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Supporting Information

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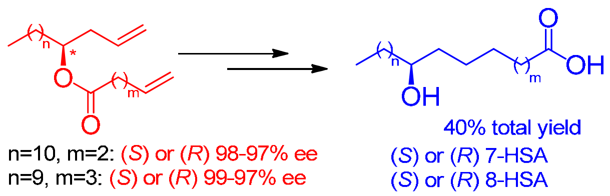
Supporting information

An easy route to enantiomerically enriched 7- and 8-Hydroxystearic Acids by olefin metathesis-based approach



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General methods

IR spectra were recorded on a Thermo Nicolet AVATAR 320 FT/IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were run on a Jeol (Tokyo, Japan) EX-400 spectrometer (400 MHz for proton, 100 MHz for carbon), on a Jeol EX-270 spectrometer (270 MHz for proton, 68 MHz for carbon) and on a Varian Mercury 400 or an Inova 300 or 600 spectrometer (Varian, Palo Alto, CA) using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants are given in Hz. Signal multiplicities were assigned by DEPT experiments. ^{19}F NMR spectra were recorded on a Varian Mercury 400 at 376 MHz in $CDCl_3$ using hexafluorobenzene (δ = –163.0 ppm) as internal standard. Optical rotations at 589 nm were determined on a Perkin Elmer (Boston, MA) Model 241 and a Jasco P-2000 polarimeter; optical rotatory power values are given in 10^{-1} deg cm^{2} g^{-1}. Capillary gas chromatographic measurements were performed on a Shimadzu (Kyoto, Japan) GC-14B instrument, equipped with a flame ionization detector, the capillary column being a DiMePe ß-cyclodextrin (25 m x 0.25 mm) (ß-CDX) (carrier gas He, 110 KPa, split 1:50). Melting points were measured with a Büchi apparatus and were not corrected. Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer (Copenhagen, Denmark). Mass spectra were recorded on a ESI-MS ion trap Bruker (Karlsruhe, Germany) Esquire 4000 instrument and on a ion trap instrument Finnigan GCQ (70 eV). TLC's were performed on Polygram Sil G/UV_{254} silica gel pre-coated plastic sheets (eluent: light petroleum-ethyl acetate). Flash chromatography was run on silica gel 230-400 mesh ASTM (Kieselgel 60, Merck, Darmstadt, Germany). For mehylation and derivatization of HSAs, thin-layer chromatography (TLC) was carried out using silica gel precoated on TLC Alu foils from Fluka and spots were revealed using an aqueous solution of $(NH_4)_6MoO_{24}$(25%), $(NH_4)_4Ce(SO_4)_4$(1%) in 10% H_2SO_4 as staining reagent. For preparative TLC 20x20 silica gel plates (Merck Kieselgel $60F_{254}$) were used. Light petroleum refers to the fraction with b.p. 40–70 °C and ether to diethyl ether. Anhydrous ether was prepared by distillation over sodium benzophenone ketyl. Anhydrous CH_2Cl_2 was prepared by washing with water and drying overnight over anhydrous $CaCl_2$, after filtration the solvent was gentle refluxed with P_2O_5 for 6-8 h then distilled and kept over 4 Å molecular sieves.

Alcohols **6a** and **6b** were prepared according to the literature.[1] HRGC: Chiral HRGC DiMePe ß-cyclodextrin (ß-CDX), 100°C for 2 min, 3°C/min until 150°C, retention time [t_R] = 43.1 min for (*S*)-(–)-**6a**; t_R = 43.9 min for (*R*)-(+)-**6a**; t_R = 31.0 min for (*S*)-(–)-**6b,** t_R = 31.5 min for (*R*)-(+)-**6b**.

Synthesis of racemic substrates 7a and 7b.

To a solution of 2.5 mmol of alcohol **6a** or **6b** in 10 mL of 1,4-dioxane, 0.6 g (5 mmol) of 4-(dimethylamino)pyridine (DMAP) and 0.7 mL (7.5 mmol) of acetic anhydride were added. After stirring overnight the solvent was evaporated, HCl 2.4 N was added and extracted with ether. Organic phases were dried on anhydrous Na_2SO_4, and evaporated. After purification by flash chromatography esters **7a** or **7b** were obtained in 70% yield.

1-Pentadecen-4-yl acetate 7a: oil, IR, film (cm^{-1}): 1741 (OCO), 1643 (C=C); ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 5.75 (1 H, ddt, $J_1 = J_2 = 7.1$, $J_3 = 10.3$, $J_4 = 17.0$, H-2), 5.07 (2 H, m, H-1), 4.91 (1 H, quintet, J = 6.2, H-4), 2.30 (2 H, m, H-3), 2.04 (3 H, s, CH_3CO), 1.53 (2 H, m), 1.4-1.1 (18 H, m), 0.88 (3 H, t, J = 6.5, CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 170.8 (s, OCO), 133.8 (d, C-

2), 117.5 (t, C-1), 73.3 (d, C-4), 38.6 (t), 33.6 (t), 31.9 (t), 29.6 (2 t), 29.55 (t), 29.5 (t), 29.4 (t), 29.3 (t), 25.3 (t), 22.7 (t), 21.2 (q, CH_3CO), 14.1 (q, CH_3); MS (EI), (m/z): 268 (34, M^{+}), 226 (23), 209 (22, $M^{+}\cdot$-$OCOCH_3$), 208 (25), 206 (25), 167 (28), 149 (34), 136 (18), 123 (24), 111 (80), 110 (78), 109 (58), 97 (100), 96 (61), 95 (87), 83 (45), 81 (87), 79 (42), 69 (67), 67 (91), 57 (19), 55 (61); HRGC: (ß-CDX), 100°C for 2 min, 3°C/min until 150°C, t_R = 45.8 min for (*R*)-(+)-**7a**; t_R = 46.6 min for (*S*)-(–)-**7a**.

1-Tetradecen-4-yl acetate 7b: oil, IR, film (cm^{-1}): 1741 (OCO), 1643 (C=C); ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 5.75 (1 H, ddt, $J_1 = J_2$ = 7.0, J_3 = 10.2, J_4 = 17.1, H-2), 5.07 (2 H, m, H-1), 4.91 (1 H, quintet, J = 6.2, H-4), 2.29 (2 H, m, H-3), 2.03 (3 H, s, CH_3CO), 1.52 (2 H, m), 1.4-1.1 (16 H, m), 0.88 (3 H, t, J = 6.5, CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 170.8 (s, OCO), 133.8 (d, C-2), 117.5 (t, C-1), 73.3 (d, C-4), 38.6 (t), 33.5 (t), 31.9 (t), 29.6 (t), 29.55 (t), 29.5 (t), 29.4 (t), 29.3 (t), 25.3 (t), 22.7 (t), 21.2 (q, $\underline{C}H_3CO$), 14.1 (q, CH_3); MS, (EI) (m/z): 254 (13, $M^{+\cdot}$), 239 (10), 213 (12), 195 (15, $M^{+\cdot}$-$OCOCH_3$), 181 (15), 167 (51), 155 (23), 149 (94), 111 (39), 109 (16), 97 (100), 95 (39), 83 (60), 81 (43), 71 (25), 69 (33), 67 (42), 57 (28), 55 (43); HRGC: (ß-CDX), 100°C for 2 min, 3°C/min until 150°C, t_R = 32.7 min for (*R*)-(+)-**7b**; t_R = 33.2 min for (*S*)-(–)-**7b**.

Enzymatic hydrolyses

To 2.7 mmol of ester **7a** or **7b** in 70 mL of phosphate buffer at pH 7.4, 0.35 g of Novozym 435 (7000 U/g) was added, the mixture was stirred while maintaining the pH value constant by addition of 1M NaOH, the course of the reaction was monitored by chiral HRGC and stopped at about 50% conversion. When the reaction became too slow 50-100 mg of enzyme was added, after about 8 days the enzyme was filtrated and the buffer solution was extracted with ether. After separation by flash chromatography alcohols (*S*)-(–)-**6a** or (*S*)-(–)-**6b** were obtained in 31% yield and esters (*R*)-(+)-**7a** or (*R*)-(+)-**7b** in 28% yield. If necessary, to increase the enantiomeric excess, the recovered esters could be resubmitted to enzymatic hydrolysis. The moderate yields might be due to the difficult extraction process after significant degradation of the supported enzyme.

(*S*)-(–)-1-Pentadecen-4-ol 6a: all spectroscopic data are in accordance with the literature.[2,3]
98% ee, $[\alpha]_D^{25}$ = – 5.2 (c = 1.03, $CHCl_3$), [lit.[4] $[\alpha]_D^{25}$ = – 6.63 (c = 1.69, $CHCl_3$), lit.[5] $[\alpha]_D^{23}$ = – 6.3 (c = 1.23, $CHCl_3$)].

(*S*)-(–)-1-Tetradecen-4-ol 6b: all spectroscopic data are in accordance with the literature.[6,7]
99% ee, $[\alpha]_D^{25}$ = – 4.8 (c = 0.85, $CHCl_3$).

(*R*)-(+)-1-Pentadecen-4-yl acetate 7a: 97%ee, $[\alpha]_D^{25}$ = + 16.8 (c = 0.51, $CHCl_3$).

(*R*)-(+)-1-Tetradecen-4-yl acetate 7b: 97%ee, $[\alpha]_D^{25}$ = + 14.5 (c = 1.00, CH_2Cl_2).

0.260 g (1.02 mmol) of ester (*R*)-(+)-**7a** or **7b** were dissolved in 22,3 mL of MeOH, 0.282 g (2.04 mmol) of K_2CO_3 were added under stirring at room temperature, the reaction mixture was stirred for 24h at r.t. Solvent was evaporated, 30 mL of water were added to dissolve the solid and extracted with ether. The organic solvent was dried on anhydrous Na_2SO_4 and evaporated to furnish alcohols (*R*)-(+)-**6a** or **6b** in 92% yield.

(*R*)-(+)-1-Pentadecen-4-ol 6a: 97% ee, $[\alpha]_D^{25}$ = + 5.5 (c =1.00, $CHCl_3$) [lit.[2] $[\alpha]_D^{25}$ = + 5.5 (c =1.0, $CHCl_3$), lit.[3] $[\alpha]_D^{25}$ = +4.5 (c = 1.0, $CHCl_3$), lit.[8] $[\alpha]_D^{25}$ = + 5.78 (c =2.89, $CHCl_3$), lit.[9] $[\alpha]_D^{25}$ = + 6 (c =1.7, $CHCl_3$)

(*R*)-(+)-1-Tetradecen-4-ol 6b: 97% ee, $[\alpha]_D^{25}$ = + 4.3 (c =1.04, $CHCl_3$).

Synthesis of esters 4a and 4b.

The condensation of commercially available 4-pentenoic acid **5a** and 5-hexenoic acid **5b** with chiral non racemic alcohols **6a** and **6b** was carried out using the Yamaguchi's esterification reaction[10] that furnished dienes **4a** and **4b** respectively in 79 and 80% yield.

2,4,6-Trichlorobenzoyl chloride (TCBC, 0.312 mL, 1.99 mmol) was added to a stirred solution of 4-pentenoic acid **5a** (0.14 mL, 1.4 mmol) and triethylamine (0.37 mL, 2.7 mmol) in 6.4 mL of THF at 0 °C, under argon atmosphere. The reaction was stirred for 1h and 1-pentadecen-4-ol **6a** (0.3 g, 1.34 mmol) and 4-(dimethylammino)pyridine DMAP (0.448 g, 4 mmol) in 5 mL of THF were added. The reaction mixture was stirred at room temperature for 44 h, the course of the reaction was monitored by TLC (light petroleum : ethyl acetate 95:5). The reaction mixture was quenched with a saturated $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with ether (5 X 5mL). The combined organic layers were extracted with 3N HCl (1 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude was purified on a short column of SiO_2, washed with light petroleum: ethyl acetate 98:2. Compound **4a** (0.326 g, 1.06 mmol) was obtained in 79% yield. The same procedure was applied for the synthesis of **4b**.

1-Pentadecen-4-yl 4-pentenoate 4a: oil, IR (film, cm^{-1}): 1736 (C=O), 1642 (C=C) , 1174 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 5.86–5.68 (m, 2H, 2 C<u>H</u>=CH_2), 5.10–4.96 (m, 4H, 2 CH=C<u>H</u>$_2$), 4.92 (quintet, J= 6.2, 1H, CHOC=O), 2.37 (m, 4H), 2.29 (m, 2H), 1.52 (m, 2H), 1.33–1.19 (m, 18H), 0.87 (t, J= 6.8, 3H, CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 172.9 (s, C=O), 136.7 (d, $OCHCH_2$<u>C</u>H=CH_2), 133.8 (d, C=OCH_2CH_2<u>C</u>H=CH_2), 117.5 (t, $OCHCH_2CH$=<u>C</u>H_2), 115.4 (t, C=OCH_2CH_2CH=<u>C</u>H_2), 73.3 (d, <u>C</u>HOC=O), 38.5 (t), 33.6 (t), 33.4 (t), 31.8 (t), 29.5 (2t), 29.39 (t), 29.35 (t), 29.3 (t), 29.2 (t), 28.8 (t), 25.1 (t), 22.5 (t), 13.9 (q, CH_3) MS-ESI (CH_3OH): m/z 331 $[M+Na]^+$. Chiral HRGC: (ß-CDX), isotherm 150 °C, t_R = 110.0 min for (*R*)-(+)-**4a**, t_R = 112.0 min for (*S*)-(–)-**4a,**

(*S*)-(–)-**4a**: yield 79%, $[\alpha]^{25}_{D}$ = –22.2 (*c* 0.35, CH_3CN), 98 % e.e.

(*R*)-(+)-**4a**: yield 80%, $[\alpha]^{25}_{D}$ = +21.5 (*c* 0.41, CH_3CN), 97 % e.e.

1-Tetradecen-4-yl 5-hexenoate 4b: oil, IR (film, cm^{-1}): 1736 (C=O), 1642 (C=C), 1087 (C-O); ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 5.90-5.65 (m, 2H, 2 $C\underline{H}=CH_2$), 5.15-4.85 (m, 5H, 2 $CH=C\underline{H}_2$ and $C\underline{H}OC=O$), 2.40-2.20 (m, 4H), 2.15-2.00 (m, 2H), 1.80-1.65 (m, 2H), 1.60-1.45 (m, 2H), 1.40-1.10 (m, 16H, CH_2), 0.87 (t, 3H, CH_3, J=6.6); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 173.4 (s, C=O), 137.7 (d, $OCHCH_2\underline{C}H=CH_2$), 133.8 (d, $C=O(CH_2)_3\underline{C}H=CH_2$), 117.4 (t, $OCHCH_2CH=\underline{C}H_2$), 115.2 (t, $C=O(CH_2)_3CH=\underline{C}H_2$), 73.1 (d, $\underline{C}HOC=O$), 38.7 (t), 33.8 (t), 33.6 (2t), 33.1 (t), 31.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 25.2 (t), 24.1 (t), 22.6 (t), 14.1 (q, CH3). MS-ESI (CH_3OH): m/z 331 $[M+Na]^+$. Chiral HRGC: (ß-CDX), isotherm 150 °C, t_R = 102.5 min for (*R*)-(+)-**4b**, t_R =104.1 min for (*S*)-(–)-**4b**.

