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Recycling Mitsunobu coupling: a shortcut for troublesome esterifications

Boudjema Menhour [a], Firmin Obounou Akong [a], Patrick Mayon [a], Karen Plé [b], Sandrine Bouquillon [a], Stéphan Dorey [c], Christophe Clément [c], Magali Deleu [d], Dominique Harakat [e], Arnaud Haudrechy [a,*]

[a] Institut de Chimie Moléculaire de Reims, UMR CNRS 7312, Université de Reims, 51687 Reims Cedex, France
[b] Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, 45067 Orléans Cedex, France
[c] Unité de Recherche Vignes et Vins de Champagne, EA 4707, Université de Reims, 51687 Reims Cedex, France
[d] Laboratoire de Biophysique Moléculaire aux Interfaces, Université de Liège, Passage des Déportés, 2, 5030 Gemboux, Belgium
[e] Service commun d'analyses, Institut de Chimie Moléculaire de Reims, UMR CNRS 7312, Université de Reims, 51687 Reims Cedex, France

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ABSTRACT

An unusual recycling Mitsunobu reaction proved to be successful to couple two fragments in the course of the synthesis of the hydrophobic moiety of rhamnolipid derivatives. Based on the obtained pivotal intermediate, a one pot 'cross-metathesis/reduction' approach gave access to structural variations of the side chains. Further study of these molecules will contribute to a better understanding of the role of the lipid moiety in immunostimulatory and plant defense eliciting properties.

1. Introduction

Reviewing the literature has shown that Mitsunobu reactions[1] with allylic alcohols can be performed with saturated carboxylic acids, giving a clean inversion of configuration. Examples with formic acid and two carbon-'acetic acid derivatives' have been described but we wish to focus our attention on particularly interesting cases with more complex carboxylic acid derivatives (with at least three carbons).[2]

In the literature, benzene, THF and toluene are the solvents of choice with diethyl ether, methylene chloride, DME or acetonitrile being used more rarely.[2j,3]

In the course of our studies on bacterial rhamnolipids,[4] especially those produced by *Pseudomonas aeruginosa*[5] and *Burkholderia plantarii*,[6] all of our attempts to couple **1** (***S***) and **2** (***S***) via diverse esterification procedures were unsuccessful (DCC/DMAP, EDCI and TBTU).

Surprisingly, compound **3** (***S***) was the only observed product resulting from intermolecular acetate migration of the DCC intermediate as previously described by Duynstee et al.[8]

2. Results and discussion

Our starting material, acetoxyester **3** (***S***),[9] was easily prepared on a convenient scale using PS Amano lipase as a biocatalyst for the enantioselective acetylation (Scheme 2).[10] Loss of half of the starting material, inherent in an enzymatic resolution was an initial drawback, but this fact later proved beneficial.

While attempting the various coupling reactions, work was also in progress to recycle the unwanted enantiomer **1** (***R***) via a Mitsunobu approach.

The idea was to perform the Mitsunobu reaction between diverse carboxylic acids derived from the acetoxyester **3** (***S***) and the allylic alcohol **1** (***R***), the ***undesired*** enantiomer, thus solving the problems of recycling and coupling in only one step.

Two preliminary tests gave very promising results in encouraging yields (Scheme 3). The first example allowed us to recycle the undesired enantiomer **1**(***R***) to give the (***S***) intermediate **3**, while the

* Corresponding author. E-mail address: arnaud.haudrechy@univ-reims.fr (A. Haudrechy).

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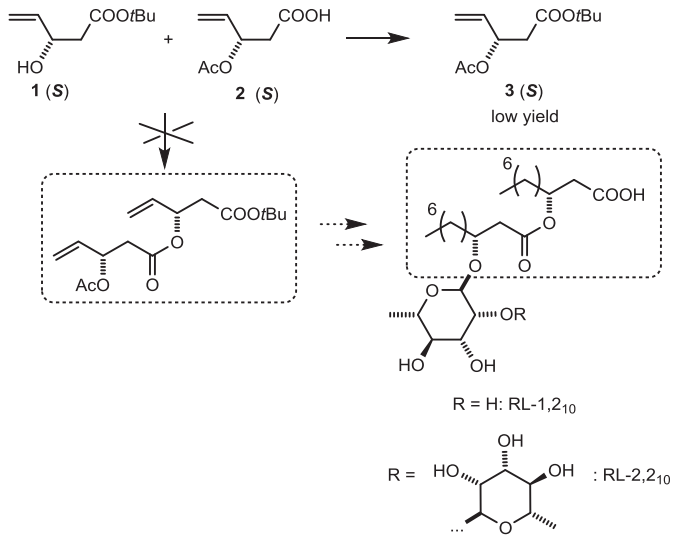
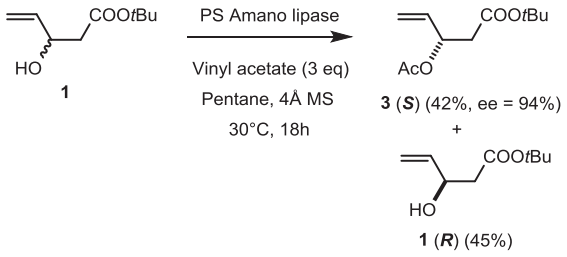
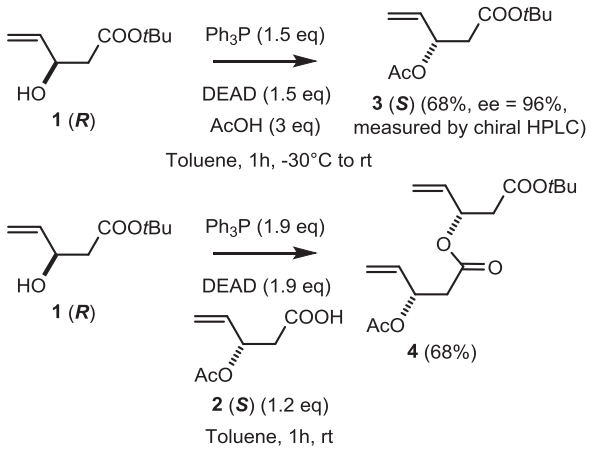


