-C, x2), 128,43 (*para*-C), 128,66 (*meta*-C, x2), 135,52 (*ipso*-C), 177,21 (C=O); *MS (CG inlet, EI, 70 eV) m/z (%)* = 234 (1) [M^+], 216 (2) [M^+-H_2O], 125 (1) [216-C_7H_7], 110 (3) [M^+-$C_7H_8O_2$], 99 (100) [M^+-$C_8H_7O_2$], 91 (36) [M^+-$C_7H_{11}O_3$], 81 (47) [216-$C_8H_7O_2$], 55 (10) [81-C_2H_2].

1-Hydroxy-1-cycloheptancarboxylic acid benzyl ester ***(9g)***

Colourless oil (2,12 g, 8,57 mmol, 97%) from 1,40 g (8,84 mmol) of 1-hydroxycycloheptanecarboxylic acid and 3,01 g (9,57 mmol) of *O*-benzyl isourea **5** dissolved in 50 mL of dry THF, stirring and heating at 50 ºC for 15 h under argon atmosphere. The product was purified by column chromatography on SiO_2 using n-hexane / ethyl acetate (5 / 1) mixture as eluent. R_f (SiO_2) = 0,60 (n-hexane : ethyl acetate, 5 : 1, v : v).

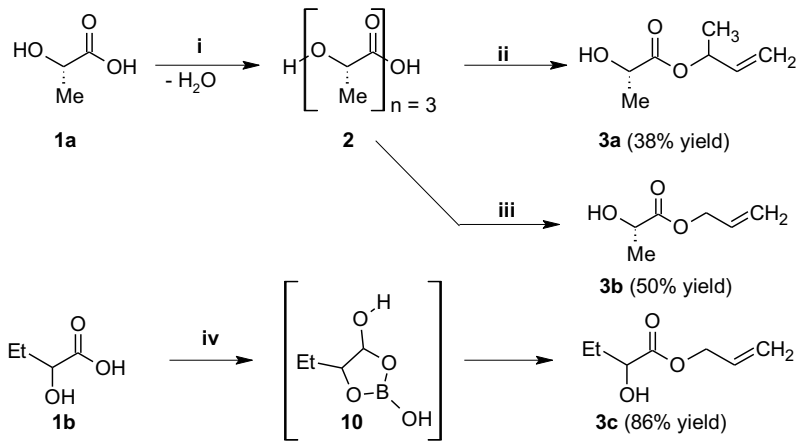


IR (KBr) σ (cm^{-1}) = 3517 (W) [ν(OH)], 3070 (W), 3039 (W), 2931 (M), 2854 (M), 1727 (M) [ν(C=O)], 1604 (VW), 1542 (VW), 1496 (W), 1450 (M) [ν(COOH]; *^{1}H-NMR (400 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm)* = 1,45-2,04 (m, 12H, cycloalkane-H), 3,35 (s, 1H, O-H), 5,18 (s, 2H, CH_2PH), 7,32 (t, 1H, *para*-H), 7,34 (td, 2H, *meta*-H), 7,36 (d, 2H, *ortho*-H); *^{13}C-NMR (100 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm)* = 22,62 (3-C, x2), 29,60 (5-C, x2), 38,87 (4-C, x2), 67,23 (CH_2-Ph), 76,96 (2-C), 127,98 (*ortho*-C, x2), 128,39 (*para*-C), 128,65 (*meta*-C, x2), 135,60 (*ipso*-C), 178,06 (C=O); *MS (CG inlet, EI, 70 eV) m/z (%)* = 157 (1) [M^+-C_7H_6], 124 (1) [M^+-$C_7H_8O_2$], 113 (100) [157-CO_2], 95 (43) [M^+-H_2O-$C_7H_6O_2$], 91 (44) [M^+-$C_7H_{11}O_3$], 67 (10) [124-C_4H_7], 55 (10) [124-C_4H_3O].

RESULTS AND DISCUSSION

The synthesis of allyl and benzyl α-hydroxyesters has been reported to work properly through a transesterification reaction from the α-hydroxyacid self-condensed product; in the case of lactic acid, a linear oligomer (of about 3 units) is initially formed (Scheme 1) and it can be converted into the corresponding ester using an excess of allyl alcohol, according to previous reports in the literature.[11,13] Modified Fischer esterification reaction is not completely effective due to the dual functional groups existence in the α-hydroxyacid and is a common

mistake confirm the formation of products via IR or NMR (secondary products have similar vibration bands and chemical shifts to the expected product); when following the progress of the reaction using GC, the formation of secondary compounds can be clearly observed.