(*S*)-(–)-**4b**: yield 79%, $[\alpha]^{25}_{D}$ = –17.7 (*c* 0.32, CH_3CN), 99 % e.e.

(*R*)-(+)-**4b**: yield 80%, $[\alpha]^{25}_{D}$ = +15.5 (*c* 0.44, CH_3CN), 97 % e.e.

Synthesis of 7-HSA 1a

To 0.143 g (0.46 mmol) of (–)-(*S*)-**4a** in 14 mL of anhydrous DCM, 0.41 mL (1.38 mmol) of $Ti(O\text{-}^{i}Pr)_4$ was added at room temperature. The stirred solution was refluxed under Ar for 30 min and then left cooled for 15 min. 2nd Generation Grubbs' catalyst (0.0236 g, 0.027 mmol) dissolved in 1 mL of anhydrous DCM was added, the reaction was refluxed with stirring for 7 h in Ar atmosphere then left at room temperature overnight. The solution was filtered on a SiO_2 pad, and washed with DMC. The solvent was evaporated and to the crude reaction mixture (0.095 g) 4.75 mL of MeOH and 0.095 g of Pd/C (10%) were added. The reaction mixture was stirred under H_2 atmosphere for 24 h then filtered on a short column of SiO_2 and washed with DMC. The solvent was evaporated and the crude was treated with 3.0 mL of 10% KOH/MeOH, the mixture was stirred at 46 °C for 3 days. After removing the solvent, 10 mL of water were added and repeatedly extracted with ether. The organic phase was dried on anhydrous Na_2SO_4 and evaporated to afford diol **11a** (0.0045g, 0.01 mmol). Basic mother liquors were acidified to pH 1 and extracted with ether. The organic phase was dried on anhydrous Na_2SO_4 and evaporated to furnish the acid (*S*)-7-HSA **1a** (0.038 g, 0.12 mmol). Evaporation of acidic mother liquors furnished diacid **12a**. The same procedure was applied on (+)-(*R*)-**4a**. Total yields are related to the substrate concentration adopted in the metathetic process: when concentration of diene **4a** was 3mM, acids **1a** were recovered in about 40% yield, which gradually lowered to about 30% as concentration of **4a** raised up to 18 and 30 mM

(12*R*, 17*R*)-Octacosandiol 11a: white solid, m.p. 95-97 °C; IR (cm^{-1}, nujol): 3297 (OH); ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 3.65–3.50 (m, 2H, CH-OH), 1.60–1.15 (m, 48H), 0.88 (t, 6H, CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 71.9 (d, CHOH), 37.5 (t), 37.4 (t), 31.9 (t), 29.7 (t), 29.65 (t), 29.62 (2t), 29.6 (t), 29.3 (t), 25.65 (t), 25.64 (t), 22.7 (t), 14.1 (q, CH_3), $[\alpha]^{25}_D = -6.6$ (*c* 0.34, $CHCl_3$); MS-ESI (CH_3OH): m/z 449 $[M+Na]^+$.

Octanedioic acid 12a: ^{1}H-NMR (270 MHz, $CDCl_3$/DMSO-d6, δ, ppm): 2.26 (t, 4H), 1.62 (quintet, 4H), 1.30-1.62 (m, 4H); MS-ESI (negative mode): m/z 173 $[M-H]^-$.

Purification by flash chromatography of the metathesis crude reaction mixture, carried out on racemic **4a**, and hydrogenation of some fractions, allowed to isolate the head-to-tail dimer **8a**.

8,16-Diundecyl-1,9-dioxacyclohexadeca-2,10-dione 8a: ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 4.96–4.84 (m, 2H, CHOC=O), 2.31 (t, 4H, CH_2C=O), 1.79-1.04 (m, 56H), 0.88 (t, 6H, CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 173.8 (s, C=O), 74.1 (d, CHOC=O), 33.9 (t), 33.9 (t), 33.5 (t), 31.8 (t), 29.5 (t), 29.5 (t), 29.4 (t), 29.4 (t), 29.3 (t), 29.2 (t), 28.6 (t), 25.4(t), 24.6 (t), 24.1 (t), 22.5 (t), 13.9 (q, CH_3); MS-ESI (CH_3OH): m/z 587 $[M+Na]^+$

Synthesis of 8-HSA 1b

To 0.077 g (0.25 mmol) of (–)-(*S*)-**4b** in 72 mL of anhydrous DCM, 0.22 mL (0.75 mmol) of $Ti(O\text{-}^iPr)_4$ was added at room temperature. The stirred solution was refluxed under Ar for 30 min and then left cooled for 15 min. 1st Generation Grubbs' catalyst (0.012 g, 0.015 mmol) dissolved in 7.5 mL of anhydrous DCM was added, the reaction was refluxed with stirring for 8 h in Ar atmosphere. The solution was filtered on a SiO_2 pad, and washed with DMC. The solvent was evaporated and the brown crude reaction mixture was purified on a SiO_2 pad washing with 200 mL of petroleum ether/ethyl acetate (95/5), solvent was evaporated and to the crude reaction mixture (0.048 g) 2 mL of MeOH and 0.005 g of Pd/C (10%) were added. The reaction mixture was stirred under H_2 atmosphere for 24 h then filtered on a short column of SiO_2 and washed with DMC. The solvent was evaporated and the crude was treated with 2 mL of 10% KOH/MeOH, the mixture was stirred at 46 °C for 3 days. After removing the solvent, 10 mL of water were added and repeatedly extracted with ether. The organic phase was dried on anhydrous Na_2SO_4 and evaporated to afford traces of diol **11b**. Basic mother liquors were acidified to pH 1 and extracted with ether. The organic phase was dried on anhydrous Na_2SO_4 and evaporated to furnish the acid (*S*)-8-HSA **1b** (0.03 g, 0.10 mmol). The same procedure was applied on (+)-(*R*)-**4b**.

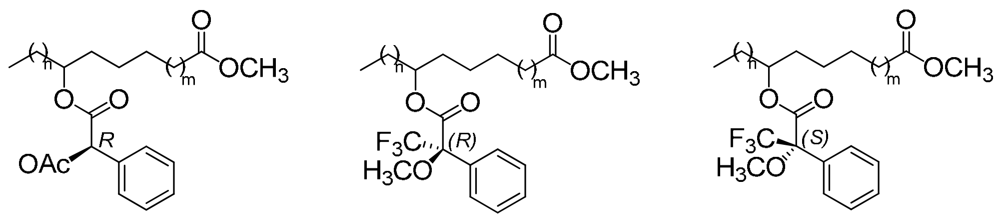
11,16-Hexacosandiol 11b: ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 3.60 (m, 2H, CH-OH), 1.95–1.15 (m, 46H), 0.87 (t, 6H, CH_3);^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 71.8 (d, CHOH), 37.5 (t), 37.3 (t), 31.8 (t), 29.6 (t), 29.53 (t), 29.51 (2t), 29.2 (t), 25.55 (t), 25.52 (t), 22.6 (t), 14.0 (q, CH_3).

Purification by flash chromatography of the metathesis crude reaction mixture and hydrogenation of some fractions, allowed to isolate the head-to-tail dimer **8b**.

(9*R*,18*R*)-9,18-didecyl-1,10-dioxacyclooctadeca-2,11-dione 8b: ^{1}H-NMR (270 MHz, $CDCl_3$, δ, ppm): 5.00-4.80 (m, 2H, 2 CHC=O), 2.45-2.10 (m, 4H), 1.80-1.00 (m, 56H), 0.87 (t, J=6.4, 6H, 2 CH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$, δ, ppm): 173.9 (s, C=O), 74.1 (d, CHOC=O), 35.2 (t), 34.8 (t), 34.4 (t), 32.0 (t), 29.8 (t), 29.65 (t), 29.62 (t), 29.6 (t), 29.4 (t), 29.1 (t), 29.0 (t), 25.5 (t), 25.3 (t), 25.2 (t), 22.7 (t), 14.1 (q, CH_3); MS-ESI (CH_3OH): m/z 587 $[M+Na]^+$.

Determination of optical purity of 1a and 1b

The optical purity of 7- and 8-hydroxystearic acids **1a** and **1b** was determined by NMR spectrometry after their esterification of the carboxylic moiety with diazomethane and derivatization with both (*R*)-(–)-*O*-acetylmandelic acid[11] (affording derivatives **13a** and **13b**, Figure 1) or enantiopure Mosher acid (**14a** and **14b**).



n = 10, m = 2: **13a**
n = 9, m = 3: **13b**

n = 10, m = 2: **14a**

n = 9, m = 3: **14b**

Figure S1. 7-HSA and 8-HSA acetyl mandelate derivatives **13a** and **13b** and Mosher derivatives **14a** and **14b**.

For derivatization with (*R*)-(–)-O-acetylmandelic acid and related ^{1}H NMR signals, see ref. 11. Integration of the ^{1}H NMR signals at δ = 5.869 ppm and at 5.861 ppm relative to H-2′ proton of (7*R*,2′*R*)- and (7*S*,2′*R*)-**13a** and that of the signals at δ = 5.871 ppm and at 5.867 ppm relative to H-2′ proton of (8*R*,2′*R*)- and (8*S*,2′*R*)-**13b** gave diastereomeric ratios of 99/1 for (7*R*,2′*R*)-**13a** and (7*S*,2′*R*)-**13a**, of 94/6 and 90/10 for (8*R*,2′*R*)-**13b** and (8*S*,2′*R*)-**13b**, respectively.

General procedure for derivatization with Mosher acid

0.012g of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid [(+)-MTPA, for derivatization of 7-HSA methyl esters], or (*S*)-(−)-α-methoxy-α-trifluorophenylacetic acid [(−)-MTPA, for 8-HSA methyl esters], and 0.003g of DMAP were dissolved, under nitrogen atmosphere, in anhydrous CH_2Cl_2 (300 μL) and stirred at 0°C (ice-bath). To this solution, 0.008 g of methyl hydroxystearate and 0.010g of DCC dissolved in anhydrous CH_2Cl_2 (500 μL) was added dropwise. After a few minutes, a white solid precipitated. The reaction was monitored by TLC (eluent: *n*-hexane – AcOEt 3:1) until completion (sometimes addition of a further amount of DCC and DMAP was necessary to reach completion). The solvent was removed and the crude was dissolved in $CDCl_3$ and analysed by ^{1}H NMR and ^{19}F NMR. The diastereomeric ratio was calculated by integration of the ^{19}F NMR signals; hexafluorobenzene (δ = –163.0 ppm) was used as internal standard. The following diastereomeric ratios were found about 99/1 for (7*R*,2′*R*)-**14a** and (7*S*,2′*R*)-**14a**, 94/6 and 90/10 for (8*R*,2′*S*)-**14b** and (8*S*,2′*S*)-**14b** (see spectra at pag.28).

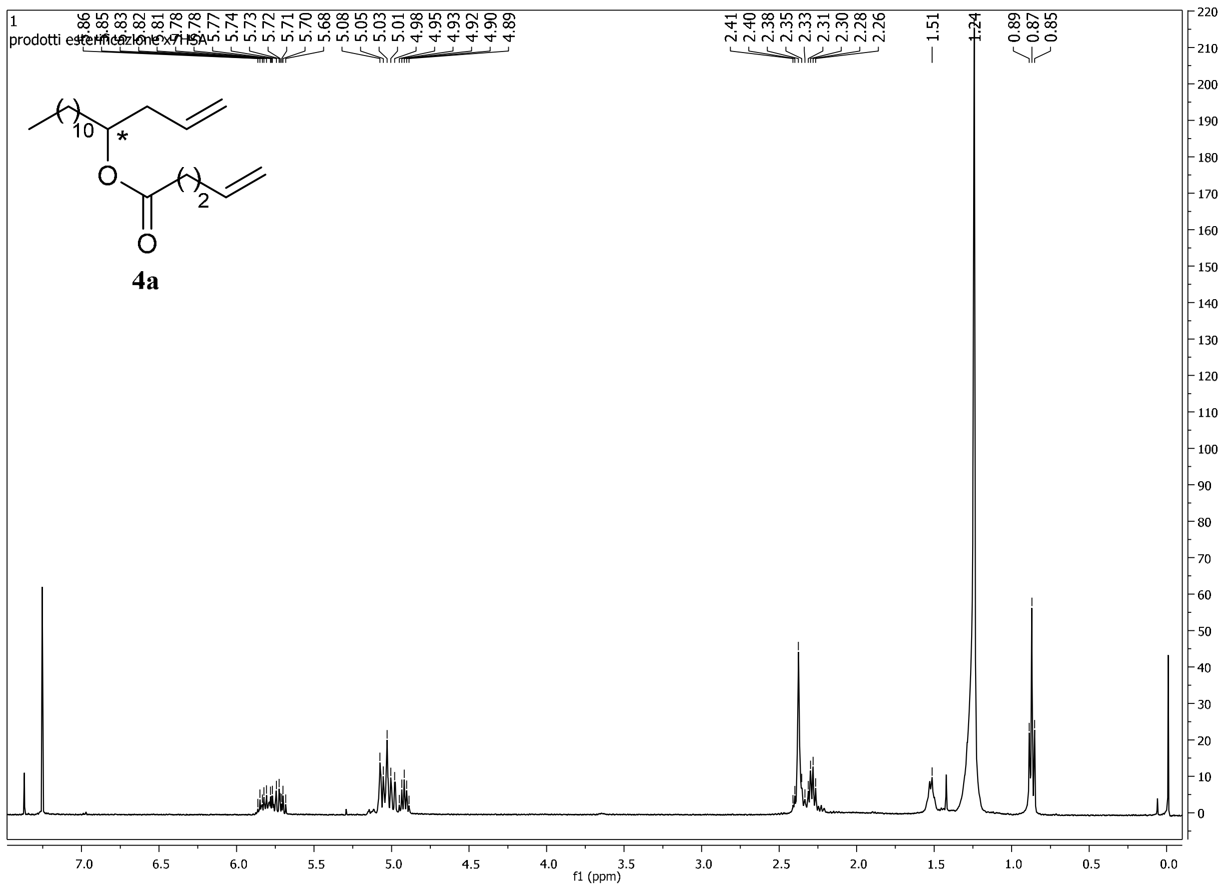
(*R*)-Methyl 7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (7*R*,2'*R*)-14a ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 7.58-7.50 (m, 2 H, phenyl), 7.42-7.37 (m, 3 H, phenyl), 5.07 (quint., 1 H, *J* = 6.4 Hz, C<u>H</u>OH), 3.66 (s, 3 H, $COOCH_3$), 3.55 (brs, 3 H, OCH_3), 2.28 (t, 2 H, *J* = 7.3 Hz, CH_2CO), 1.80–1.40 (m, 6 H, CH_2), 1.40 – 1.10 (m, 22 H, CH_2), 0.88 (t, 3 H, *J* = 6.2 Hz, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): –72.360 ppm.