Scheme 1. Unsuccessful esterification to produce natural rhamnolipids used as elicitors.[7]



Scheme 2. Enzymatic resolution using PS Amano lipase.

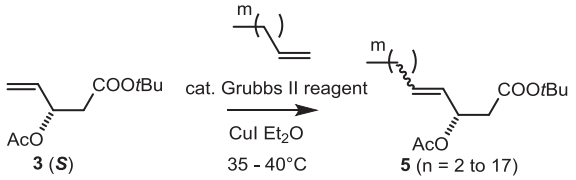
second one solved two problems, the aforementioned desired inversion of configuration and coupling to furnish compound **4**. This second example proved to be an esthetic alternative to the desired but unsuccessful DCC coupling reaction.



Scheme 3. Mitsunobu reactions on hydroxylester **1** (***R***) (1).

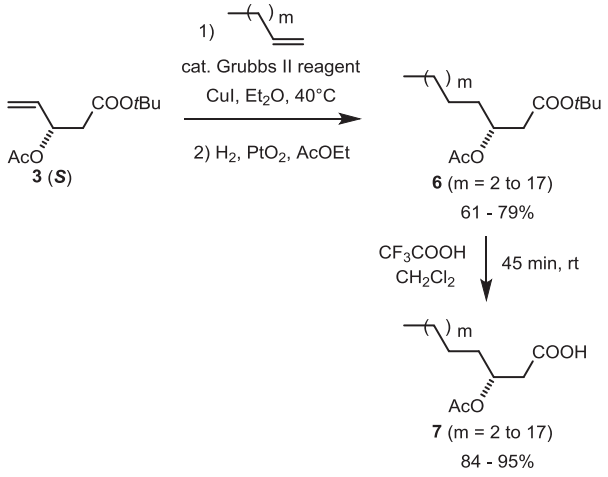
In order to apply this concept to longer chains carboxylic acids, attracted by the moieties involved in the natural Rhamnolipids (see Scheme 1), we used our pivotal substrate **3** (***S***)[11] with 16 different alkenes to give the desired unsaturated long chain acids using conditions recently described by Voigtritter et al. (Table 1).[12]

Table 1
Cross-metatheses with compound **3** (***S***)



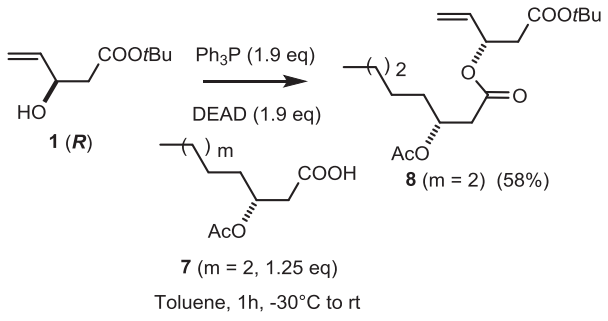
m	Yield (*E*: *Z*)	*m*	Yield (*E*: *Z*)
2	89 (5.2: 1)	10	70 (7.3: 1)
3	57 (4.0: 1)	11	55 (9.0: 1)
4	65 (5.2: 1)	12	76 (6.1: 1)
5	55 (6.1: 1)	13	65 (10.1: 1)
6	54 (4.0:1)	14	85 (8.1: 1)
7	74 (8.1: 1)	15	74 (7.3: 1)
8	78 (7.3: 1)	16	62 (5.7: 1)
9	59 (5.7: 1)	17	91 (5.7: 1)

As the separation of *Z* and *E*-alkenes proved to be difficult in certain cases, we decided to directly hydrogenate the crude mixture in a one-pot sequence (Scheme 4).



Scheme 4. Cross metathesis-hydrogenation of ester **3** (***S***).

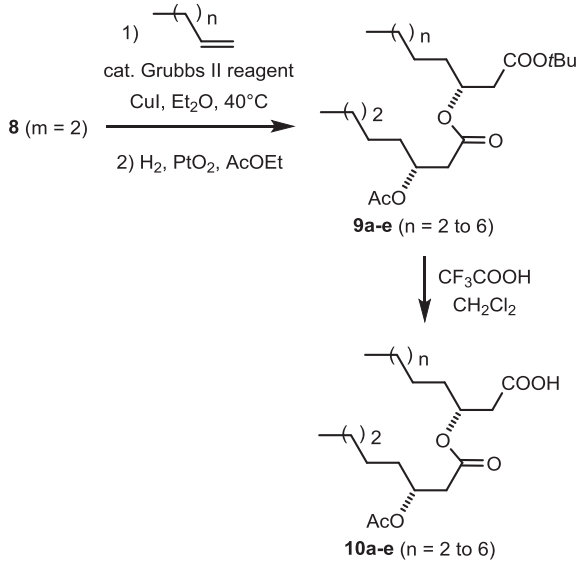
Compound **7** (*m*=2) was then subjected to a Mitsunobu coupling with hydroxylester **1** (***R***) giving the expected compound **8** (*m*=2) in 58% yield (Scheme 5).



