Hydroxystearic acids (HSAs) and their derivatives are interesting molecules whose presence is crucial in many biological processes. For instance, 9- and 10-HSA have shown a natural negative regulatory activity on tumor cell proliferation: in HT29 cells, a human colon adenocarcinoma cell line, both enantiomers of 9-HSA were able to inhibit the enzymatic activity of HDAC1, HDAC2 and HDAC3 histone deacetylases, the (R)-isomer resulting more active. Furthermore, HSAs have been studied recently for a wide range of technological applications. For instance, in the material chemistry field, the crystalline symmetry of monolayers at the air-water interface of some monohydroxystearic acid (namely, 1, 7- and 8-HSA) has shown a specific correlation with the position of the crystalline symmetry of monohydroxystearic acid (namely, 1, 7- and 8-HSA) has shown a specific correlation with the position of the secondary hydroxy group. In another application, HSAs and their derivatives were studied as low molecular weight organogelators (LMOGs). To underline that the type of supramolecular architecture depends on the chirality of the molecule, enantiopure (R)-12-HSA has been found to form fibrillar networks, while racemic 12-HSA forms platelets under the same conditions. Therefore, the production of HSAs in enantiopure forms seems an attractive challenge. Sometimes, the natural chiral pool is a valuable source of enantiopure precursors of these acids. For example, a convenient route to (R)-9-HSA starts from 9-hydroxyoctadecanoic acid present in large amount in the seed oil of genus Dimorphotheca. Similarly, (R)-12-HSA can be obtained from castor oil that contains up to 90% of D-ricinoleic acid. Less accessible are enantiopure racemic precursors of 8-HSA, such as isonicolic acid (from seed oils of Santalaceae and Olacaceae) and laetisaric acid whereas, to the best of our knowledge, no useful precursors of 7-HSA are available. Recently, enantioenriched 7-, 8-, 9-, and 10-hydroxystearic acids have been obtained for the first time by enzymatic kinetic resolution of their racemates but the best enantiomeric excesses obtained were around 55%. In this communication we propose an efficient enantioselective synthesis of 7-HSA and 8-HSA through a multistep approach starting from racemic precursors. An inspection of the molecules of HSAs would suggest the ring closing olefin metathesis substrates 4 as potential key precursors to the target molecules, via a sequence of intermediates, as shown retrosynthetically in Scheme 1. This approach was already successfully applied to the synthesis of analogues of Topsentolides by Bracher and coworkers. Hydroxystearic acids 1 are equivalent to saturated macrocyclic lactones 2, which would be obtained by reduction of the unsaturated macrocyclic lactones 3. Intermediates 3 could be the products of ring-closing metathesis (RCM) of \( \alpha,\omega \)-diene 4. Access to 4 would be possible via condensation of terminally unsaturated carboxylic acids 5 and the appropriate homoallylic alcohols 6. Thus it is evident that the configuration at the carbonyl carbon atom in the final hydroxystearic acids is determined by the chirality of the parent homoallylic alcohol. According to this retrosynthetic disconnection, we faced the synthesis of both enantiomers of 7-HSA \( (n = 10, m = 2) \) and of 8-HSA \( (n = 9, m = 3) \).
Condensation of commercially available 4-pentenoic acid 5a (m = 2) and 5-hexenoic acid 5b (m = 3) with chiral non racemic 1-pentadecen-4-ol 6a15,16 (n = 10) and 1-tetradecen-4-ol and 6b17,18 (n = 9) respectively was performed by using the Yamaguchi's esterification reaction19 and afforded the dionic esters 4a and 4b in good chemical yield (Scheme 2). Yamaguchi's esterification resulted a clean and easy to perform reaction that gave higher yield than other method reported in literature for esterification of long chain homomallylic alcohols.20

![Scheme 1 Retrosynthetic analysis of HSAs.](image)

Scheme 1: Retrosynthetic analysis of HSAs.

In this manner (S)-(−)-1-pentadecen−4-ol 6a,22,23 with 98% ee and (S)-(−)-1-tetradecen−4-ol 6b with 99% ee were isolated in about 30% yield. The moderate yields in the enzymatic resolution process might be due to the difficult extraction process after significant degradation of the supported enzyme. The unreacted esters (R)-(+)−7a and (R)-(+)−7b, both in 97% ee, were then hydrolyzed with 2 equivalents of K2CO3 in MeOH at room temperature for 24 h to furnish the corresponding acids (R)-(+)−6a15,16,22,24 and (R)-(+)−6b, without affecting their enantiomeric composition.

