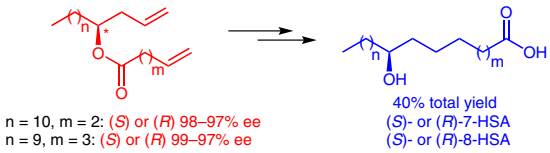
Synlett C. Boga et al. Letter

An Easy Route to Enantiomerically Enriched 7- and 8-Hydroxystearic Acids by Olefin-Metathesis-Based Approach

Carla Boga[a]
Sara Drioli[b]
Cristina Forzato[b]
Gabriele Micheletti[a]
Patrizia Nitti*[b]
Fabio Prati[c]

[a] Dipartimento di Chimica Industriale 'Toso Montanari', Università di Bologna, Viale del Risorgimento 4, 40136 Bologna, Italy
[b] Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, Via Licio Giorgieri 1, 34127 Trieste, Italy
pnitti@units.it
[c] Dipartimento di Scienze della Vita, Università di Modena e Reggio Emilia, Via Giuseppe Campi 103, 41125 Modena, Italy



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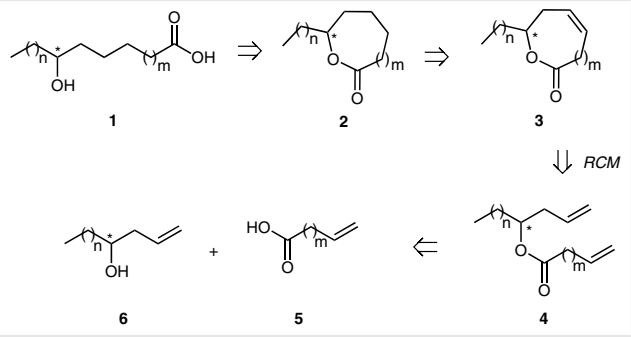
Abstract The synthesis of enantiomerically enriched 7- and 8-hydroxystearic acids (7- and 8-HSA) has been successfully accomplished starting from chiral nonracemic 1-pentadecen-4-ol and 1-tetradecen-4-ol, respectively. Their Yamaguchi's esterification with 4-pentenoic and 5-hexenoic acids, respectively, afforded the suitable dienic esters which were submitted to ring-closing metathesis reaction. After hydrogenation and basic hydrolysis of the complex reaction mixture, chiral nonracemic 7- and 8-HSA were obtained in about 40% total yield.

Key words hydroxystearic acid, ring closing metathesis, cross metathesis, homoallylic alcohols, lipase B from *Candida antarctica*, kinetic enzymatic resolution

Hydroxystearic acids (HSAs) and their derivatives are interesting molecules whose presence is crucial in many biological processes.[1] For instance, 9- and 10-hydroxystearic acids (9- and 10-HSA) have shown a natural negative regulatory activity on tumor-cell proliferation.[2] 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.[3] 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, 2-, 7-, 9-, and 12-HSA) has shown a specific correlation with the position of the secondary hydroxy group.[4] In another application, HSAs and their derivatives were studied as low-molecular-weight organogelators (LMOGs).[5,6] To underline that the type of supramolecular architectures depends on the chirality of the molecule, enantiopure (*R*)-12-HSA[7] has been found to form fibrillar networks, while racemic 12-HSA forms platelets under the same conditions.[8] 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.[9] For example, a convenient route to (*R*)-9-HSA starts from 9-hydroxyoctadeca-*trans*-10,*trans*-12-dienoic acid [(*S*)-dimorphecolic acid] present in large amount in the seed oil of genus *Dimorphotheca*.[9] Similarly, (*R*)-12-HSA[10] can be obtained from castor oil that contains up to 90% of D-ricinoleic acid. Less accessible are enantiomerically pure natural precursors of 8-HSA, such as isanolic acid[11] (from seed oils of *Santalaceae* and *Olacaceae*) and laetisaric acid[12] whereas, to the best of our knowledge, no useful precursors of 7-HSA are available. Recently, enantioenriched 7-, 8-, 9-, and 10-HSA have been obtained for the first time by enzymatic kinetic resolution of their racemates but the best enantiomeric excesses obtained were around 55%.[13]