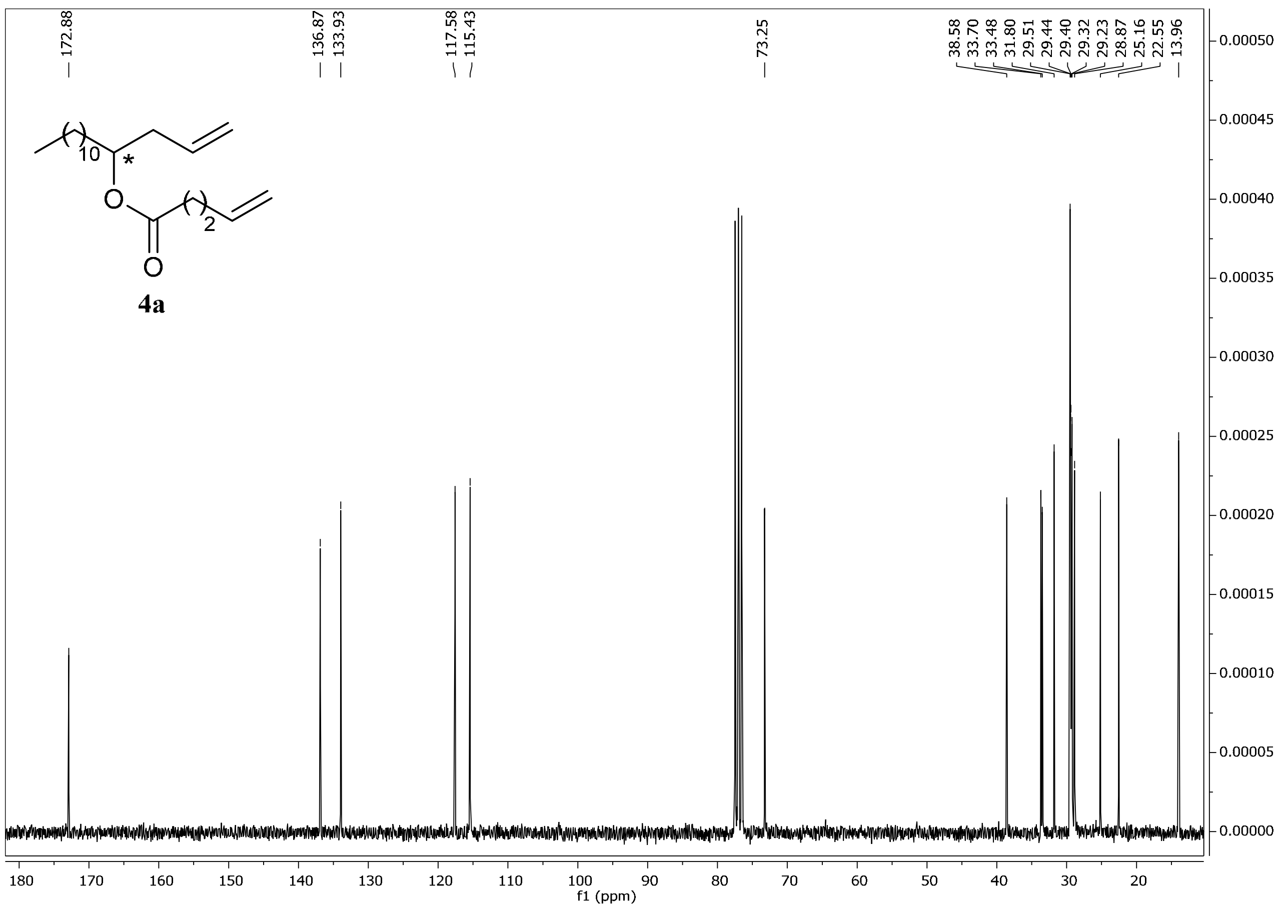
(*S*)-Methyl 7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (7*S*,2'*R*)-14a. ^{1}H NMR signals undiscernible from those of the (7*R*,2'*R*)-diastereomer. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): –72.323 ppm.

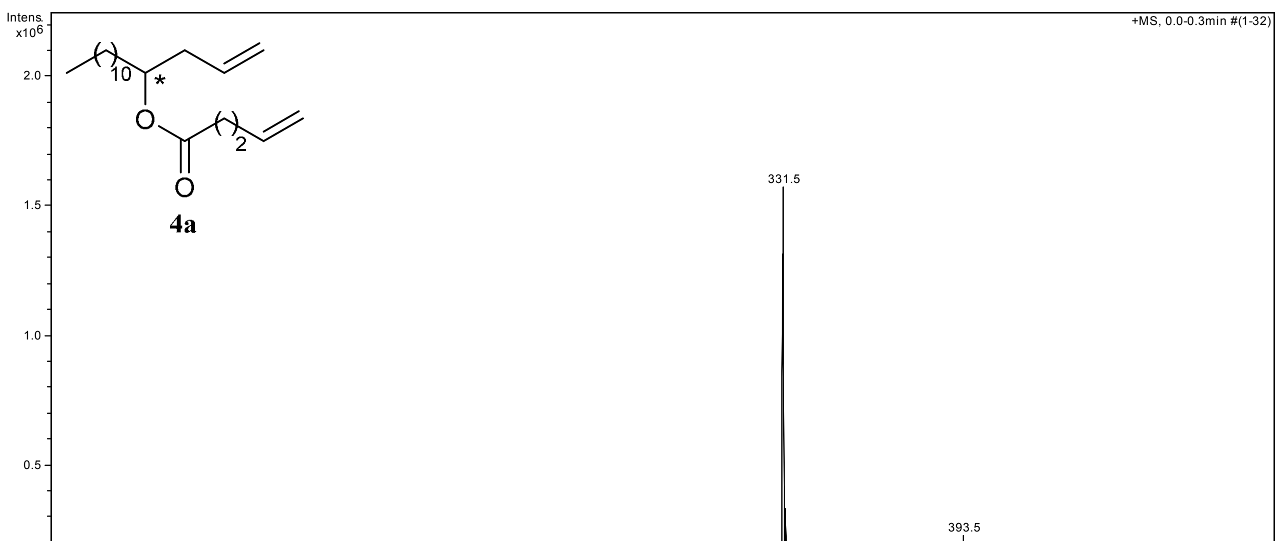
(*R*)-Methyl 8-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (8*R*,2'*S*)-14b. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.59-7.50 (m, 2 H, phenyl), 7.45-7.36 (m, 3 H, phenyl), 5.07 (quint., 1 H, *J* = 6.5 Hz, C<u>H</u>OH), 3.67 (s, 3 H, $COOCH_3$), 3.55 (brs, 3 H, OCH_3), 2.27 (t, 2 H, *J* = 7.5 Hz, CH_2CO), 1.82–1.40 (m, 6 H, CH_2), 1.40 – 1.10 (m, 22 H, CH_2), 0.87 (t, 3 H, *J* = 7.0 Hz, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): –72.369 ppm.

(*S*)-Methyl 8-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (8*S*,2'*S*)-14b. ^{1}H NMR signals are undiscernible from those of the (*8R,2'S*)-diastereomer. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): –72.405 ppm.

^{1}H NMR, ^{13}C NMR, ESI MS, chiral HRGC of 1-pentadecen-4-yl 4-pentenoate 4a

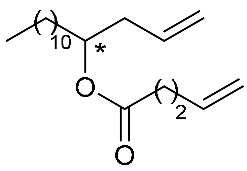



172.88
136.87
133.93
117.58
115.43
73.25
38.58
33.70
33.48
31.80
29.51
29.44
29.40
29.32
29.23
28.87
25.16
22.55
13.96
10
*
O
2
O
4a
f1 (ppm)


Intens.
x10^6
+MS, 0.0-0.3min #(1-32)
10
*
O
2
O
4a
331.5
393.5
439.5
265.5
279.4
301.4
m/z

Estere dienico per 7-HSA racemo

File : c:\class-vp\chrom\cris\Lb1
Method : c:\class-vp\methods\Cris2.met
Sample ID : LB estere 7OH
Printed 14:07:07
User : System

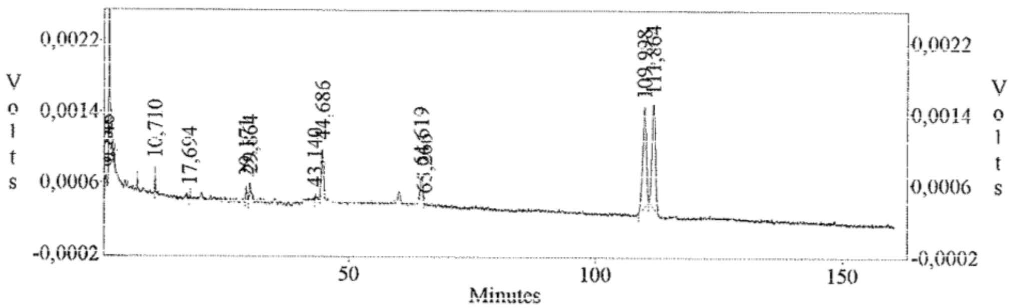


4a

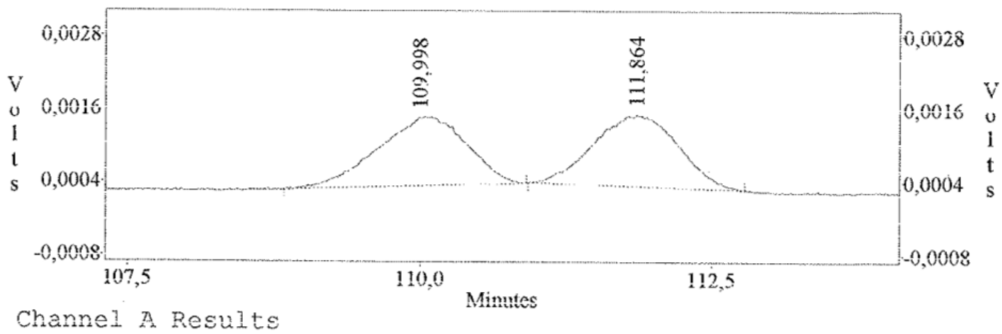
b-ciclodestrine
condizioni:

150°

c:\class-vp\chrom\cris\Lb1 -- Channel A



c:\class-vp\chrom\cris\Lb1 -- Channel A

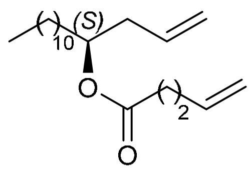


Channel A Results

Peak	Time	Area	Area %
1	0,53	621	0,411
2	0,85	944	0,624
3	10,71	1392	0,920
4	17,69	109	0,072
5	29,17	2179	1,441
6	29,86	2191	1,448
7	43,14	112	0,074
8	44,69	15692	10,374
9	64,62	10361	6,850
10	65,27	122	0,081
11	110,00	58634	38,763
12	111,86	58904	38,942
Totals :		151261	100,000

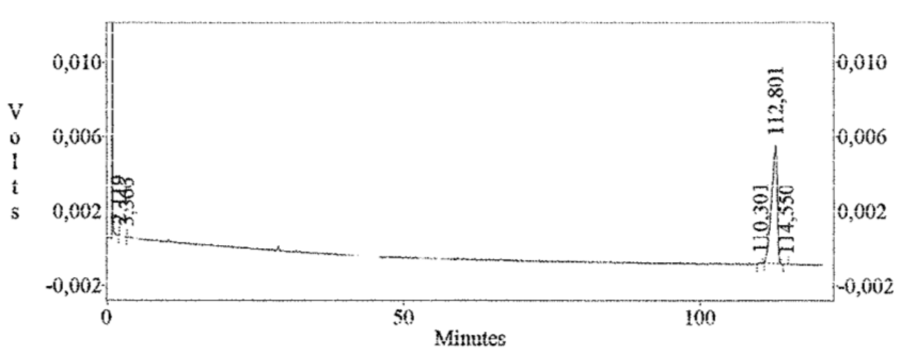
Estere dienico per (S)-7HSA da alcol (S) con 98%ee

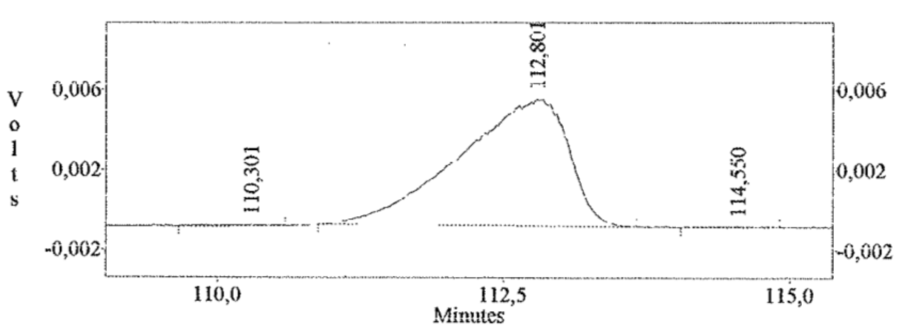
File : c:\class-vp\chrom\patty\Gl1
Method : c:\class-vp\methods\Patty.met
Sample ID : grezzo yamaguchi_S
Printed 08:36:25
User : System