For the ring closing metathesis of α,ω-dienes 4a and 4b, first (cat1) and second generation Grubbs' catalysts (cat2) were checked (Figure 1). The more active catalyst25 cat2 well worked with both dienes, whereas cat1 resulted active on 4b and ineffective on 4a, underlining the known26 ability of cat2 to promote the formation of 16- and 18-membered dimeric ring-closed products instead of unfavorable eight- and nine-membered rings.24

![Scheme 2 Synthesis of esters 4a and 4b.](image)

Scheme 2: Synthesis of esters 4a and 4b.

Access to enantioenerally enriched homomallylic alcohols 6a,b was possible via kinetic enzymatic resolution of the corresponding racemic acetates 7a and 7b (Scheme 3), which were in turn synthesized following a literature procedure20 by reaction of allylmagnesium chloride with dodecanal and undecanal respectively. Enzymatic hydrolyses were catalyzed by Novozym 435 (Lipase B from Candida antarctica) that displayed high enantioselectivity (E > 100). It is worth noting that the same Novozym 435 displayed much slower enantioselectivity in catalysing the acylation of alcohols 6a,b with vinyl acetate (E = 12 and 15 respectively).

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![Scheme 3 Kinetic enzymatic resolution of acetates 7a,b.](image)

Scheme 3: Kinetic enzymatic resolution of acetates 7a,b.

The ring closing metathesis of 4a and 4b was performed28 in refluxing dichloromethane using 6 mol% Grubbs’ catalyst, at low substrate concentration (3 mM) and in the presence of 3 eq of titanium isopropoxide27 (Scheme 4); in case of diene 4a other substrate concentrations (18 and 30 mM) were also investigated.

![Figure 1 1st Generation (cat1) and 2nd Generation (cat2) Grubbs’ catalysts.](image)

In all cases the crude reaction mixtures revealed the presence of many species, such as configurational isomers and double bond regioisomers,29 as suggested by an analysis of 1H and 13C NMR spectra. In order to have a clearer view of the products formed in the ring-closing metathesis reactions, the crude products were subjected to hydrogenation, thus decreasing the number of species. Three main products were identified for each reaction, namely a small amount of the expected 8- and 9-membered lactones 2a,b (Scheme 4) along with 16- and 18-membered lactones 8a,b and 9a,b, originated by cross-metathesis (CM) and subsequent ring closure; in addition, in case of 4a, the larger macroyclic 10a was also detected. Therefore it is clear that in this metathetic process the desired RCM product 3 (Scheme 1) was only a minor product, the major products deriving from CM+RCM. This outcome was expected, since formation of eight- and nine-membered cyclic olefins from RCM is known to be extremely difficult.30,31 The formation of eight- and nine-membered unsaturated lactones 3 could be increased performing the metathesis reaction in very low concentration (0.1 mM) at the expense of the use of a large quantity of a not environmentally friendly solvent and stoichiometric amount of catalyst.14
Of all products, only head-to-tail dimers 8a and 8b were isolated by flash chromatography and characterized, while monomers 2a and 2b were identified as main components in mixtures of different composition. Essentially identification was made through 1H NMR, 13C NMR and ESI-MS spectra, this latter playing a decisive role in assignments. For instance compound 2b (m/z 305, [M+Na]+) was present in a fraction also containing a mixture of symmetric dimers (m/z 587, [M+Na]+), whereas compound 2a was present only in traces and the main products were 8a and 9a (m/z 587, [M+Na]+) and the trimer 10a (m/z 869, [M+Na]+). Since 8a and 9a are constitutional isomers, they could be recognized only in the subsequent synthetic step, namely in the hydrogenation reaction which gave different fragments for the two isomers. In fact basic hydrogenation carried out on the hydrogenated mixtures allowed the isolation of diols 11a and 11b. On the contrary, of the two diacids formed from 9a and 9b only 12a could be isolated (Scheme 4). It is worth noting that the main hydrogenation products were the target molecules 1a and 1b, namely 7- and 8-hydroxy stearic acids respectively, derived from monomers 2a and 2b, from dimers 8a and 8b and, in case of 7-HSA, from the trimer 10a. Total yields are related to the substrate concentration adopted in the metathetic process: when concentration of diene 4a,b was 3mM, acids 1a,b were recovered in about 40% yield, which gradually lowered to about 30% as concentration of 4a raised up to 18 and 30 mM due to the increased formation of the undesired adduct 9a.