In this communication we propose an efficient enantioselective synthesis of 7-HSA (**1a**)[13] and 8-HSA (**1b**)[13] 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 a analogues of Topsentolides by Bracher and coworkers.[14]

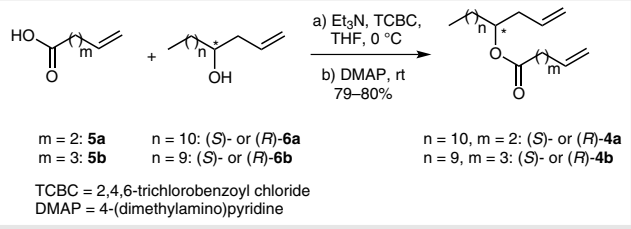
Hydroxystearic acids **1** are equivalent to saturated macrocyclic lactones **2**, which would be obtained by reduction of the unsaturated macrocyclic lactones **3**. Intermediates **3** could be the products of ring-closing metathesis (RCM) of α,ω-diene **4**. Access to **4** would be possible via condensation of terminally unsaturated carboxylic acids **5** and the appropriate homoallylic alcohols **6**. Thus it is evident that the configuration at the carbinol carbon atom in the final hydroxy stearic acids is determined by the chirality of the par-



Scheme 1 Retrosynthetic analysis of HSAs

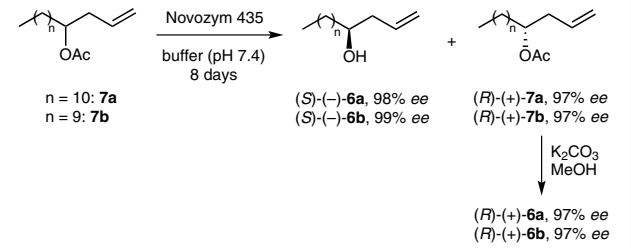
ent homoallylic alcohol. According to this retrosynthetic disconnection, we faced the synthesis of both enantiomers of 7-HSA (**1a**, n = 10, m = 2) and of 8-HSA (**1b**, n = 9, m = 3).

Condensation of commercially available 4-pentenoic acid (**5a**, m = 2) and 5-hexenoic acid (**5b**, m = 3) with chiral nonracemic 1-pentadecen-4-ol (**6a**)[15,16] (n = 10) and 1-tetradecen-4-ol (**6b**)[17,18] (n = 9), respectively, was performed by using the Yamaguchi's esterification reaction[19] and afforded the dienic esters **4a** and **4b** in good chemical yields (Scheme 2). Yamaguchi's esterification resulted a clean and easy-to-perform reaction that gave higher yield than another method reported in the literature for esterification of long-chain homoallylic alcohols.[14]



Scheme 2 Synthesis of esters **4a** and **4b**

Access to enantiomerically enriched homoallylic 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 procedure[20] 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 enantioselection (E^{21}> 200). It is worth noting that the same Novozym 435 displayed much lower enantioselectivity in catalyzing the acylation of alcohols **6a**,**b** with vinyl acetate (E = 12 and 15, respectively).



Scheme 3 Kinetic enzymatic resolution of acetates **7a**,**b**

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 two equivalents of K_2CO_3 in MeOH at room temperature for 24 hours to furnish the corresponding alcohols (*R*)-(+)-**6a**[15,16,22,24] and (*R*)-(+)-**6b**,without affecting their enantiomeric composition.