4a

beta-ciclodestrine
condizioni:
150°C





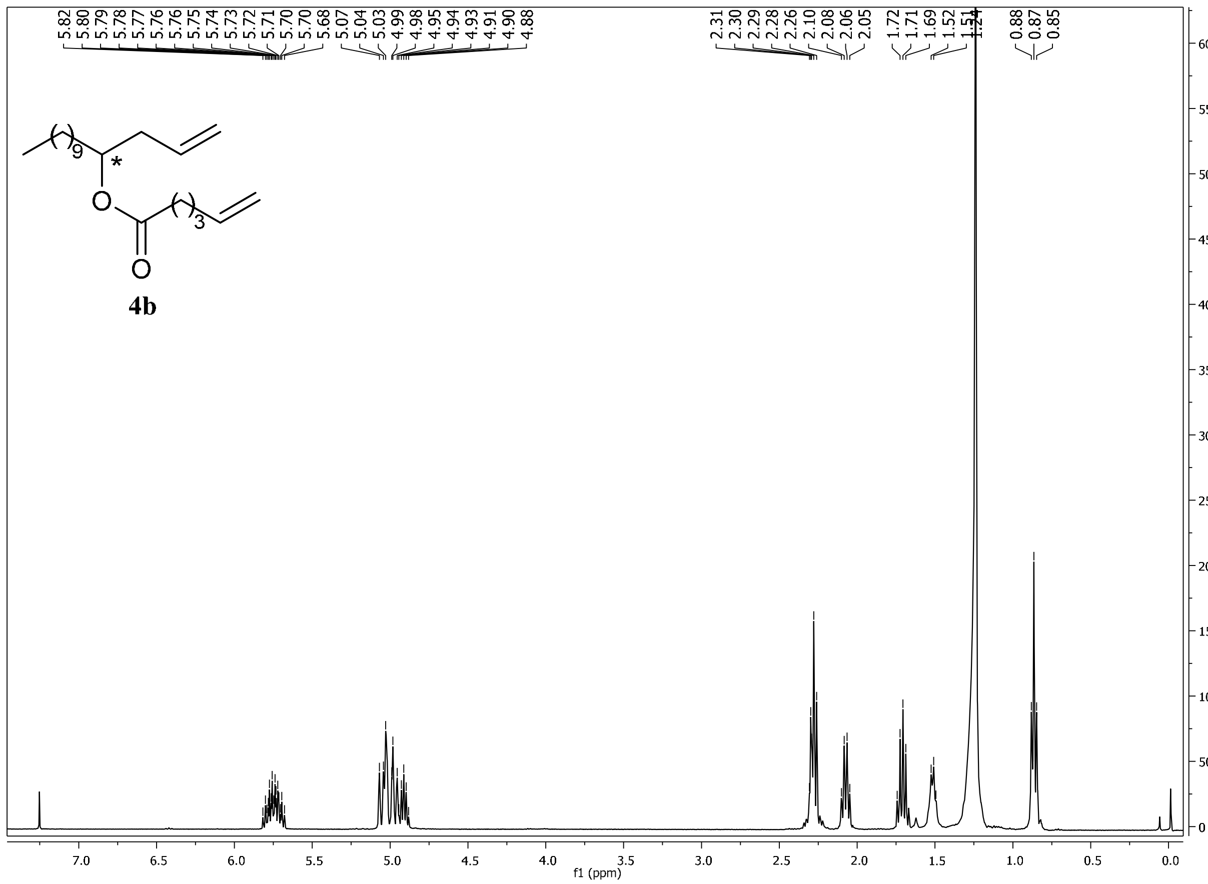
Channel A Results

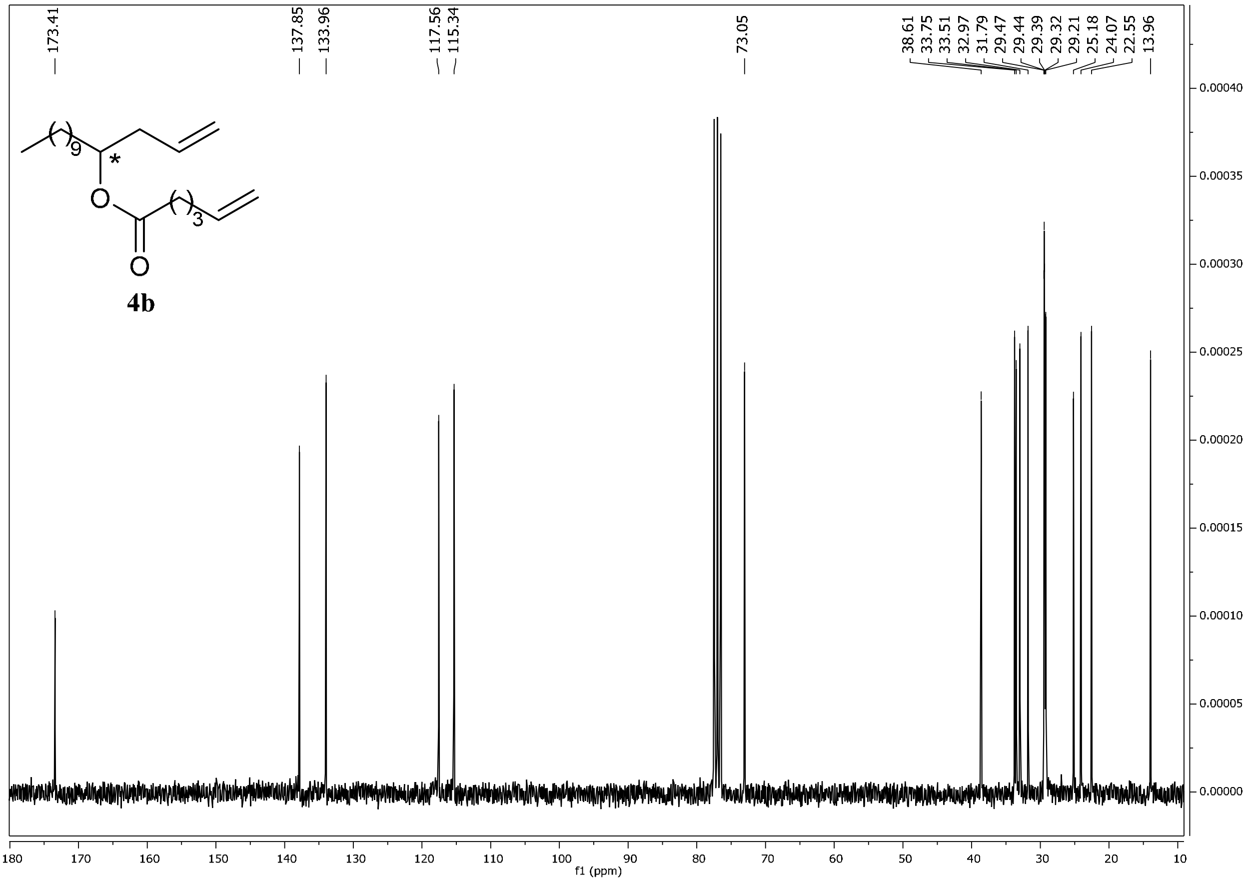
Peak	Time	Area	Area %
1	2,12	191	0,045
2	3,37	288	0,069
3	110,30	1341	0,319
4	112,80	417156	99,346
5	114,55	927	0,221

Totals :

		419903	100,000

[1]H NMR, [13]C NMR, ESI MS, chiral HRGC of 1-tetradecen-4-yl 5-hexenoate 4b




173.41
137.85
133.96
117.56
115.34
73.05
38.61
33.75
33.51
32.97
31.79
29.47
29.44
29.39
29.32
29.21
25.18
24.07
22.55
13.96
4b
f1 (ppm)

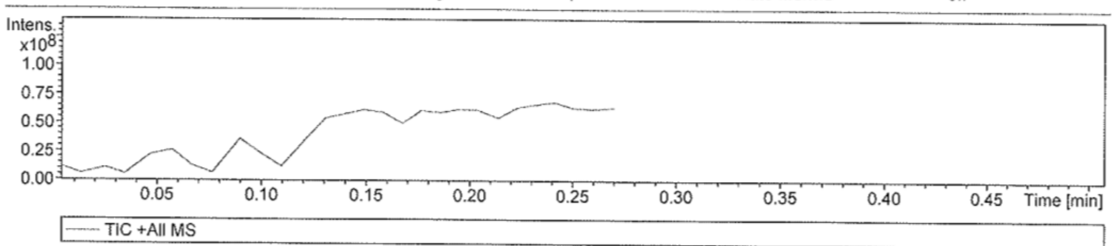
Display Report

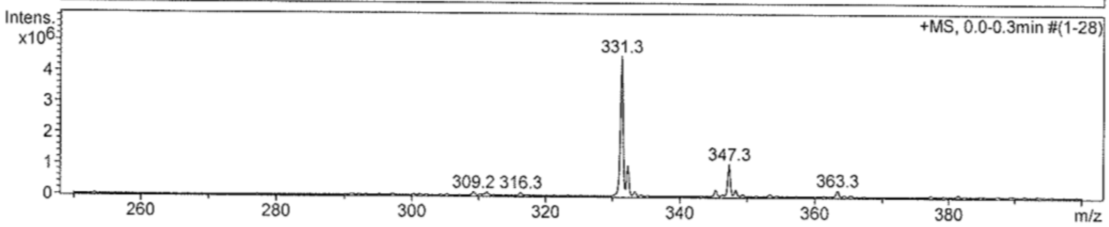
Analysis Info

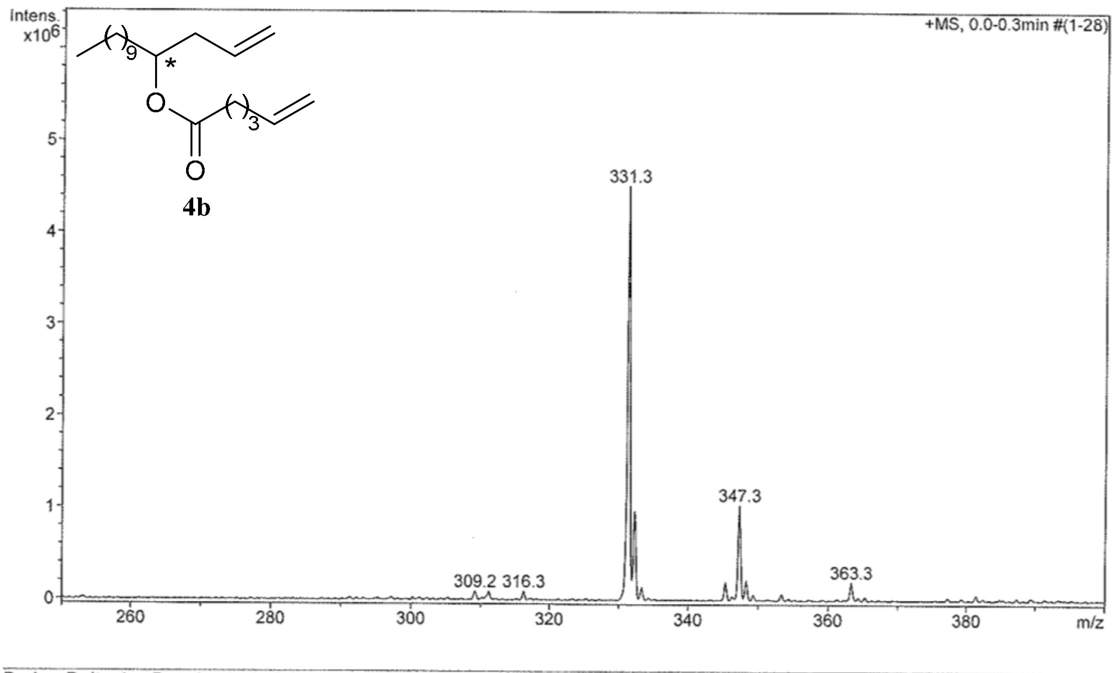
Analysis Name	D:\Data\2-HOLLAN\EDCC.d	Acquisition Date	3/26/2012 3:55:22 PM
Method	standard.m	Operator	bruker
Sample Name	Dummy	Instrument	esquire4000
Comment			

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive	Alternating Ion Polarity	off
Mass Range Mode	Std/Normal	Scan Begin	250 m/z	Scan End	400 m/z
Capillary Exit	105.7 Volt	Skim 1	33.2 Volt	Trap Drive	28.1
Accumulation Time	1435 µs	Averages	5 Spectra	Auto MS/MS	off



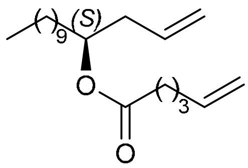




Bruker Daltonics DataAnalysis 3.3 printed: 3/26/2012 3:56:46 PM Page 1 of 1

compound 4b

File : c:\class-vp\chrom\patty\cn10
Method : c:\class-vp\methods\Patty.met
Sample ID : estere S e.e. 97%
User : System

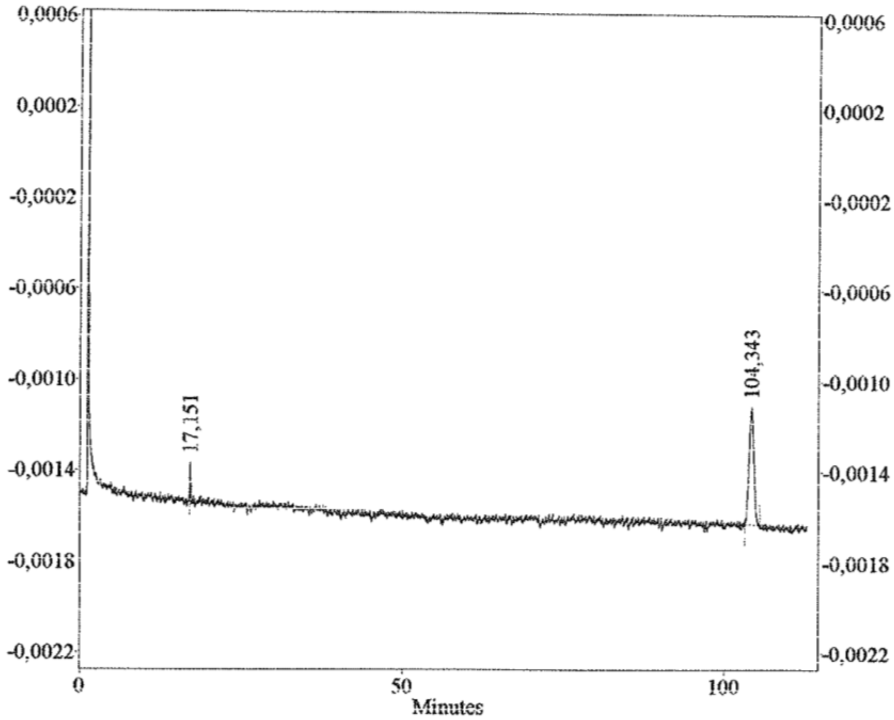


4b

b-ciclodestrine
condizioni:

150°

c:\class-vp\chrom\patty\cn10 -- Channel A



Channel A Results

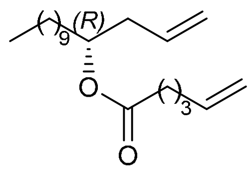
Peak	Time	Area	Area %
1	17,15	1230	4,288
2	104,34	27456	95,712

Totals :