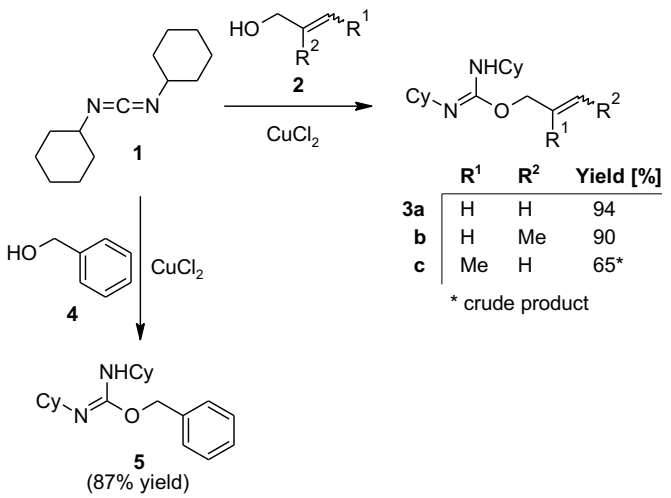
Reagents and conditions: (**i**) Benzene, H_2SO_4 (cat), reflux, 4-6 h. (**ii**) Methallyl alcohol, 60 ∝C, 20 h. (**iii**) Allyl alcohol, 60 ∝C, 20 h. (**iv**) Allyl alcohol (as solvent), H_3BO_3 (10% mol), reflux, 18 h.

Scheme 1. Preparation of allyl (an methallyl) esters from α-hydroxy acids

After using this methodology it was possible to form methallyl lactate and allyl lactate in relatively good yields (Scheme 1). Unfortunately ester interchange occurs and polylactic acid (as linear polyester) was also formed. A small amount of the dimer of lactic acid allyl ester was also found in the NMR spectra. Preparation of methallyl lactate was not wholly satisfactory because the acid catalyzes the rearrangement of methallyl alcohol to isobutyraldehyde.[11] Trying to avoid this problem, boric acid was used as catalyst (the proposed intermediate is a boron complex between the carboxylic and the hydroxyl function, as shown in Scheme 1); the allyl alcohol attack the complex formed, thus the dimer is not formed. Unfortunately the boric acid catalyzed reaction works very well only when a high amount of allyl alcohol is used.[14] The use of borane in the synthesis of lactones by ester exchange has been also reported.[15]

Another common way to esterify carboxylic acids is to treat them with an alcohol in the presence of a dehydrating agent. One of most known agents is DCC (dicyclohexylcarbodiimide) **1**, which over the past years has proven to be an exceptionally useful reagent.[16] The carbodiimide is converted in the process to an isourea and eventually to *N,N'*-dicyclohexylurea (DCU): the urea is the more thermodynamically stable of the two isomers and its formation provides the driving force for the ready conversion of the isourea to the urea via loss of the oxygen substituent. It is this driving force the basis for the synthetic applications of isoureas.

Given the relatively low yields (and formation of secondary products) of the modified Fischer and the boric acid mediated esterification, the synthesis of α-hydroxycarboxylic acid allyl **7** and benzyl esters **9** was achieved by the carbodiimide method. Work in this field of chemistry has been restarted since it facilitates the convenient preparation and use of polymer supported O-allyl(benzyl)isoureas.[17]



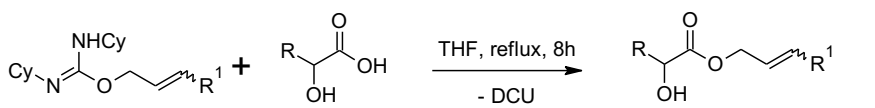
Scheme 2. Preparation of benzyl and substituted allyl isoureas.

According to Faure et al. when using Steglich conditions for the synthesis of allyl lactate (DCC + DMAP+ allyl alcohol + lactic acid), the dimer was also formed but to a minor degree.[18] It is also worth mentioning that with this normal method, the thermally unstable *O*-alkylisourea is the intermediate in the reaction. Rearrangement of this species to the *N*-alkylurea decreases the overall yield and more importantly, this side product is often difficult to remove from the desired material. Thus, the need for careful temperature control, and the formation of impurities somewhat limits the application of the Steglich method. Furthermore, exclusion of water is necessary to prevent hydrolysis of the isourea intermediates **3/5**.