For the RCM of α,ω-dienes **4a** and **4b**, first (**cat1**) and second-generation Grubbs catalysts (**cat2**) were checked (Figure 1). The more active catalyst[25] **cat2** well worked with both dienes, whereas **cat1** resulted active on **4b** and ineffective on **4a**, underlining the known[26] ability of **cat2** to promote the formation of 16- and 18-membered dimeric ring-closed products instead of unfavorable eight- and nine-membered rings.[14]

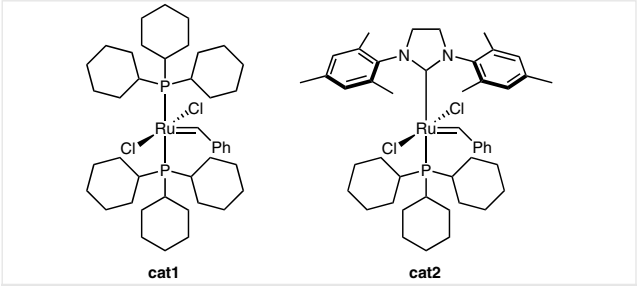
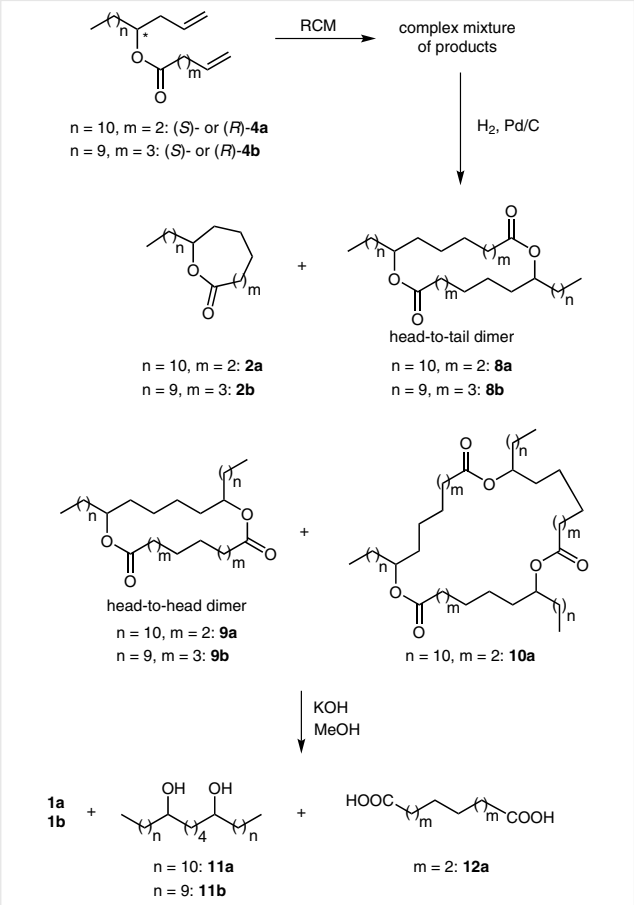


Figure 1 First-generation (**cat1**) and second-generation (**cat2**) Grubbs catalysts

The RCM of **4a** and **4b** was performed[27] in refluxing dichloromethane using 6 mol% Grubbs catalyst, at low substrate concentration (3 mM) and in the presence of three equivalents of titanium isopropoxide[28] (Scheme 4); in the case of diene **4a** other substrate concentrations (18 and 30 mM) were also investigated.

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 ^{1}H NMR and ^{13}C NMR spectra. In order to have a clearer view of the products formed in the RCM reactions, the crudes 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 eight- and nine-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 the case of **4a**, the larger macrocyclic



Scheme 4 Hydrogenation products of RCM reaction mixtures and subsequent basic hydrolysis

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.[30–32]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 ^{1}H NMR, ^{13}C 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 hydrolysis reaction which gave different fragments for the two isomers. In fact basic hydrolysis 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 hydrolysis products were the target molecules **1a** and **1b**, namely 7- and 8-HSA respectively, derived from monomers **2a** and **2b**, from dimers **8a** and **8b**, and, in the 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 3 mM, 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-HSA **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 acid[33] or enantiopure Mosher acid[34] (derivatives **13a**,**b** and **14a**,**b**, respectively, Figure S1, Supporting Information). 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, 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 nonracemic 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 analyzed on the basis of the nature of the hydrogenation products, giving evidences of the formation of undesired cross-metathesis byproducts.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561570.