		28686	100,000

estere R e.e. 97% per 8-HSA

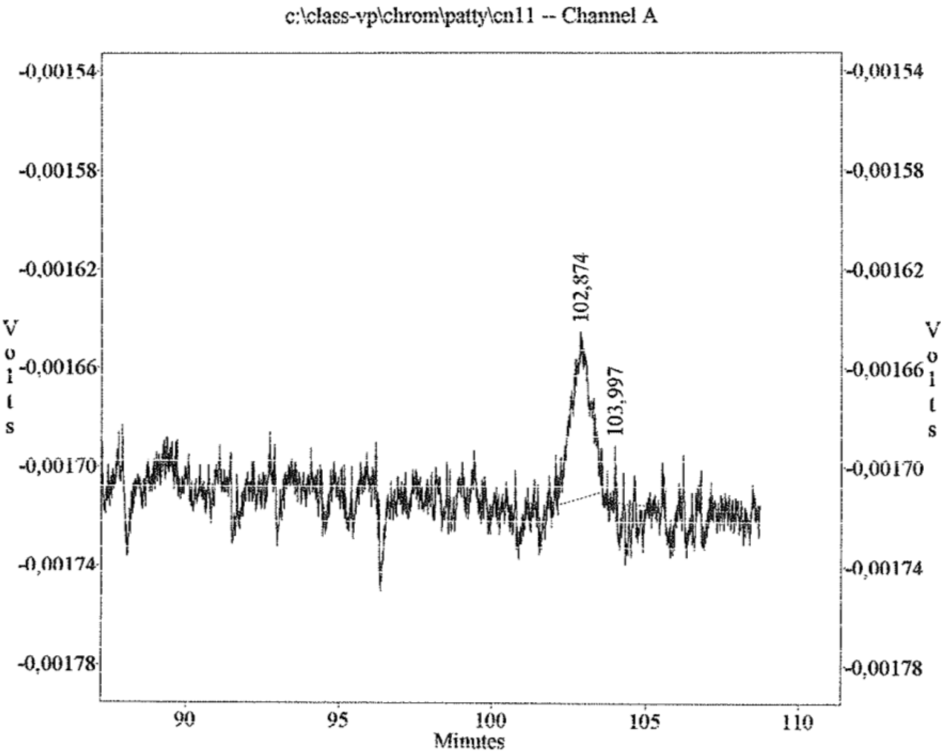
File : c:\class-vp\chrom\patty\cn11
Method : c:\class-vp\methods\patty.met
Sample ID : estere R e.e. 97%
User : System



4b

b-ciclodestrine
condizioni:

150°

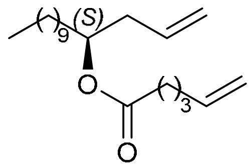


Channel A Results

Peak	Time	Area	Area %
1	102,87	2899	87,214
2	104,00	425	12,786

Totals :

		3324	100,000



4b

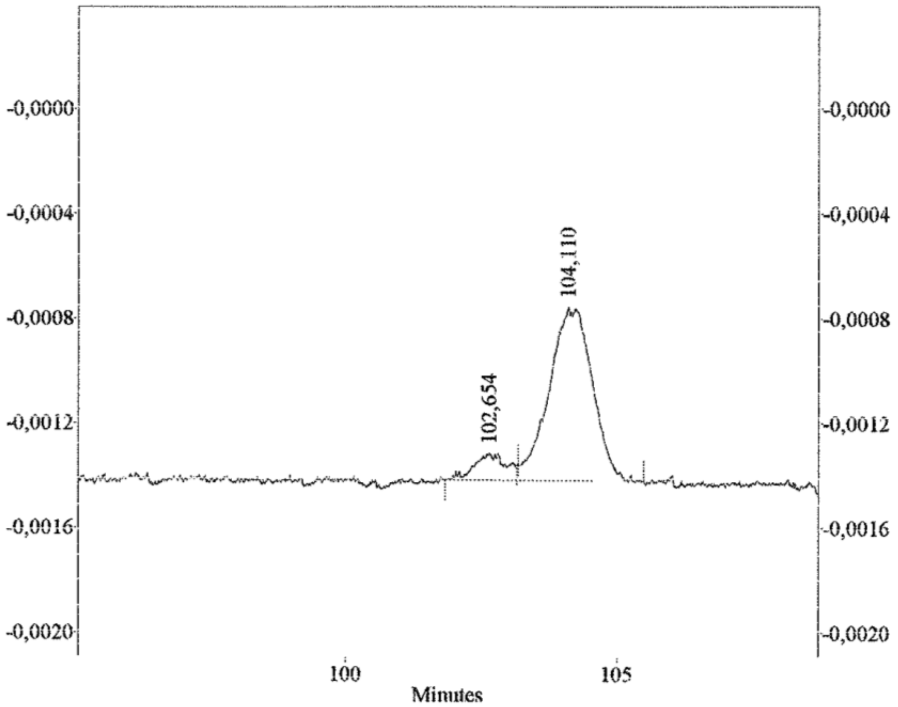
estere S e.e. 78% per 8-HSA

File : c:\class-vp\chrom\patty\cn9
Method : c:\class-vp\methods\patty.met
Sample ID : estere ee 78% per
User : System

b-ciclodestrine
condizioni:

150°

c:\class-vp\chrom\patty\cn9 -- Channel A



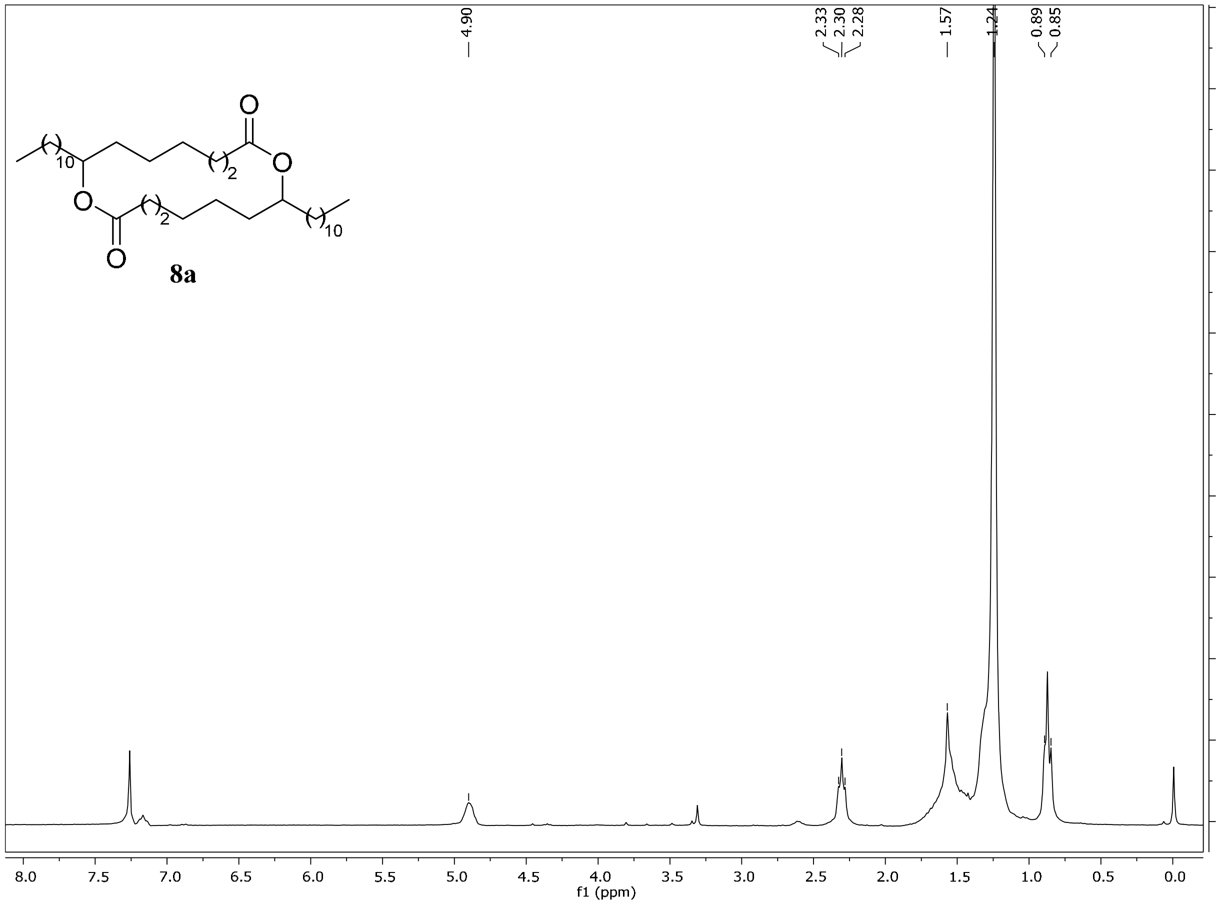
Channel A Results

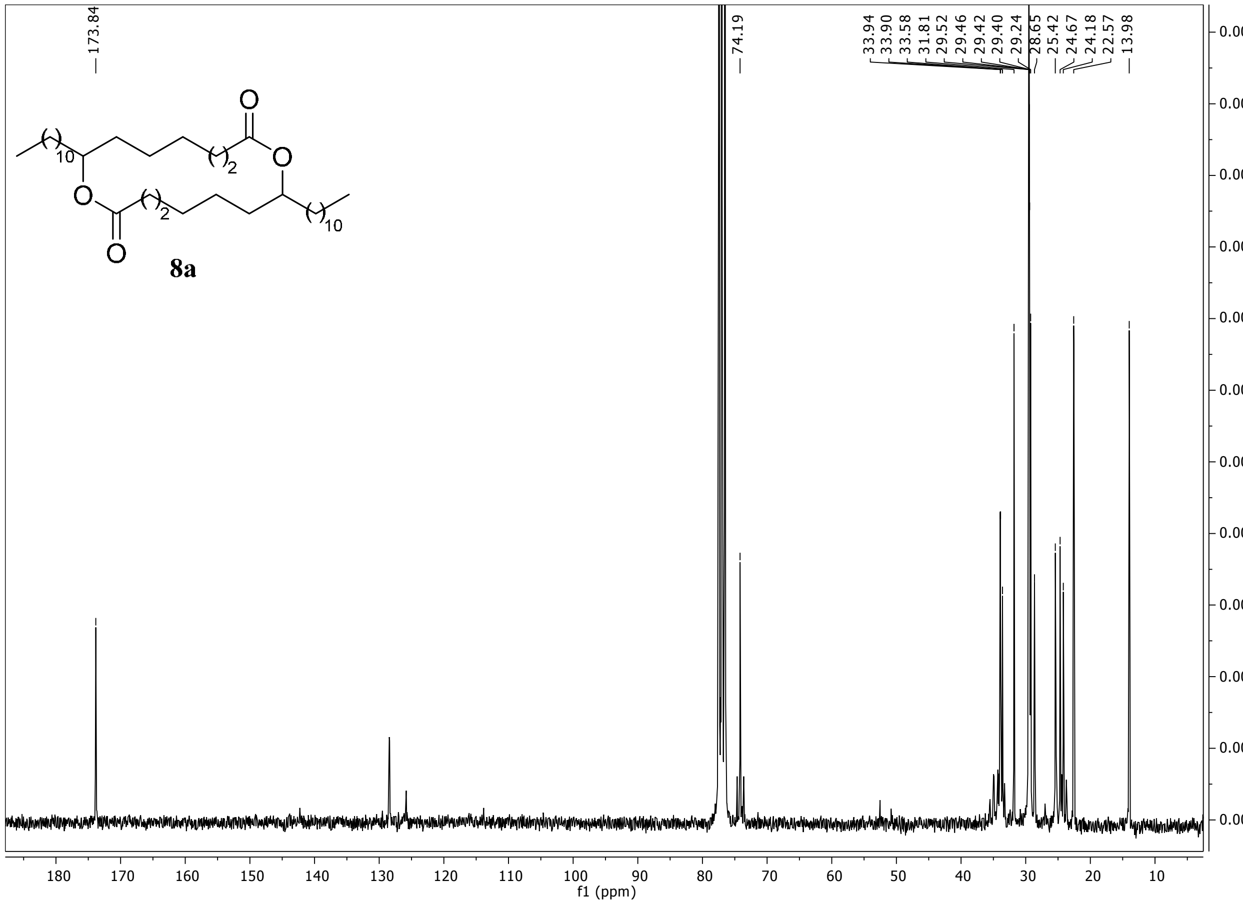
Peak	Time	Area	Area %
1	18,74	968	2,334
2	102,65	4206	10,141
3	104,11	36303	87,526

Totals :

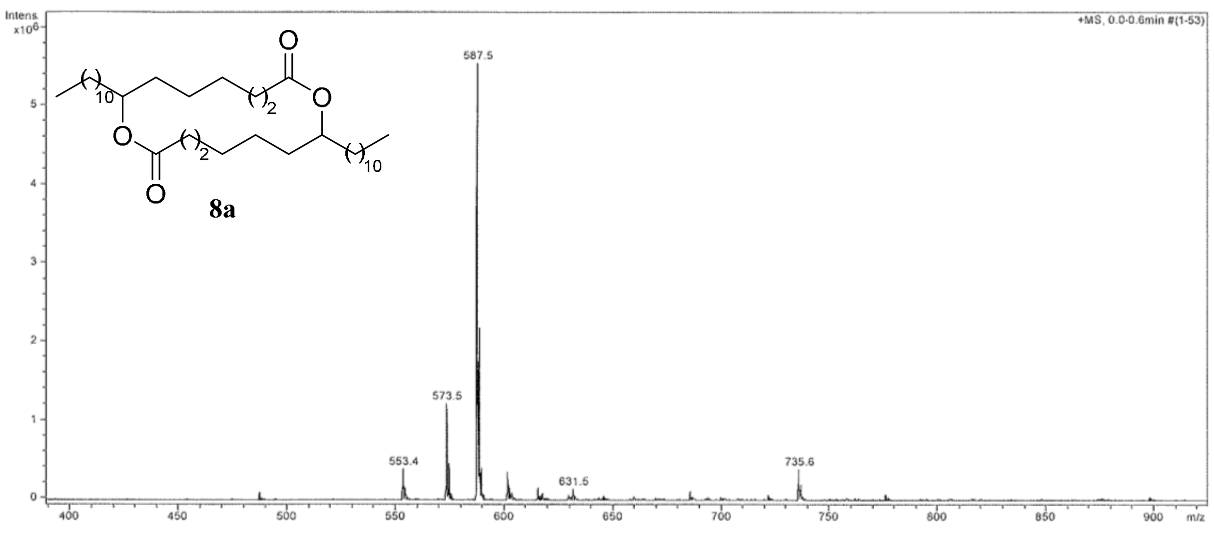
	41477	100,000

^{1}H NMR, ^{13}C NMR, ESI MS of 8,16-diundecyl-1,9-dioxacyclohexadeca-2,10-dione 8a