Scheme 5. Mitsunobu reactions with hydroxylester **1** (***R***) (2).

Finally, to demonstrate the generality of our approach, a second cross-metathesis reaction was performed with derivative **8** (m=2) with five different alkenes, followed by direct hydrogenation of the reaction mixture (Table 2). In all cases, dimeric structures from the alkenes and approximately 15% of starting material could be easily removed by silica gel column chromatography. Acidic hydrolysis then gave the desired acids in yields varying between 70 and 88% yield.

Table 2
Cross metathesis of ester **8** (m=2)



n	2	3	4	5	6
Metathesis yield **9a**–**e** (%)	60	53	48	54	54
Deprotection yield **10a**-**e** (%)	76	86	70	73	88

3. Conclusion

Using the Mitsunobu reaction for esterification allowed the recycling of an unwanted enantiomer with the simultaneous coupling of acid and alcohol fragments impossible to perform with more traditional coupling techniques, thus 'killing two birds with one stone'. This short and efficient strategy was effectively employed for the synthesis of the hydrophobic moiety of biologically important rhamnolipids. In our synthesis, two one-pot metathesis/hydrogenation sequences gave access to a large number of functionalized alkyl side chains. Work is in progress towards subsequent rhamnosylation which will allow us to obtain hybrid structures and a better understanding of the structure-activity relationships of this fascinating class of elicitors.

4. Experimental section

All reactions were carried out under argon and in oven-dried apparatus. Dry solvents were used in all experiments. Thin layer chromatography was performed on E. Merck pre-coated 60 F254 plates and compounds were observed by UV or by charring the plates with a phosphomolybdic acid system. Flash column chromatography (silica gel 40–63 μm) was carried out with light petroleum ether–ethyl acetate mixtures as eluent.

All the reported NMR spectra were recorded by dissolving the samples in $CDCl_3$ (Eurisotop) on Bruker spectrometer (250, 500 or 600 MHz for 1H and 63, 125 or 150 MHz for 13C) using standard pulse programs. Chemical shifts (δ) reported in parts per million (ppm) refer to the chloroform peak of $CDCl_3$ as reference at 7.26 ppm and the coupling constants are reported in Hz. The multiplicities are reported as follows: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The chemical shifts of the ^{13}C NMR signals were assigned by using the center peak of the triplet of $CDCl_3$ as reference (δ=77.16 ppm). FTIR spectra were recorded on Nicolet Avatar 320 FTIR films. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Electrospray ionization mass spectrometry experiments (MS and HRMS) were obtained on a hybrid tandem quadrupole/time of flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in positive mode (eV=30 V, 80 °C, injection flow 5 μL/min).

4.1. (*R*) *t*-Butyl 3-hydroxy-pent-4-enoate 1 and (*S*) *t*-Butyl 3-acetoxy-pent-4-enoate 3

Vinyl acetate (15.6 mL, 169.6 mmol) was added to a solution of **1** (9.75 g, 56.7 mmol) in pentane (120 mL). Amano lipase (from *Burkholderia cepacia* (6.2 g) and MS 4 Å (8.9 g) were added and the suspension was stirred at 30 °C for 16 h. The reaction mixture was monitored by TLC. The lipase and sieves were filtered and washed with Et_2O. The solvent was removed and the crude product was purified by silica gel column chromatography (EtOAc/Petroleum ether 1:9) to afford **1** (***R***) (4.4 g, 25.6 mmol, 45%) and **3** (***S***) (5.1 g, 23.8 mmol, 42%).

1 (***R***): $[\alpha]_{20}^{D}$=+4.1 (c=1.04, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.83 (ddd, J=16.0, 10.5, 5.5 Hz, 1H, CH=CHaHb), 5.25 (dt, J=17.2, 1.5 Hz, 1H, CH=CHaHb), 5.09 (dt, J=10.5, 1.4 Hz, 1H, CH=CHaHb), 4.45 (m, 1H, CHOH), 3.2 (br s, 1H, CHOH), 2.47 (dd, J=16.1, 4.7 Hz, 1H, COCHaHb), 2.38 (dd, J=16.1, 7.7 Hz, 1H, COCHaHb), 1.42 (s, 9H, *t*-Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=171.7, 139.0, 115.2, 81.4, 69.1, 42.2, 28.1 ppm. IR (film): ν_{max}=3434, 2979, 2931, 1726, 1645, 1393, 1368, 1256, 1157, 1039, 993, 924, 842, 763 cm^{-1}. HRMS (ESI): calcd for $C_9H_{16}O_3$ $[M+Na]^+$ 195.0997 found 195.1002.