The optical purity of 7- and 8-hydroxy stearic acids 1a and 1b thus obtained was determined by NMR spectrometry after their esterification of the carboxylic moiety with diazomethane and derivatization with both (R)-(-)-O-acetylmandelic acid31 or enantiopure Mosher acid34 (derivatives 13a,b and 14a,b respectively, Figure S1, Supporting information). Diastereomeric ratios of 99/1 for (7R,2ʹR)-13a and (7S,2ʹR)-13a, of 94/6 and 90/10 for (8R,2ʹR)-13b and (8S,2ʹR)-13b, respectively were calculated. These results were confirmed also by treatment of the methyl ester of 1a with the (R)-(+) Mosher acid [(+) -MTPA] and of 1b with the (S)-(−) Mosher acid [−]-MTPA (see Supporting information).

The synthesis of both enantiomers of 7-HSA and 8-HSA, not available from natural sources, was successfully accomplished starting from racemic homoallylic alcohols which were efficiently resolved by enzymatic resolution with Lipase B from *Candida antarctica*. Their esterification with suitable unsaturated acids furnished terminal dienes, which underwent ring closure metathesis. Hydrogenation of the crude reaction mixtures, containing different types of chiral non-racemic macrocyclic lactones, followed by hydrolysis under basic conditions allowed the isolation of the desired R- and S-enantiomer of 7-HSA and 8-HSA in about 40% total yield. The outcome of the ring closure metathesis reaction was analysed on the basis of the nature of the hydrogenation products, giving evidences of the formation of undesired cross metathesis by-products.

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**Supporting Information**

YES (this text will be updated with links prior to publication)

**Primary Data**

NO (this text will be deleted prior to publication)

**References and Notes**


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-trifluoropropionic acid ([+]-MTPA, for 8-HSA methyl esters), and 0.003g of DMAP were dissolved, under nitrogen atmosphere, in anhydrous CHCl₃ (300 μL) and stirred at 0°C (ice-bath). To this solution, 0.008 g of methyl hydroxyisobutyrate and 0.010g of DCC dissolved in anhydrous CH₂Cl₂ (500 μL) was added dropwise. After a few minutes, a white solid precipitated. The reaction was monitored by TLC (eluent: n-hexane – AcOEt 1:1 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 CHCl₃ and analysed by ¹H NMR and ¹³C NMR. The d.r. was calculated by integration of the ¹⁹F NMR signals; hexafluorobenzene (δ = -163.0 ppm) was used as internal standard.

(R)-Methyl 7-(((3,3,3-trifluorophenyl)oxy)octadecanoate (79.2 g))

HMNMR (400 MHz, CDCl₃, 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, CHO), 3.66 (s, 3 H, COOCH₃), 3.55 (brs, 3 H, OCH₃), 2.28 (t, 2 H, J = 7.3 Hz, CD₂O), 1.80-1.40 (m, 6 H, CH₃), 1.40 - 1.10 (m, 22 H, CH₃), 0.88 (t, 3 H, J = 6.2 Hz, CH₃). ¹³C NMR (376 MHz, CDCl₃, δ ppm): -72.360 ppm. (S)-Methyl 7-(((3,3,3-trifluorophenyl)oxy)octadecanoate (75.2 g))

HMNMR (376 MHz, CDCl₃, δ ppm): -72.323 ppm. (R)-Methyl 8-(((S)-3,3,3-trifluorophenyl)oxy)octadecanoate (82.5 g)

HMNMR (400 MHz, CDCl₃, 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, CHO), 3.67 (s, 3 H, COOCH₃), 3.55 (brs, 3 H, OCH₃), 2.27 (t, 2 H, J = 7.5 Hz, CH₂O), 1.82-1.40 (m, 6 H, CH₃), 1.40 - 1.10 (m, 22 H, CH₃), 0.87 (t, 3 H, J = 7.0 Hz, CH₃). ¹³C NMR (376 MHz, CDCl₃, δ ppm): -72.369 ppm. (S)-Methyl 8-(((S)-3,3,3-trifluorophenyl)oxy)octadecanoate (80.3 g)

HMNMR (376 MHz, CDCl₃, δ ppm): -72.405 ppm.