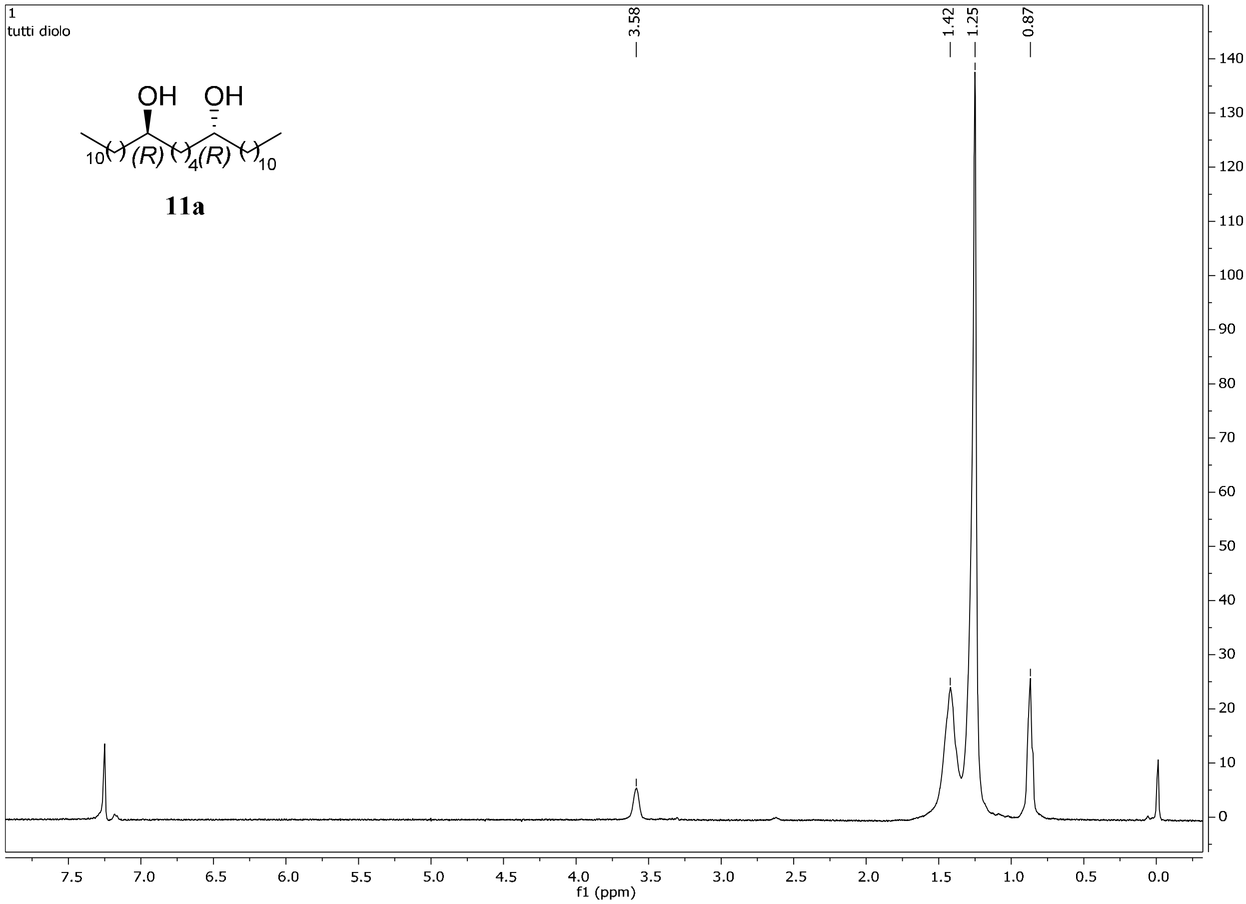
173.84
74.19
33.94
33.90
33.58
31.81
29.52
29.46
29.42
29.40
29.24
28.65
25.42
24.67
24.18
22.57
13.98
8a
f1 (ppm)

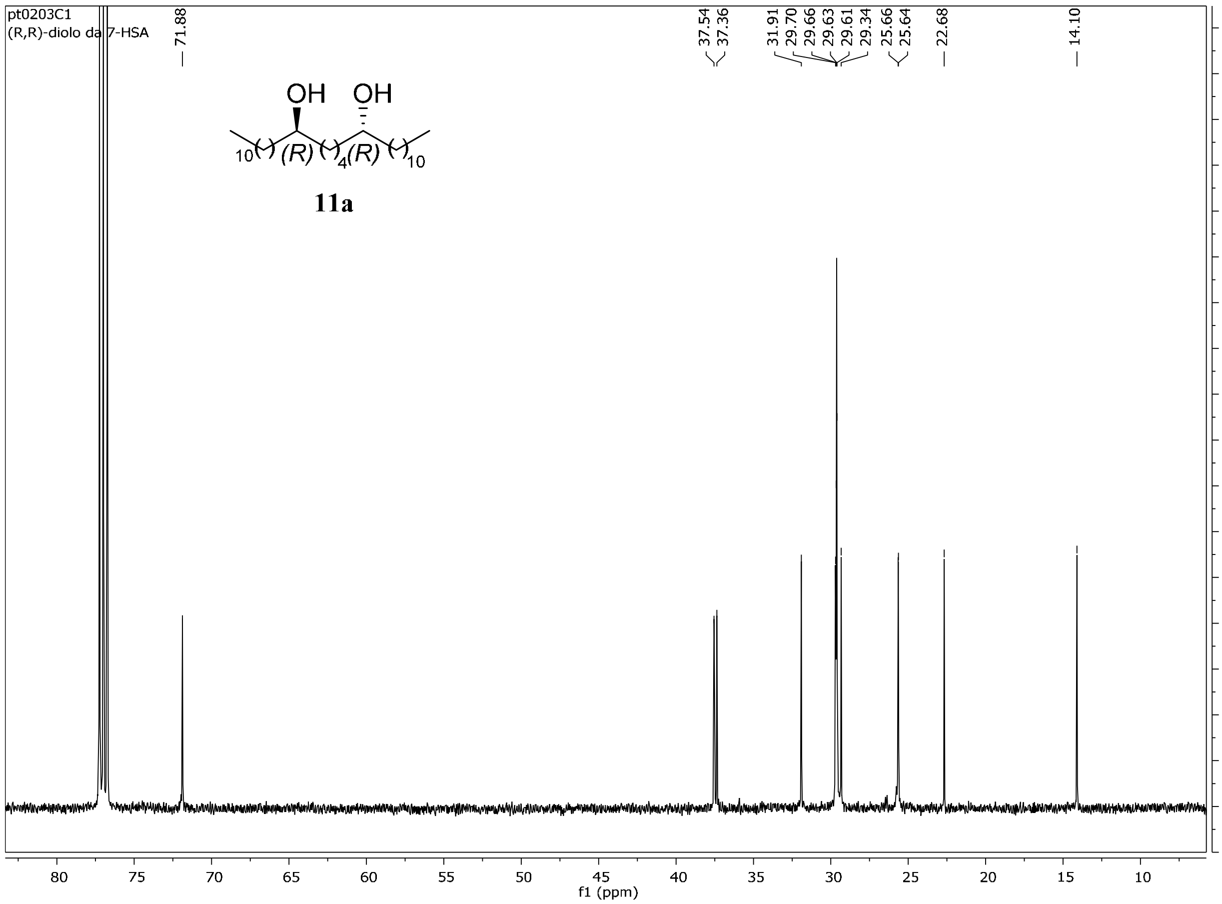


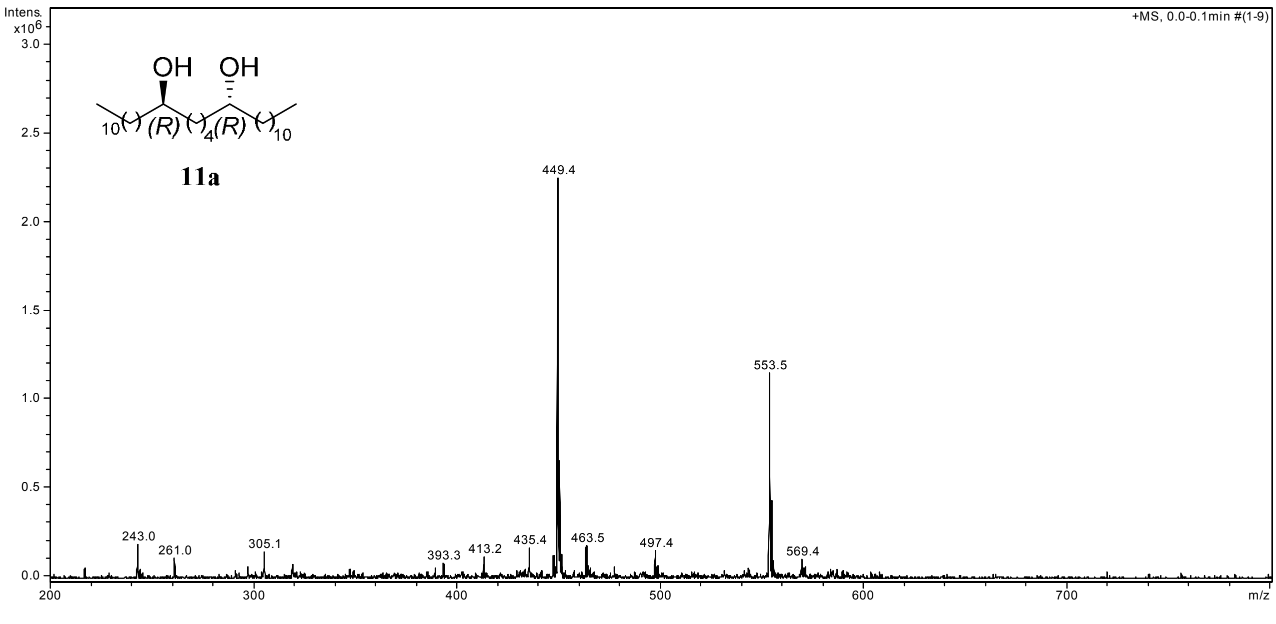
Intens.
x10^6
+MS, 0.0-0.6min #(1-53)
8a
587.5
573.5
553.4
631.5
735.6
m/z

TARGEHT 870

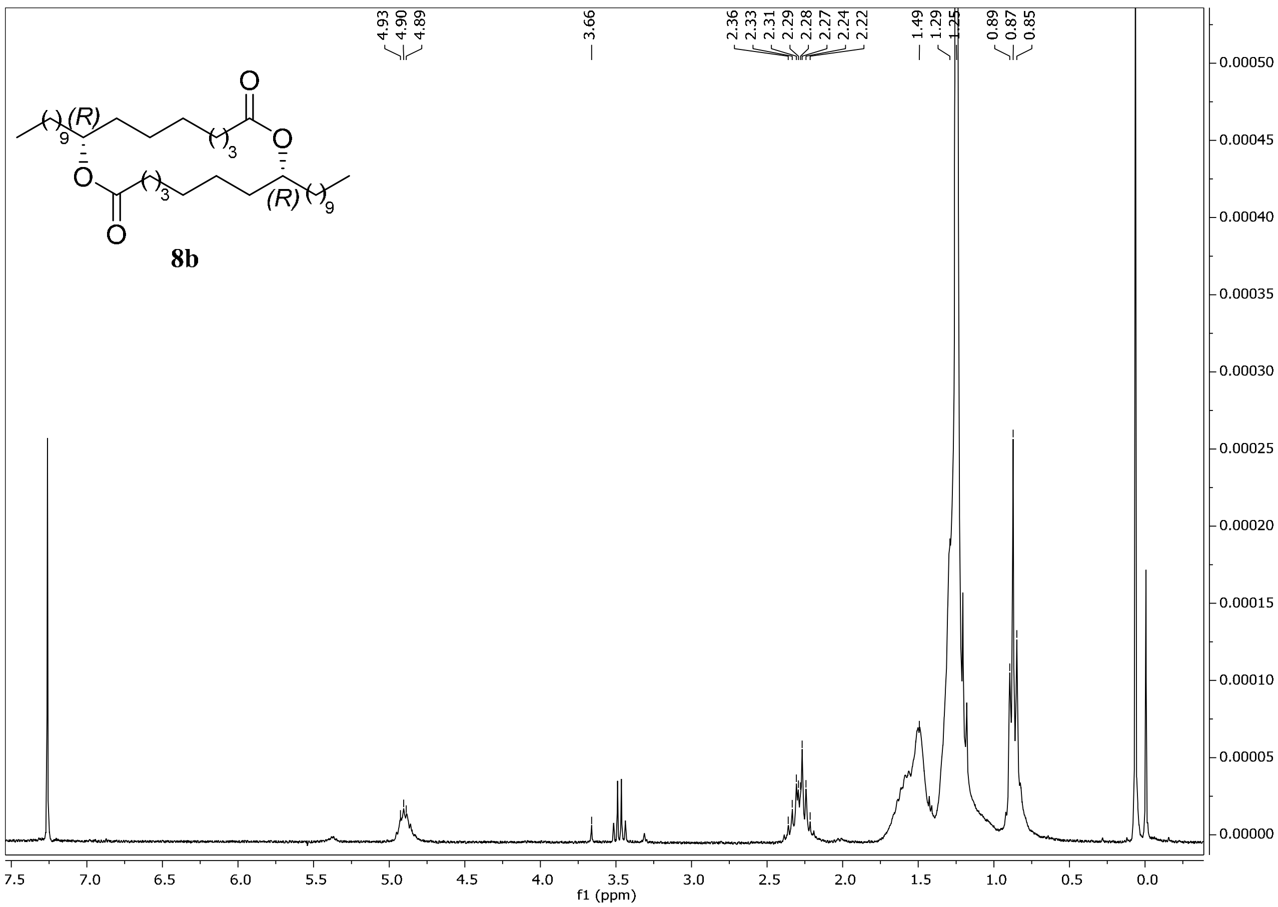
^{1}H NMR, ^{13}C NMR, ESI MS of (12*R*, 17*R*)-Octacosandiol 11a