Consequently the reactions were carried out by initially preparing the isoureas (Scheme 2) and reacting them with diverse α-hydroxyacids (Schemes 3 and 4). The diverse *O*-alkyl isoureas employed as mild esterification reagents were prepared following the initial survey by Vowinkel.[10] Only the O-but-2-enyl isourea **3c** derived from crotyl alcohol was not purified, but used directly without further separation (it decomposes during the SiO_2 column chromatography). Thus, *in situ* isourea generation in a *one-pot* reaction was a viable alternative for the use of the reactive isourea intermediate **3c**.

The individual steps in the process were carried out separately; thus, the isourea was isolated before conversion to the ester. This offers two advantages over the normal procedure: the *O*-alkylisourea is not converted into the *N*-alkylisourea due to thermal rearrangement, the *O*-alkylisourea may be purified prior to use, and, more importantly, they may be stored for extended periods of time. In the absence of moisture, typical isoureas may be stored in the cold or on the shelf for several months with little or no change in quality. Moisture causes gradual hydrolysis to the alcohol and the urea, although it was found that absolute drying of solvents was not necessary for high yields.

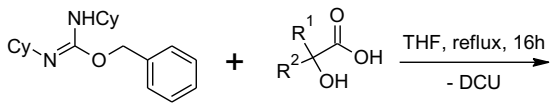
Ester formation via the isourea is mild, have a simple work up and proceeds in excellent yields with high purity of the final products (Schemes 3 and 4); also, no large excess of alcohol is necessary.[19] When comparing with other methodologies, the isourea method initially failed in the case of the synthesis of allyl lactate **7a** because of the high amount of water inside the commercial lactic acid (up to 20% water inside) which hydrolyzes the isourea formed. Removal of water using a THF solution of lactic acid with Na_2SO_4 overnight result in a lactic acid solution dry enough to perform the reaction, giving the corresponding ester **7a** with a similar reaction yield but without those secondary products observed by GC when using the transesterification methodology.



	R	R^1	Yield [%]
7a	Me	H	50
7b	Et	H	73
7c	*n*-Bu	H	97
7d	*n*-Bu	Me	98
7e	*n*-Hex	H	94

Scheme 3. Preparation of allyl α-hydroxyesters.

To facilitate both the reaction and purification, THF was used as solvent once the side-product *N,N'*-dicyclohexylurea (DCU) is insoluble. DCU can also be effectively separated out washing the reaction mixture with methylene chloride. After diverse derivatives 7 were prepared, several examples of *O*-benzylesters **9** were also prepared using the same reaction conditions (Scheme 4). Purity of final products and yields are in the same range although cyclic α-hydroxycarboxylic acid esters preparation presented slightly lower yields due presumable to sterical reasons. For lactic and mandelic acid benzyl esters (**9a** and **9d** respectively) the reaction was completed also using toluene as solvent, giving comparable results.



	R^1	R^2	Yield [%]
9a	H	Me	94
9b	H	*n*-Bu	87
9c	H	*n*-Hex	94
9d	H	Ph	85
9e	-$(CH_2)_4$-		60
9f	-$(CH_2)_5$-		72
9g	-$(CH_2)_6$-		70

Scheme 4. Preparation of benzyl α-hydroxyesters.

All compounds were purified by column chromatography and obtained in high yields as colourless oils; white crystals were obtained in the case of **9d** and cyclic α-hydroxyester **9f**. Mass spectra at 70 eV (electron impact) show typical fragmentation of esters and alcohols; in all cases molecular ion can be observed as well as water loss; for benzyl esters **9a-g**, benzyl fragments appear in all MS spectra in *(m/z)* 91, 77 and 65. ^{13}C-NMR data for all compounds show clearly the C=O between 173-178 ppm. Benzyl methylene carbon is registered at 77 ppm while allyl methylene carbon appears nearby 66 ppm. ^{1}H-NMR show CH_2-Ph protons as singlets around 5,19 ppm. Different multiplicity was observed for allyl hydrogens; complete coupling constant assignments are reported in the experimental section.