3 (***S***): $[\alpha]_{20}^{D}$=−5.5 (c=1.09, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.81 (ddd, J=17.0, 10.5, 6.2 Hz, 1H, CH=CHaHb), 5.59 (m, 1H, $CHOCOCH_3$), 5.28 (dt, J=17.2, 1.2 Hz, 1H, CH=CHaHb), 5.18 (dt, J=10.5, 1.2 Hz, 1H, CH=CHaHb), 2.60 (dd, J=15.3, 7.9 Hz, 1H, *t*BuO-COCHaHb), 2.50 (dd, J=15.3, 5.9 Hz, 1H, *t*BuOCOCHaHb), 2.04 (s, 3H, $OCOCH_3$), 1.42 (s, 9H, t-Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=169.9, 169.1, 135.3, 117.4, 81.2, 71.2, 40.8, 28.1, 21.2 ppm. IR (film): ν_{max}=2979, 2933, 1736, 1646, 1457, 1369, 1290, 1235, 1159, 1024, 991, 947, 847, 764 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{18}O_4$ $[M+Na]^+$ 237.1103 found 237.1109.

4.2. (*S*) *t*-Butyl-3-(((*S*)-3-acetoxy-pent-4-enoyl)oxy)-pent-4-enoate 4

To a solution of alcohol **1** (***R***) (514 mg, 2.98 mmol) in toluene (15 mL) were added PPh_3 (1.46 g, 5.57 mmol, 1.9 equiv) and acid **2** (***S***) (550 mg, 3.48 mmol, 1.2 equiv) in toluene (5 mL) at room temperature. After 10 min, diethyl azodicarboxylate (0.90 mL, 1.0 g, 5.75 mmol, 1.9 equiv) was added dropwise over a period of 15 min. The mixture was stirred at room temperature for 1 h and quenched with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue which was purified by silica gel column chromatography (EtOAc/Petroleum ether 1:9) to afford **4** (628 mg, 2.01 mmol, 68%).

4: $[\alpha]_{20}^{D}$=−8.0 (c=0.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.88–5.69 (m, 2H, 2CH=CHaHb), 5.66–5.54 (m, 2H, 2CH–OCO), 5.32–5.14 (m, 4H, $2CH{=}CH_2$), 2.72–2.44 (m, 4H, $2COCH_2$), 2.02 (s,

3H, $OCOCH_3$), 1.41 (s, 9H, *t*-Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=169.9, 168.9, 168.6, 135.0, 134.9, 117.8, 117.6, 81.2, 71.6, 70.7, 40.6, 39.5, 28.1, 21.1 ppm. IR (film): ν_{max}=3090, 2979, 2934, 1739, 1647, 1456, 1369, 1236, 1160, 1025, 938, 844, 764 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{24}O_6$ $[M+Na]^+$ 335.1471 found 335.1469.

4.2.1. General procedure for the cross-metathesis and hydrogenation, access to compound ***6*** *(m=2–17).* To a solution of **3** (***S***) (1 mmol) in anhydrous ethyl ether (10 mL) were added Grubbs2 catalyst (42.4 mg, 50 μmol, 5 mol %), CuI (13.3 mg, 70 μmol, 7% eq) and alkene (4 mmol, 4 equiv) under an Ar atmosphere. The mixture was heated to 40 °C for 1h30 until the color of the reaction mixture went from brown to dark green, corresponding to disappearance of starting material by tlc. After cooling to room temperature, the mixture was filtered through a short column of sand and $MgSO_4$. The solid was washed with ethyl ether and the solvent was evaporated under reduced pressure. The obtained residue was used in the next step without further purification. To a solution of the residue in dry EtOAc (10 mL) at room temperature, a catalytic amount of PtO_2 was added. The flask was purged and filled with H_2 gas and the mixture was stirred vigorously at room temperature for 2 h. The reaction was filtered through a Celite pad and washed with EtOAc. The solvent was removed and the crude product was purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:19) to afford the corresponding adduct **6** (*m*=2 to *m*=17) (yield from 61 to 79% for two steps).

*4.2.1.1. (R) t-Butyl 3-acetoxy-octanoate (****6****, m=2).* Yield 64%. $[\alpha]_{20}^{D}$=+3.9 (*c*=1.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.26–5.08 (m, 1H, CH–O), 2.52–2.37 (m, 2H, $COCH_2$), 2.0 (s, 3H, $COCH_3$), 1.66–1.48 (m, 2H, CH–CH_2), 1.41 (s, 9H, *t*-Bu), 1.35–1.15 (m, 6H, $(CH_2)_3CH_3$), 0.85 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.7, 80.9, 70.9, 40.7, 34.1, 31.7, 28.1, 24.9, 22.6, 21.2, 14.1 ppm. IR (film): ν_{max}=2958, 2933, 2862, 1743, 1456, 1369, 1240, 1159, 1026, 949, 845 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{14}H_{26}O_4Na$ $[M+Na]^+$ 281.1729, found 281.1723.

*4.2.1.2. (R) t-Butyl 3-acetoxy-nonanoate (****6****, m=3).* Yield 69%. $[\alpha]_{20}^{D}$=+2.3 (*c*=3.12, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.09 (m, 1H, CH–O), 2.49–2.34 (m, 2H, $COCH_2$), 1.97 (s, 3H, $COCH_3$), 1.64–1.46 (m, 2H, CH–CH_2), 1.38 (s, 9H, *t*-Bu), 1.33–1.12 (m, 8H, $(CH_2)_4CH_3$), 0.82 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.3, 169.7, 80.8, 70.9, 40.7, 34.1, 31.7, 29.1, 28.0, 25.1, 22.6, 21.1, 14.1 ppm. IR (film): ν_{max}=2959, 2930, 2860, 1740, 1461, 1368, 1240, 1158, 1028, 951, 847 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{15}H_{28}O_4Na$ $[M+Na]^+$ 295.1885, found 295.1891.