References and Notes

(1) (a) Gunstone, F. D. *Fatty Acid and Lipid Chemistry*; Springer: Berlin, **1996**. (b) Fulco, A. J. *Progr. Lipid Res.* **1983**, *22*, 133. (c) Harwood, J. L.; Russell, N. J. *Lipids in Plants and Microbes*; Allen and Unwin: London, **1984**.

(2) (a) Masotti, L.; Casali, E.; Gesmundo, N.; Sartor, G.; Galeotti, T.; Borrello, S.; Piretti, M. V.; Pagliuca, G. *Ann. N.Y. Acad. Sci.* **1989**, *51*, 47. (b) Masotti, L.; Casali, E.; Gesmundo, N. *Mol. Aspects Med.* **1993**, *14*, 209. (c) Bertucci, C.; Hudaib, M.; Boga, C.; Calonghi, N.; Cappadone, C.; Masotti, L. *Rapid Commun. Mass Spectrom.* **2002**, *16*, 859.

(3) Parolin, C.; Calonghi, N.; Presta, E.; Boga, C.; Caruana, P.; Naldi, M.; Andrisano, V.; Masotti, L.; Sartor, G. *Biochim. Biophys. Acta* **2012**, *1821*, 1334.

(4) Cristofolini, L.; Fontana, M. P.; Boga, C.; Konovalov, O. *Langmuir* **2005**, *21*, 11213.

(5) (a) Rogers, M. A.; Wright, A. J.; Marangoni, A. G. *Soft Matter* **2008**, *4*, 1483. (b) Rogers, M. A.; Wright, A. J.; Marangoni, A. G. *Curr. Opin. Coll. Interf. Sci.* **2009**, *14*, 33. (c) Rogers, M. A.; Kim, J. H. J. *Food Res. Int.* **2011**, *44*, 1447.

(6) (a) Mallia, V. A.; Weiss, R. G. *J. Phys. Org. Chem.* **2014**, *27*, 310. (b) Abraham, S.; Lan, Y.; Lam, R. S. H.; Grahame, D. A. S.; Kim, J. J. H.; Weiss, R. G. A.; Rogers, M. A. *Langmuir* **2012**, *28*, 4955.

(7) Laupheimer, M.; Preisig, N.; Stubenrauch, C. *Colloids Surf., A* **2015**, *469*, 315.

(8) (a) Grahame, D. A. S.; Olauson, C.; Lam, R. S. H.; Pedersen, T.; Borondics, F.; Abraham, S.; Weiss, R. G.; Rogers, M. A. *Soft Matter* **2011**, *7*, 7359. (b) Tachibana, T.; Kambara, H. *J. Colloid Interface Sci.* **1968**, *28*, 173. (c) Tachibana, T.; Mori, T.; Hori, K. *Bull. Chem. Soc.* **1980**, *53*, 1714.

(9) Badami, R. C.; Patil, K. B. *Prog. Lipid Res.* **1981**, *19*, 119; and references cited therein.

(10) Murakami, S.; Satou, K.; Kijima, T.; Watanabe, M.; Izumi, T. *Eur. J. Lipid Sci. Technol.* **2011**, *113*, 450.

(11) Miller, R. W.; Weisleder, D.; Kleiman, R.; Plattnera, R. D.; Smith, C. R. Jr. *Phytochemistry* **1977**, *16*, 947.

(12) (a) Bowers, S.; Hoch, H. C.; Evans, P. H.; Katayama, M. *Science* **1986**, *232*, 105. (b) Brodowsky, I. D.; Oliw, E. H. *Biochim. Biophys. Acta* **1993**, *1168*, 68. (c) Garscha, U.; Oliw, E. H. *Anal. Biochem.* **2007**, *367*, 238; and references cited therein.