CONCLUSIONS

Several examples of allyl and benzyl α-hydroxyesters were prepared using a mild modified Steglich isourea procedure in a two steps process avoiding the use of DMAP. The soft conditions used and high reaction yields obtained favored this methodology while standard methods normally use expensive halide compounds, metal salts, non-green solvents or the alkylating agent itself as solvent. Due to the dual functionality of α-hydroxyacids, modified Fischer esterification reaction generate also unknown esters as secondary products, which can be easily confused with the target compound when no GC (or GC-MS) control is used. Detailed conditions for the preparation of diverse allyl and benzyl α-hydroxyesters as well as their complete 1H and 13C-NMR assignments is given.

AKNOWLEDGMENTS

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REFERENCES

1. Otera J. Esterification: Methods, Reactions, and Applications. Weinheim: Wiley-VCH; 2003.
2. Sato T, Otera J, Nozaki H. Cesium fluoride-promoted esterification of carboxylic acids. A practical alternative to the diazomethane method and direct conversion of organotin carboxylates J Org Chem. 1992; 57: 2166-2169.
3. Sato T, Otera J. CsF in Organic Synthesis. Malonic Ester Synthesis Revisited for Stereoselective Carbon-Carbon Bond Formation. J Org Chem. 1995; 60: 2627-2629.
4. Masaki Y, Tanaka N, Miura T. Mild Esterification and Transesterification of Carboxylic Acids Catalyzed by Tetracyanoethylene and Dicyanoketene Dimethyl Acetal. Chem Lett. 1997; 26: 55-56.
5. Weng S-S, Chen F-K, Ke C-S. Direct Esterification of Carboxylic Acids with Alcohols Catalyzed by Iron(III) Acetylacetonate ComplexSynth Commun. 2013; 43: 2615-2621.
6. Weng S-S, Li H-C, Yang T-M. Chemoselective esterification of α-hydroxyacids catalyzed by salicylaldehyde through induced intramolecularity. RSC Adv. 2013; 3: 1976-1986.
7. Badache L, Rahal S, Ghosez L. Synthese et caracterisation d'une serie de O-alkyl-N,N'-dialylisourees. J Soc Alger Chim. 2002; 12: 11-19.
8. Chighine A, Crosignani S, Arnal M-C, Bradley M, Linclau B. Microwave-Assisted Ester Formation Using O-Alkylisoureas: A Convenient Method for the Synthesis of Esters with Inversion of Configuration. J Org Chem. 2009; 74: 4753-4762.
9. Inoue Y, Taguchi M, Hashimoto H. Direct N-Allylation of Amides with 2-Allylisourea Catalyzed by Palladium(0). Bull Chem Soc Jpn. 1985; 58: 2721-2722.
10. Vowinkel E. Darstellung von Arylalkyläthern mittels O-Alkyl-N.N′-dicyclohexyl-isoharnstoffen. Chem Ber. 1966; 99: 1479.
11. Rehberg CE. Allyl Lactate. Org Synth. 1946; 26: 4.
12. Raddatz P, Minck K-O, Rippmann F, Schmitges CJ. Non-peptide renin inhibitors containing 2-(((3-phenylpropyl)phosphoryl)oxy)alkanoic acid moieties as P2-P3 replacements.J Med Chem. 1994; 37: 486-497.
13. Rehberg CE, Fisher CH. Preparation and polymerization of acrylic esters of olefinic alcohols.J Org Chem. 1947; 12: 226-231.
14. Houston TA, Wilkinson BL, Blanchfield JT. Boric acid catalyzed chemoselective esterification of alpha-hydroxycarboxylic acids.Org Lett. 2004; 6: 679-681.
15. Konoike T, Araki Y. Practical Synthesis of Chiral Synthons for the Preparation of HMG-CoA Reductase Inhibitors. J Org Chem. 1994; 59: 7849-7854.
16. Neises B, Steglich W. Simple Method for the Esterification of Carboxylic Acids Angew Chem Int Ed Engl. 1978; 17: 522-524.
17. Crosignani S, White PD, Steinauer R, Linclau B. Polymer-Supported O-Benzyl and O-Allylisoureas: Convenient Preparation and Use in Ester Synthesis from Carboxylic Acids. Org Lett. 2003; 5: 853-856.
18. Faure S, Piva-Le-Blanc S, Bertrand C, Pete JP, Faure R, Piva O. Asymmetric intramolecular [2 + 2] photocycloadditions: alpha- and beta-hydroxy acids as chiral tether groups. J Org Chem. 2002; 67: 1061-1070.
19. Mathias LJ. Esterification and alkylation reactions employing isoureas. Synthesis. 1979; 8: 561.