*4.2.1.3. (R) t-Butyl 3-acetoxy-decanoate (****6****, m=4).* Yield 79%. $[\alpha]_{20}^{D}$=+4.5 (*c*=2.90, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.08 (m, 1H, CH–O), 2.52–2.37 (m, 2H, $COCH_2$), 1.99 (s, 3H, $COCH_3$), 1.67–1.48 (m, 2H, CH–CH_2), 1.41 (s, 9H, *t*-Bu), 1.35–1.15 (m, 10H, $(CH_2)_5CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.8, 70.9, 40.7, 34.2, 32.0, 29.7, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2959, 2928, 2858, 1739, 1461, 1369, 1240, 1158, 1027, 952, 846 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{16}H_{30}O_4Na$ $[M+Na]^+$ 309.2042, found 309.2047.

*4.2.1.4. (R) t-Butyl 3-acetoxy-undecanoate (****6****, m=5).* Yield 76%. $[\alpha]_{20}^{D}$=+3.7 (*c*=3.50, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.07 (m, 1H, CH–O), 2.51–2.36 (m, 2H, $COCH_2$), 2.00 (s, 3H, $COCH_3$), 1.66–1.47 (m, 2H, CH–CH_2), 1.41 (s, 9H, *t*-Bu), 1.33–1.15 (m, 12H, $(CH_2)_6CH_3$), 0.85 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.9, 70.9, 40.7, 34.2, 31.9, 29.5, 29.4, 29.3, 28.1, 25.2, 22.7, 21.2, 14.2 ppm. IR (film): ν_{max}=2956, 2925, 2854, 1742, 1458, 1368, 1238, 1156, 1024, 950, 845 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{17}H_{32}O_4Na$ $[M+Na]^+$ 323.2198, found 323.2193.

*4.2.1.5. (R) t-Butyl 3-acetoxy-dodecanoate (****6****, m=6).* Yield 79%. $[\alpha]_{20}^{D}$=+4.8 (*c*=2.95, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.23–5.07 (m, 1H, CH–O), 2.51–2.35 (m, 2H, $COCH_2$), 1.99 (s, 3H, $COCH_3$), 1.65–1.46 (m, 2H, CH–CH_2), 1.40 (s, 9H, *t*-Bu), 1.32–1.13 (m, 14H, $(CH_2)_7CH_3$), 0.84 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.8, 70.9, 40.7, 34.2, 31.9, 29.7, 29.6, 29.5, 29.4, 28.1, 25.2, 22.7, 21.2, 14.2 ppm. IR (film): ν_{max}=2951, 2925, 2854, 1742, 1459, 1368, 1239, 1158, 1025, 952, 847 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{18}H_{34}O_4Na$ $[M+Na]^+$ 337.2355, found 337.2363.

*4.2.1.6. (R) t-Butyl 3-acetoxy-tridecanoate (****6****, m=7).* Yield 67%. $[\alpha]_{20}^{D}$=+3.5 (*c*=1.94, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.08 (m, 1H, CH–O), 2.52–2.37 (m, 2H, $COCH_2$), 2.00 (s, 3H, $COCH_3$), 1.66–1.47 (m, 2H, CH–CH_2), 1.41 (s, 9H, *t*-Bu), 1.35–1.14 (m, 16H, $(CH_2)_8CH_3$), 0.85 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.8, 70.9, 40.7, 34.2, 32.0, 29.7, 29.6, 29.6, 29.5, 29.4, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2954, 2926, 2855, 1742, 1456, 1368, 1239, 1156, 1026, 952, 845 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{19}H_{36}O_4Na$ $[M+Na]^+$ 351.2511, found 351.2515.

*4.2.1.7. (R) t-Butyl 3-acetoxy-tetradecanoate (****6****, m=8).* Yield 62%. $[\alpha]_{20}^{D}$=+3.3 (*c*=2.66, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.25–5.08 (m, 1H, CH–O), 2.53–2.37 (m, 2H, $COCH_2$), 2.01 (s, 3H, $COCH_3$), 1.67–1.48 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.37–1.16 (m, 18H, $(CH_2)_9CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.5, 169.8, 80.9, 71.0, 40.7, 34.2, 32.0, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2958, 2925, 2855, 1743, 1461, 1368, 1240, 1156, 1025, 952, 847 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{20}H_{38}O_4Na$ $[M+Na]^+$ 365.2668, found 365.2676.

4.2.1.8. (R) t-Butyl 3-acetoxy-pentadecanoate ***6*** *(m=9).* Yield 61%. $[\alpha]_{20}^{D}$=+2.6 (*c*=4.01, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.10 (m, 1H, CH–O), 2.53–2.37 (m, 2H, $COCH_2$), 2.02 (s, 3H, $COCH_3$), 1.67–1.49 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.36–1.17 (m, 20H, $(CH_2)_{10}CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.5, 169.9, 80.9, 71.0, 40.7, 34.2, 32.0, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2958, 2924, 2854, 1743, 1467, 1368, 1239, 1158, 1026, 953, 845 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{21}H_{40}O_4Na$ $[M+Na]^+$ 379.2824, found 379.2813.