(13) 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.

(14) Wetzel, I.; Krauss, J.; Bracher, F. *Lett. Org. Chem.* **2012**, *9*, 169.

(15) Harbindu, A.; Sharma, M. B.; Kumar, P. *Tetrahedron: Asymmetry* **2013**, *24*, 305.

(16) Kumar, R. S. C.; Sreedhar, E.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 1160.

(17) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.

(18) (a) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Org. Chem.* **2007**, *72*, 4763. (b) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 12250.

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

(20) Chang, Y.-H.; Uang, B.-J.; Wu, C.-M.; Yu, T.-H. *Synthesis* **1990**, 1033.

(21) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 72.

(22) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768.

(23) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743.

(24) Tripathi, D.; Kumar, P. *Tetrahedron: Asymmetry* **2012**, *23*, 884.

(25) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496.

(26) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155.

(27) **Typical Procedure**
To (–)-(*S*)-**4a** (0.143 g, 0.46 mmol) in anhydrous CH_2Cl_2 (14 mL), Ti(O*i*-Pr)$_4$ (0.41 mL, 1.38 mmol) was added at room temperature. The stirred solution was refluxed under Ar for 30 min and then left cooled for 15 min. Second-generation Grubbs catalyst (0.0236 g, 0.027 mmol) dissolved in anhydrous CH_2Cl_2 (1 mL) 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 CH_2Cl_2. The solvent was evaporated, and to the crude reaction mixture (0.095 g) MeOH (4.75 mL) and Pd/C (10%, 0.095 g) 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 CH_2Cl_2. 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 d. After removing the solvent, H_2O (10 mL) was added and repeatedly extracted with Et_2O. The organic phase was dried on anhydrous Na_2SO_4 and evaporated to afford diol **11a** (0.0045 g, 0.01 mmol). Basic mother liquors were acidified to pH 1 and extracted with Et_2O. 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**.

(28) Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389.

(29) (a) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160. (b) Lehman, S. E. Jr.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta* **2003**, *345*, 190. (c) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865.

(30) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(31) Kadyrov, R. *Chem. Eur. J.* **2013**, *19*, 1002; and references cited therein.

(32) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783.

(33) For derivatization with (*R*)-(–)-*O*-acetylmandelic acid and related ^{1}H NMR signals, see ref. 13. The diastereomeric ratio was calculated on the crude for (*R*)-7- and (*R*)-8-HSA derivatives and on the product purified by preparative TLC for (*S*)-7- and (*S*)-8-HSA derivatives.

(34) **General Procedure for Derivatization with Mosher Acid**
(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid [(+)-MTPA, for derivatization of 7-HSA methyl esters] (0.012 g), or (*S*)-(–)-α-methoxy-α-trifluorophenylacetic acid [(–)-MTPA, for 8-HSA methyl esters], and DMAP (0.003 g) were dissolved, under nitrogen atmosphere, in anhydrous CH_2Cl_2 (300 µL) and stirred at 0 °C (ice-bath). To this solution of methyl hydroxystearate (0.008 g) and DCC (0.010 g) 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–EtOAc, 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 analyzed 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.

(*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 = 7.58–7.50 (m, 2 H, Ph), 7.42–7.37 (m, 3 H, Ph), 5.07 (quint, 1 H, *J* = 6.4 Hz, C*H*OH), 3.66 (s, 3 H, $COOCH_3$), 3.55 (br s, 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) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –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 = –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 = 7.59–7.50 (m, 2 H, Ph), 7.45–7.36 (m, 3 H, Ph), 5.07 (quint, 1 H, *J* = 6.5 Hz, C*H*OH), 3.67 (s, 3 H, $COOCH_3$), 3.55 (br s, 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) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –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 8*R*,2′*S* diastereomer. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –72.405 ppm.