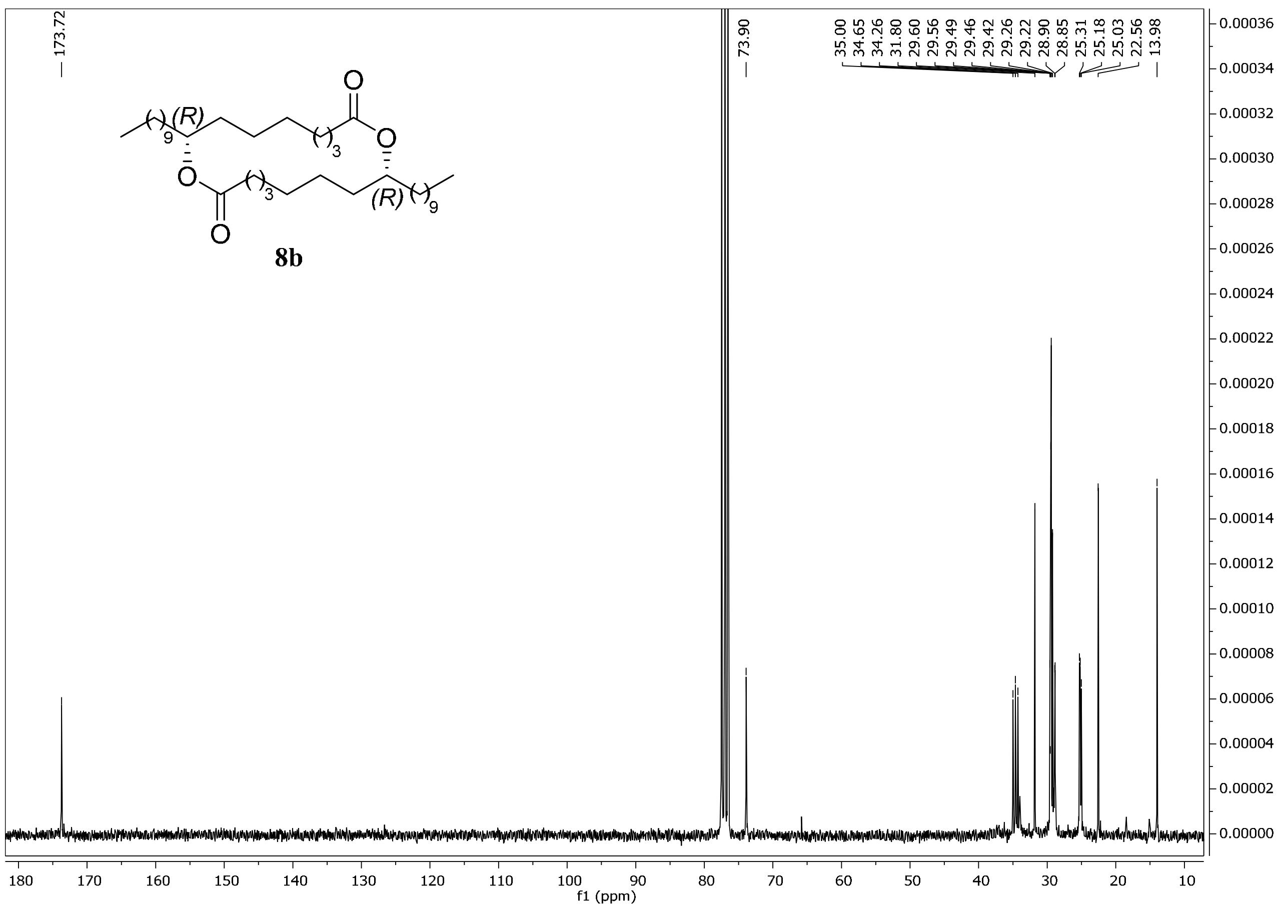



pt0203C1
(R,R)-diolo da 7-HSA
71.88
37.54
37.36
31.91
29.70
29.66
29.63
29.61
29.34
25.66
25.64
22.68
14.10
OH OH
(R) (R)
11a
f1 (ppm)


Intens.
x10^6
+MS, 0.0-0.1min #(1-9)
OH OH
(R) (R)
11a
449.4
553.5
243.0
261.0
305.1
393.3
413.2
435.4
463.5
497.4
569.4
m/z

[1]H NMR, [13]C NMR, ESI MS of (9*R*,18*R*)-9,18-didecyl-1,10-dioxacyclooctadeca-2,11-dione 8b




173.72
73.90
35.00
34.65
34.26
31.80
29.60
29.56
29.49
29.46
29.42
29.26
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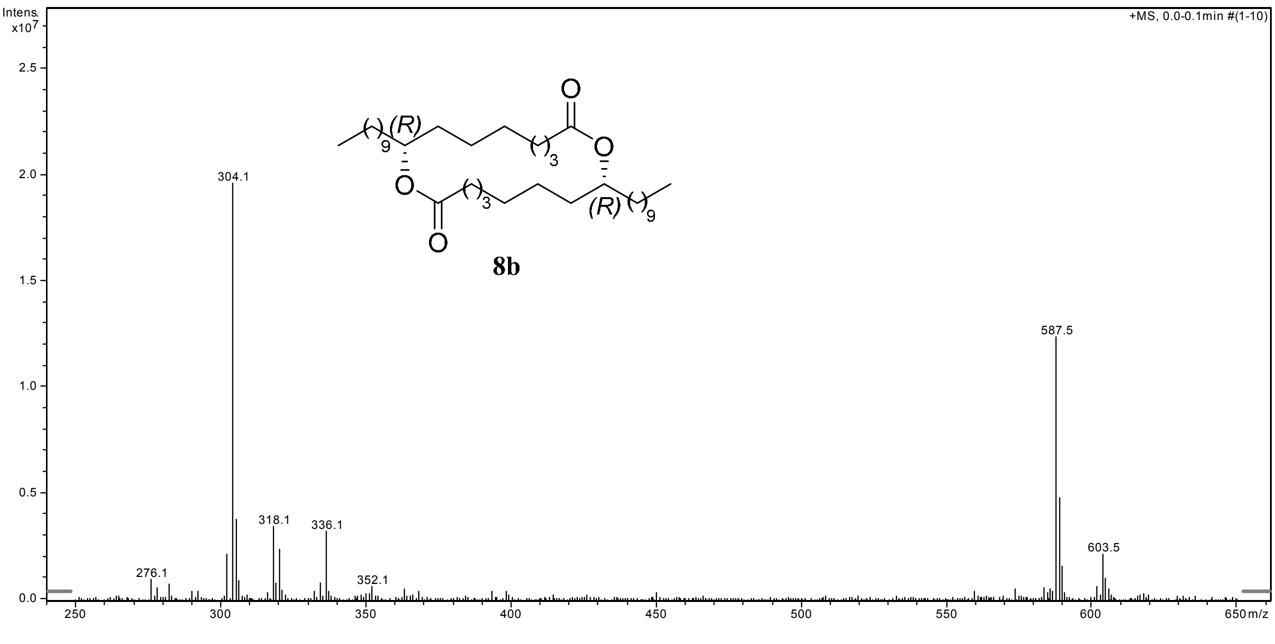
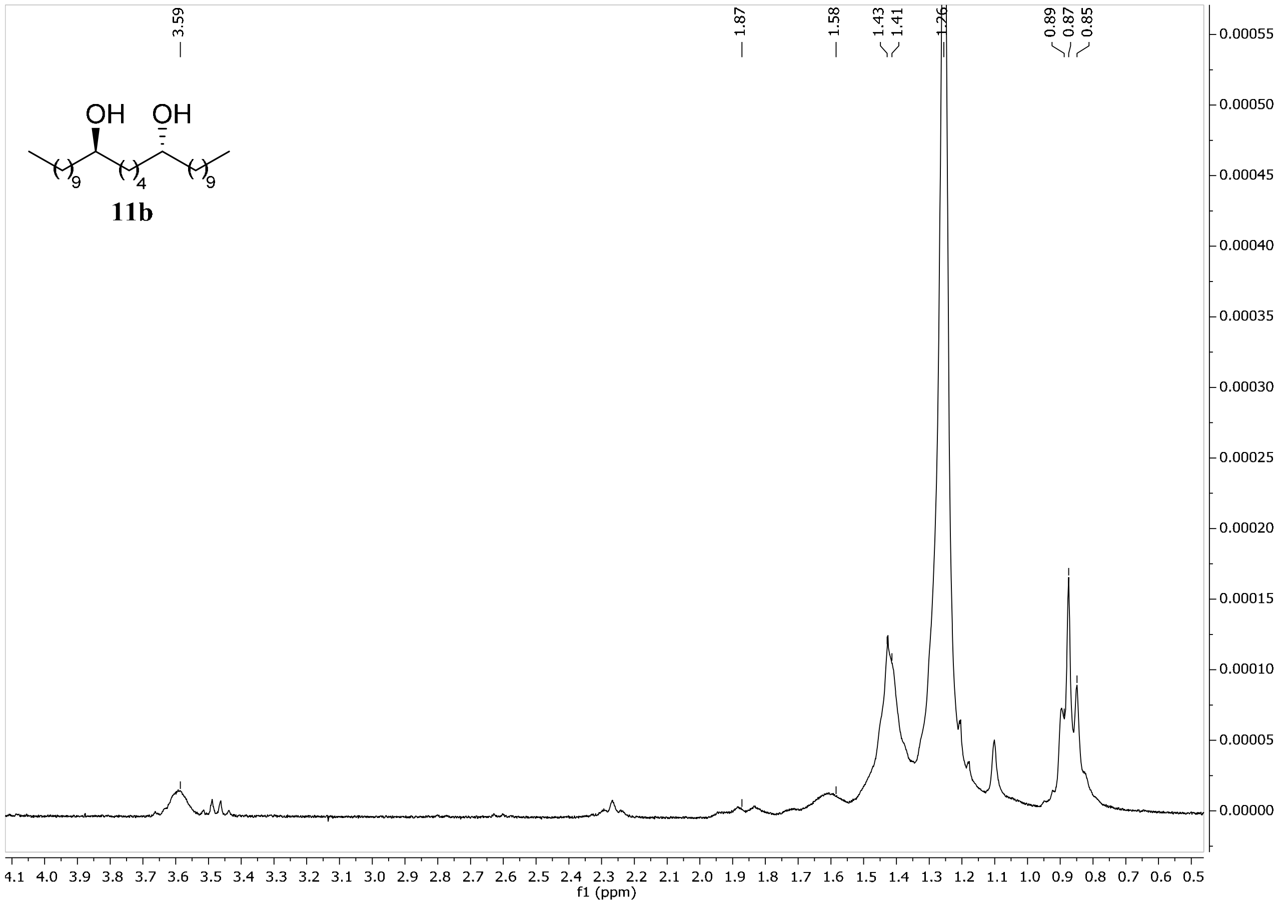
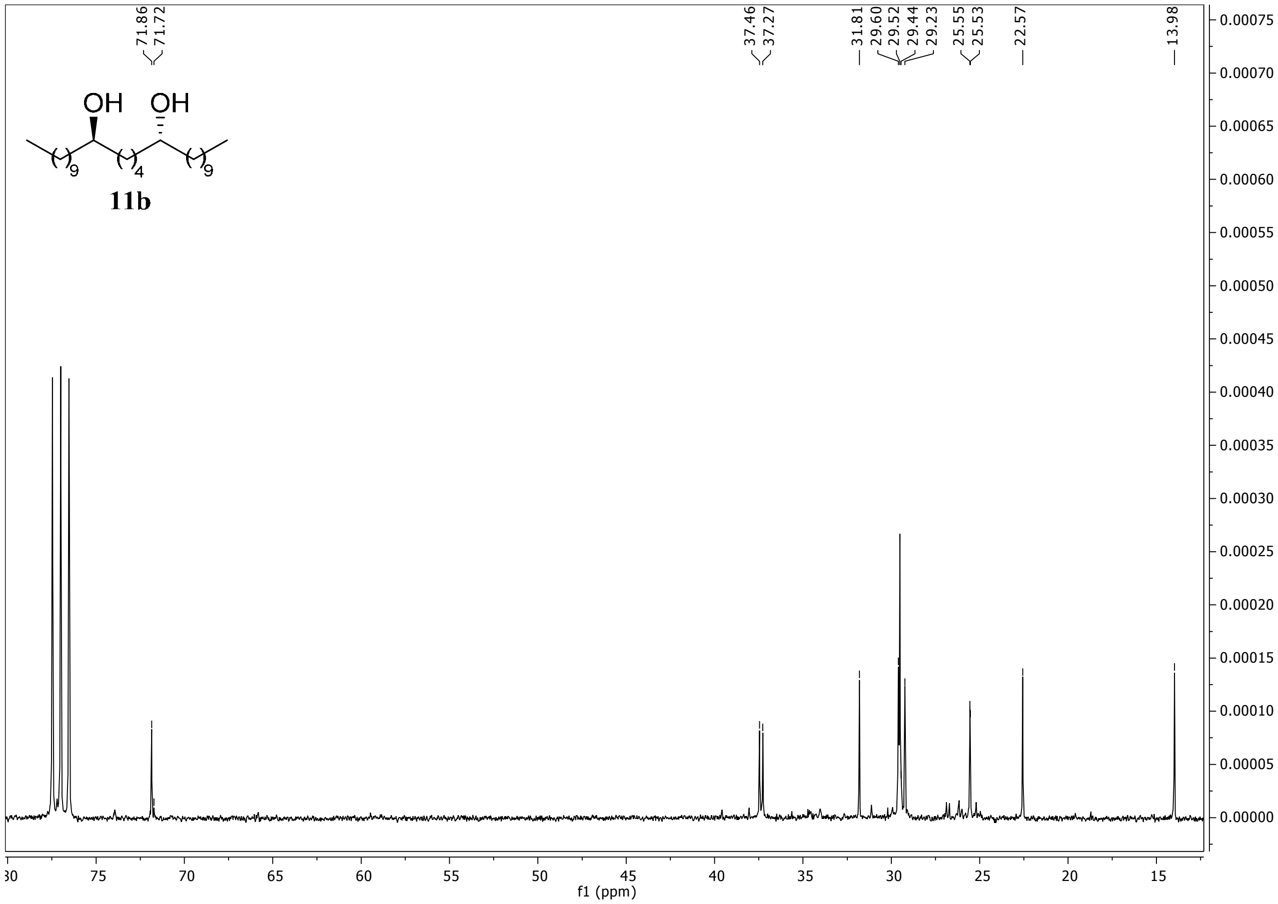
28.90
28.85
25.31
25.18
25.03
22.56
13.98
8b
f1 (ppm)