*4.2.1.9. (R) t-Butyl 3-acetoxy-hexadecanoate (****6****, m=10).* Yield 75%. $[\alpha]_{20}^{D}$=+2.1 (*c*=4.46, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.10 (m, 1H, CH–O), 2.52–2.37 (m, 2H, $COCH_2$), 2.00 (s, 3H, $COCH_3$), 1.66–1.48 (m, 2H, CH–CH_2), 1.41 (s, 9H, *t*-Bu), 1.36–1.16 (m, 22H, $(CH_2)_{11}CH_3$), 0.85 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.9, 70.9, 40.7, 34.2, 32.0, 29.8, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2957, 2924, 2853, 1743, 1467, 1368, 1239, 1155, 1026, 952, 847 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{22}H_{42}O_4Na$ $[M+Na]^+$ 393.2981, found 393.2975.

*4.2.1.10. (R) t-Butyl 3-acetoxy-heptadecanoate (****6****, m=11).* Yield 65%. $[\alpha]_{20}^{D}$=+1.5 (*c*=2.64, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.22–5.13 (m, 1H, CH–O), 2.50–2.40 (m, 2H, $COCH_2$), 2.01 (s, 3H, $COCH_3$), 1.63–1.50 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.33–1.20 (m, 24H, $(CH_2)_{12}CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.6, 80.9, 71.0, 40.7, 34.2, 32.0, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2958, 2925, 2853, 1743, 1466, 1368, 1239, 1157, 1025, 952, 847 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{23}H_{44}O_4Na$ $[M+Na]^+$ 407.3137, found 407.3141.

*4.2.1.11. (R) t-Butyl 3-acetoxy-octadecanoate (****6****, m=12).* Yield 63%. $[\alpha]_{20}^{D}$=+2.2 (*c*=2.57, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$):

δ=5.22–5.13 (m, 1H, CH–O), 2.50–2.41 (m, 2H, $COCH_2$), 2.01 (s, 3H, $COCH_3$), 1.63–1.50 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.33–1.18 (m, 26H, $(CH_2)_{13}CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.9, 71.0, 40.7, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2958, 2925, 2853, 1743, 1465, 1368, 1239, 1157, 1025, 951, 847 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{24}H_{46}O_4Na$ $[M+Na]^+$ 421.3294, found 421.3291.

*4.2.1.12. (R) t-Butyl 3-acetoxy-nonadecanoate (**6**, m=13).* Yield 76%. $[\alpha]_{20}^{D}$=+2.0 (*c*=2.05, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.23–5.13 (m, 1H, CH–O), 2.53–2.38 (m, 2H, $COCH_2$), 2.02 (s, 3H, $COCH_3$), 1.64–1.49 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.35–1.18 (m, 28H, $(CH_2)_{14}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.5, 169.9, 80.9, 71.0, 40.7, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.3, 22.8, 21.3, 14.3 ppm. IR (film): ν_{max}=2957, 2923, 2853, 1743, 1467, 1368, 1239, 1158, 1025, 953, 847 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{25}H_{48}O_4Na$ $[M+Na]^+$ 435.3450, found 435.3445.

*4.2.1.13. (R) t-Butyl 3-acetoxy-icosanoate (**6**, m=14).* Yield 62%. $[\alpha]_{20}^{D}$=+1.2 (*c*=2.22, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.23–5.11 (m, 1H, CH–O), 2.53–2.38 (m, 2H, $COCH_2$), 2.02 (s, 3H, $COCH_3$), 1.65–1.49 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.37–1.17 (m, 30H, $(CH_2)_{15}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.5, 169.9, 80.9, 70.9, 40.7, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2957, 2924, 2853, 1744, 1464, 1368, 1239, 1158, 1026, 952, 845 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{26}H_{50}O_4Na$ $[M+Na]^+$ 449.3607, found 449.3612.

*4.2.1.14. (R) t-Butyl 3-acetoxy-eicosanoate (**6**, m=15).* Yield 68%. $[\alpha]_{20}^{D}$=+1.6 (*c*=2.14, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.11 (m, 1H, CH–O), 2.53–2.38 (m, 2H, $COCH_2$), 2.01 (s, 3H, $COCH_3$), 1.64–1.49 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.36–1.17 (m, 32H, $(CH_2)_{16}CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.9, 71.0, 40.7, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=2955, 2924, 2853, 1744, 1466, 1368, 1239, 1157, 1025, 952, 847 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{27}H_{52}O_4Na$ $[M+Na]^+$ 463.3763, found 463.3755.

*4.2.1.15. (R) t-Butyl 3-acetoxy-docosanoate (**6**, m=16).* Yield 64%. $[\alpha]_{20}^{D}$=+2.7 (*c*=2.0, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.25–5.11 (m, 1H, CH–O), 2.54–2.38 (m, 2H, $COCH_2$), 2.02 (s, 3H, $COCH_3$), 1.64–1.49 (m, 2H, CH–CH_2), 1.43 (s, 9H, *t*-Bu), 1.36–1.17 (m, 34H, $(CH_2)_{17}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.5, 169.9, 80.9, 71.0, 40.8, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 28.2, 25.3, 22.8, 21.3, 14.3 ppm. IR (film): ν_{max}=2954, 2922, 2852, 1740, 1467, 1368, 1240, 1158, 1026, 952, 849 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{28}H_{54}O_4Na$ $[M+Na]^+$ 477.3920, found 477.3930.

*4.2.1.16. (R) t-Butyl 3-acetoxy-tricosanoate (**6**, m=17).* Yield 68%. $[\alpha]_{20}^{D}$=+1.1 (*c*=3.80, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.24–5.11 (m, 1H, CH–O), 2.53–2.38 (m, 2H, $COCH_2$), 2.02 (s, 3H, $COCH_3$), 1.64–1.49 (m, 2H, CH–CH_2), 1.42 (s, 9H, *t*-Bu), 1.37–1.17 (m, 36H, $(CH_2)_{18}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=170.4, 169.8, 80.9, 71.0, 40.7, 34.2, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.1, 25.3, 22.8, 21.2, 14.3 ppm. IR (film): ν_{max}=2952, 2921, 2851, 1736, 1467, 1368, 1240, 1158, 1027, 954, 849 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{29}H_{56}O_4Na$ $[M+Na]^+$ 491.4076, found 491.4081.

*4.2.2. General deprotection procedure, access to compounds **7** (m=2 to m=17).* Trifluoroacetic acid (1 mL) (20% in CH_2Cl_2) was added to a solution of **6** (*m*=2 to *m*=17) (0.1 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature for 45 min before it was quenched with H_2O (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were collected, washed with brine and dried over $MgSO_4$. The solvent was concentrated under reduced pressure and filtered through a short column of SiO_2 (EtOAc/Petroleum ether, 1:4) to afford the corresponding acid **7** (*m*=2 to *m*=17) (84–95% yield).

*4.2.2.1. (R) 3-Acetoxy-octanoic acid (**7**, m=2).* Yield 84%. $[\alpha]_{20}^{D}$=+1.8 (*c*=0.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=9.72 (br s, COOH), 5.26–5.09 (m, 1H, CH–O), 2.68–2.51 (m, 2H, $COCH_2$), 2.03 (s, 3H, $COCH_3$), 1.71–1.50 (m, 2H, CH–CH_2), 1.40–1.19 (m, 6H, $(CH_2)_3CH_3$), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.7, 171.1, 70.6, 39.0, 34.0, 31.6, 24.9, 22.6, 21.2, 14.0 ppm. IR (film): ν_{max}=3305, 3021, 2933, 2862, 1743, 1456, 1369, 1240, 1159, 1026, 757 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{10}H_{18}O_4Na$ $[M+Na]^+$ 225.1103, found 225.1107.

*4.2.2.2. (R) 3-Acetoxy-nonanoic acid (**7**, m=3).* Yield 86%. $[\alpha]_{20}^{D}$=−3.1 (*c*=0.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.71 (br s, COOH), 5.27–5.13 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.53 (m, 2H, CH–CH_2), 1.40–1.18 (m, 8H, $(CH_2)_4CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.1, 170.7, 70.5, 39.0, 34.1, 31.8, 29.1, 25.2, 22.7, 21.2, 14.2 ppm. IR (film): ν_{max}=3315, 3015, 2929, 2859, 1743, 1715, 1434, 1376, 1240, 1029, 758 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1259, found 239.1253.

*4.2.2.3. (R) 3-Acetoxy-decanoic acid (**7**, m=4).* Yield 89%. $[\alpha]_{20}^{D}$=−2.8 (*c*=0.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.45 (br s, COOH), 5.27–5.13 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.71–1.53 (m, 2H, CH–CH_2), 1.40–1.18 (m, 10H, $(CH_2)_5CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.1, 170.7, 70.5, 38.9, 34.1, 31.9, 29.4, 29.3, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3320, 3022, 2928, 2857, 1738, 1717, 1434, 1376, 1245, 1029, 757 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1416, found 253.1421.

*4.2.2.4. (R) 3-Acetoxy-undecanoic acid (**7**, m=5).* Yield 91%. $[\alpha]_{20}^{D}$=−2.2 (*c*=1.0, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.82 (br s, COOH), 5.27–5.13 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.70–1.52 (m, 2H, CH–CH_2), 1.41–1.17 (m, 12H, $(CH_2)_6CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.2, 170.7, 70.5, 39.0, 34.1, 32.0, 29.5, 29.5, 29.3, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3331, 3012, 2926, 2856, 1743, 1716, 1433, 1377, 1239, 1029, 770 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 267.1572, found 267.1568.

*4.2.2.5. (R) 3-Acetoxy-dodecanoic acid (**7**, m=6).* Yield 90%. $[\alpha]_{20}^{D}$=−1.8 (*c*=1.15, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.26 (br s, COOH), 5.26–5.11 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.53 (m, 2H, CH–CH_2), 1.40–1.17 (m, 14H, $(CH_2)_7CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.0, 170.7, 70.5, 38.9, 34.1, 32.0, 29.6, 29.6, 29.5, 29.4, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3392, 3028, 2926, 2855, 1741, 1717, 1434, 1376, 1240, 1028, 757 cm^{-1}. HRMS (ESI+) *m*/*z* calcd for $C_{14}H_{26}O_4Na$ $[M+Na]^+$ 281.1729, found 281.1733.