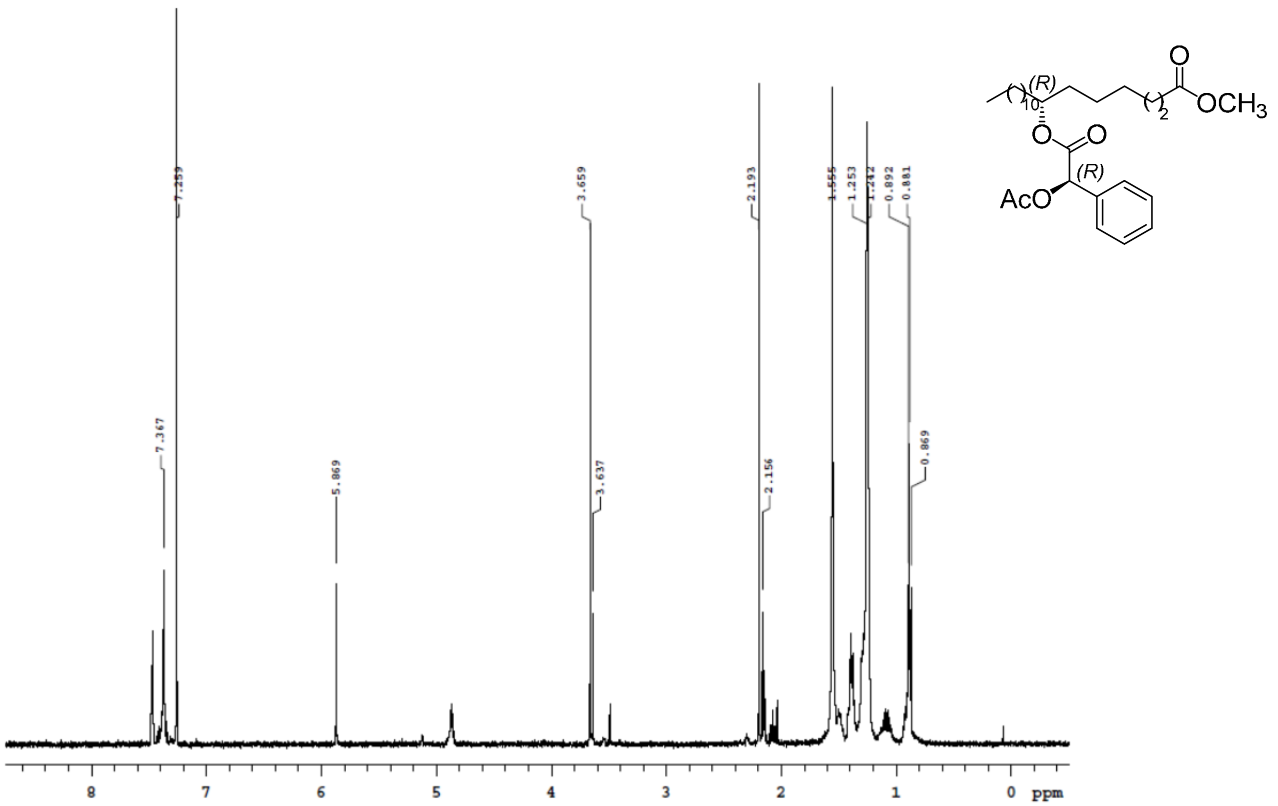

Intens.
x10^7
+MS, 0.0-0.1min #(1-10)
304.1
318.1
336.1
352.1
276.1
587.5
603.5
8b
m/z

^1H NMR, ^{13}C NMR of 11,16-hexacosandiol 11b

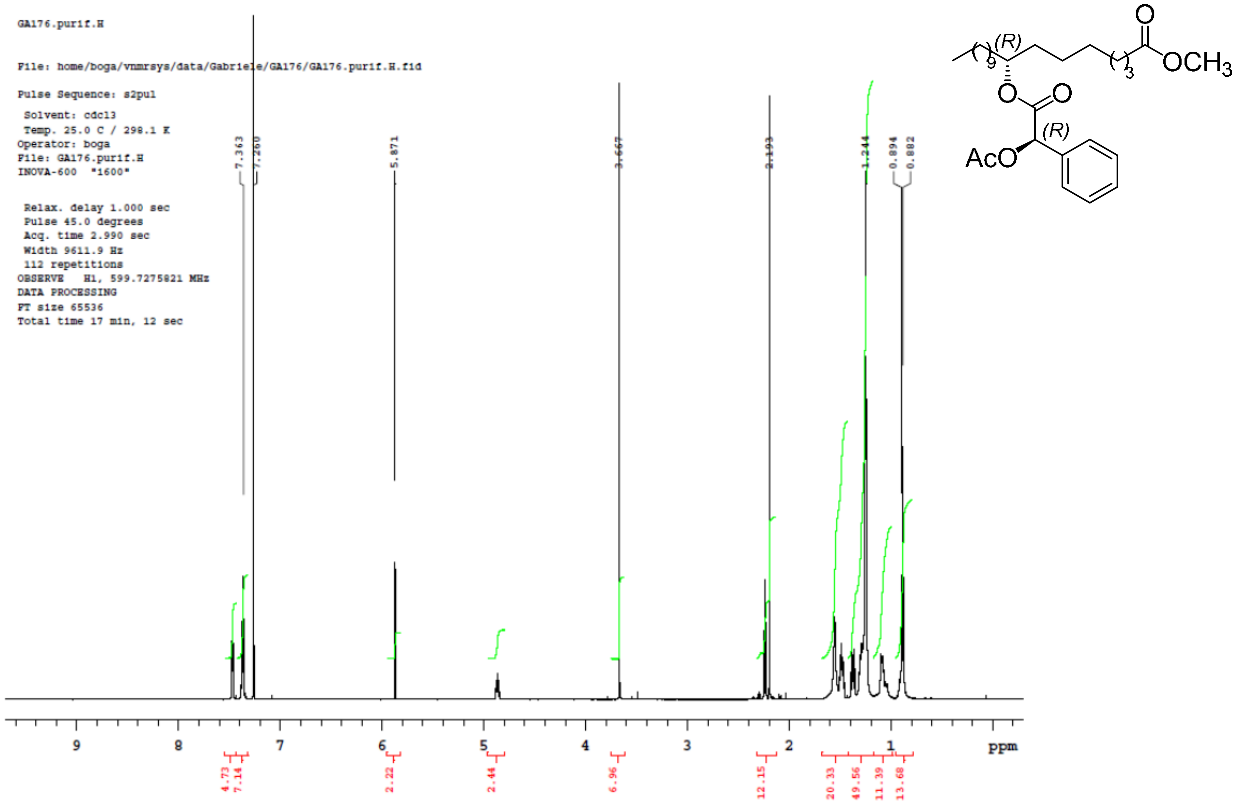




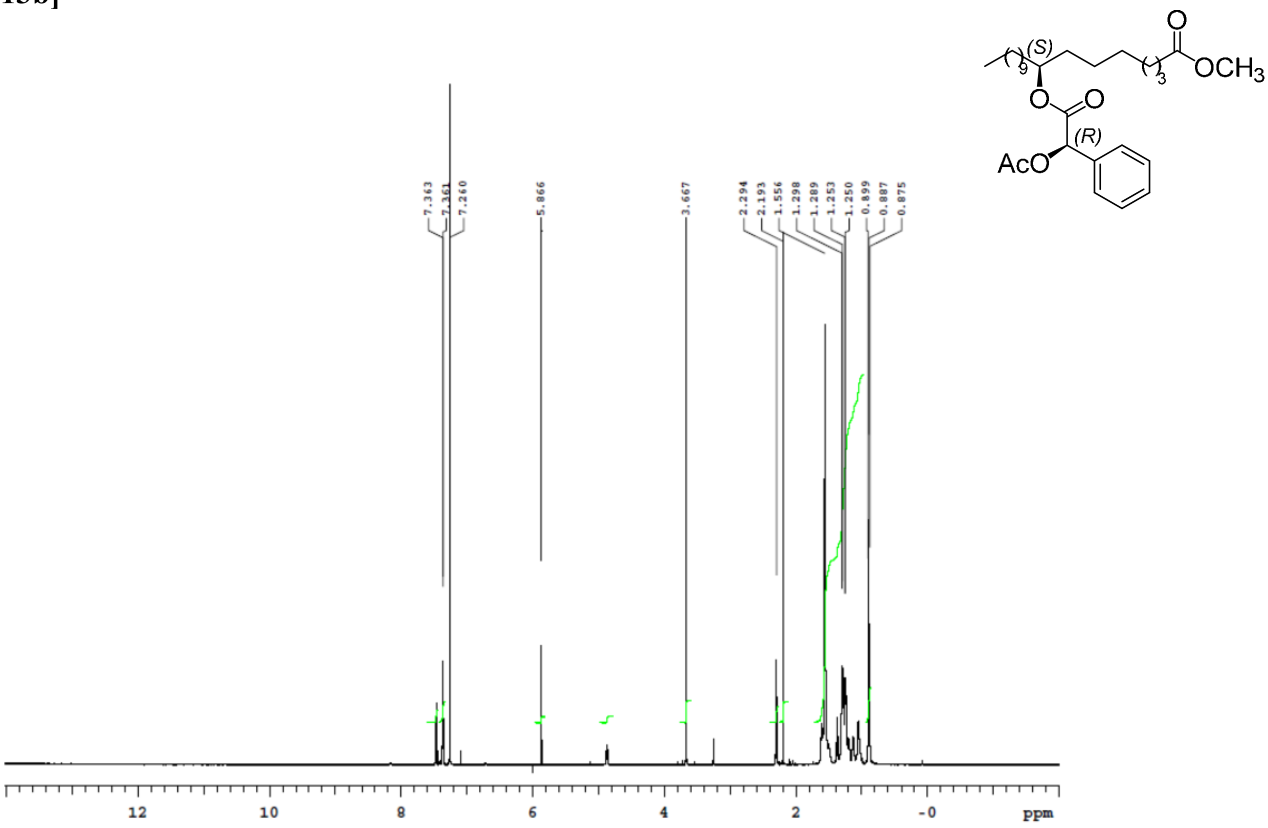
Methyl (7*R*)-7-{[(2*R*)-2-(acetyloxy)-2-phenylacetyl]oxy}octadecanoate ([(7*R*,2'*R*)-13a])



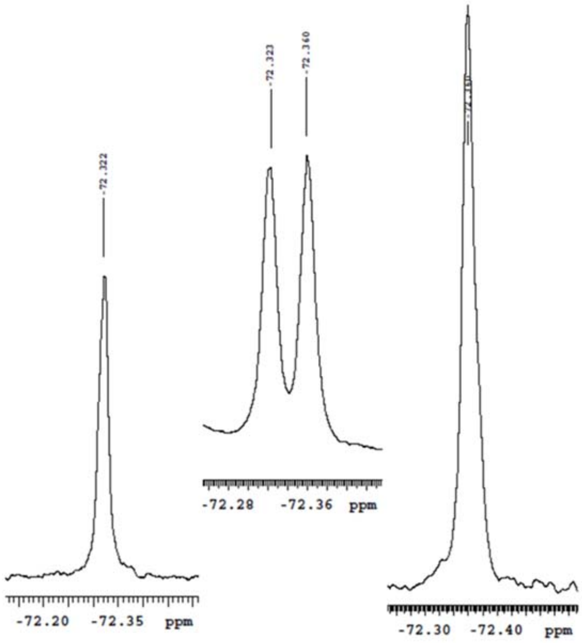
[1]H NMR of methyl (8*R*)-8-{[(2*R*)-2-(acetyloxy)-2-phenylacetyl]oxy}octadecanoate [(8*R*,2'*R*)-13b]

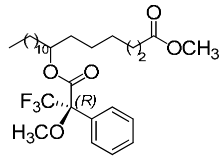


[1]H NMR of methyl (8*S*)-8-{[(2*R*)-2-(acetyloxy)-2-phenylacetyl]oxy}octadecanoate [(8*S*,2'*R*)-13b]



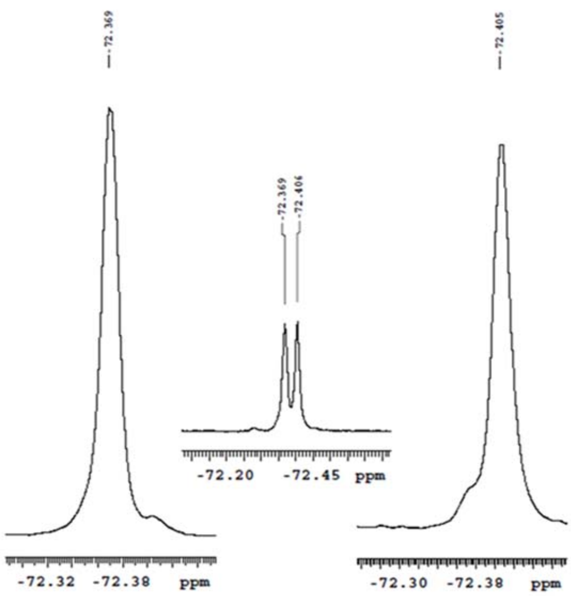
(*R*)-Methyl 7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (7*R*,2'*R*)-14a and (*S*)-Methyl 7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (7*S*,2'*R*)-14a

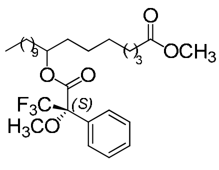




[19]F NMR spectra showing as main product (*7S,2'R*) (left), and (*7R,2'R*) (right). In the middle, the signals of the corresponding racemic mixture.

(*R*)-Methyl 8-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate(8*R*,2'*S*)-14b and (*S*)-Methyl 8-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)octadecanoate (8*S*,2'*S*)-14b.





[19]F NMR spectra showing as main product the (*8R,2'S*) (left), and the (*8S,2'S*) (right). In the middle, the signals of the corresponding racemic mixture.

[1] Chang, Y.-H.; Uang, B.-J.; Wu, C.-M.; Yu, T.-H. *Synthesis* **1990**, 1033-1034.

[2] Harbindu, A.; Sharma, M. B.; Kumar. P. *Tetrahedron: Asymmetry* **2013**, *24*, 305-314.

[3] Kumar, R. S. C.; Sreedhar, E.; Reddy, G. V.; Babu, K. S.; Rao, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1160-1163.

[4] Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem*. **1993**, *58*, 7768-7781.

[5] Ghosh, A. K.; Liu, C. *Chem. Commun*. **1999**, 1743-1744.

[6] Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc*. **2002**, *124*, 12414-12415.

[7] a) Hodgson, D. M.; Fleming, M. J.; Stanway. S. J. *J. Org. Chem*. **2007**, *72*, 4763-4773; b) Hodgson, D. M.; Fleming, M. J.; Stanway. S. J. *J. Am. Chem. Soc*. **2004**, *126*, 12250-12251.

[8] Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768-7781.

[9] Tripathi, D.; Kumar, P. *Tetrahedron: Asymmetry* **2012**, *23*, 884-890.

[10] a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993, b) Chatterjee, B.; Mondal, D.; Bera, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1170-1185.

[11] Ebert, C.; Felluga, F.; Forzato, C.; Foscato, M.; Gardossi, L.; Nitti, P.; Pitacco, G.; Boga, C.; Caruana, P.; Micheletti, G.; Calonghi, N.; Masotti, L. *J. Mol. Catal. B- Enzym.* **2012**, *83*, 38-45.