*4.2.2.6. (R) 3-Acetoxy-tridecanoic acid (**7**, m=7).* Yield 93%. $[\alpha]_{20}^{D}$=−2.5 (*c*=0.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.15 (br s, COOH), 5.26–5.12 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.71–1.52 (m, 2H, CH–CH_2), 1.40–1.18 (m, 16H, $(CH_2)_8CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.2, 170.7, 70.5, 39.0, 34.1, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 25.2,

22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3315, 3023, 2926, 2854, 1736, 1718, 1466, 1376, 1241, 1028, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{15}H_{28}O_4Na$ $[M+Na]^+$ 295.1885, found 295.1879.

*4.2.2.7. (R) 3-Acetoxy-tetradecanoic acid (**7**, m=8).* Yield 94%. $[\alpha]_{20}^{D}$=−2.2 (*c*=1.1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.25 (br s, COOH), 5.27–5.12 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.71–1.52 (m, 2H, $CH–CH_2$), 1.40–1.17 (m, 18H, $(CH_2)_9CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.0, 170.7, 70.5, 39.0, 34.1, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3379, 3015, 2925, 2854, 1739, 1716, 1466, 1375, 1241, 1028, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{16}H_{30}O_4Na$ $[M+Na]^+$ 309.2042, found 309.2033.

*4.2.2.8. (R) 3-Acetoxy-pentadecanoic acid (**7**, m=9).* Yield 95%. $[\alpha]_{20}^{D}$=−2.5 (*c*=1.4, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.31 (br s, COOH), 5.27–5.12 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.52 (m, 2H, $CH–CH_2$), 1.41–1.15 (m, 20H, $(CH_2)_{10}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.3, 170.8, 70.5, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3330, 3028, 2916, 2849, 1734, 1715, 1463, 1376, 1240, 1037, 759 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{17}H_{32}O_4Na$ $[M+Na]^+$ 323.2198, found 323.2203.

*4.2.2.9. (R) 3-Acetoxy-hexadecanoic acid (**7**, m=10).* Yield 94%. $[\alpha]_{20}^{D}$=−2.1 (*c*=1.3, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.16 (br s, COOH), 5.27–5.13 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.71–1.53 (m, 2H, $CH–CH_2$), 1.41–1.16 (m, 22H, $(CH_2)_{11}CH_3$), 0.88 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.3, 170.8, 70.5, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3293, 3023, 2925, 2854, 1736, 1716, 1466, 1376, 1242, 1028, 759 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{18}H_{34}O_4Na$ $[M+Na]^+$ 337.2355, found 337.2352.

*4.2.2.10. (R) 3-Acetoxy-heptadecanoic acid (**7**, m=11).* Yield 92%. $[\alpha]_{20}^{D}$=−1.7 (*c*=1.15, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=6.60 (br s, COOH), 5.27–5.13 (m, 1H, CH–O), 2.71–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.73–1.53 (m, 2H, $CH–CH_2$), 1.40–1.16 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.1, 170.9, 70.6, 38.9, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3300, 3021, 2926, 2854, 1736, 1715, 1466, 1376, 1246, 1028, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{19}H_{36}O_4Na$ $[M+Na]^+$ 351.2511, found 351.2503.

*4.2.2.11. **(R)** 3-Acetoxy-octadecanoic acid (**7**, m=12).* Yield 89%. $[\alpha]_{20}^{D}$=−0.7 (*c*=0.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.28–5.112 (m, 1H, CH–O), 2.70–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.53 (m, 2H, $CH–CH_2$), 1.40–1.16 (m, 26H, $(CH_2)_{13}CH_3$), 0.88 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.8, 170.7, 70.5, 38.9, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.3 ppm. IR (film): ν_{max}=3385, 3021, 2925, 2854, 1736, 1716, 1466, 1376, 1246, 1028, 757 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{20}H_{38}O_4Na$ $[M+Na]^+$ 365.2668, found 365.2663.

*4.2.2.12. (R) 3-Acetoxy-nonadecanoic acid (**7**, m=13).* Yield 91%. $[\alpha]_{20}^{D}$=−2.4 (*c*=0.8, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.95 (br s, COOH), 5.28–5.12 (m, 1H, CH–O), 2.69–2.49 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.71–1.53 (m, 2H, $CH–CH_2$), 1.38–1.16 (m, 28H, $(CH_2)_{14}CH_3$), 0.88 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.4, 170.9, 70.5, 38.9, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.3 ppm. IR (film): ν_{max}=3386, 3021, 2924, 2853, 1732, 1715, 1462, 1377, 1216, 1033, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{21}H_{40}O_4Na$ $[M+Na]^+$ 379.2824, found 379.2826.

*4.2.2.13. (R) 3-Acetoxy-icosanoic acid (**7**, m=14).* Yield 85%. $[\alpha]_{20}^{D}$=−2.3 (*c*=1.45, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=5.25–5.11 (m, 1H, CH–O), 2.69–2.51 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.73–1.51 (m, 2H, $CH–CH_2$), 1.37–1.16 (m, 30H, $(CH_2)_{15}CH_3$), 0.88 (t, 3H, CH_3) ppm. 13C NMR (62.9 MHz, $CDCl_3$): δ=176.4, 171.0, 70.6, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.3 ppm. IR (film): ν_{max}=3379, 3021, 2926, 2854, 1742, 1716, 1466, 1376, 1215, 1028, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{22}H_{42}O_4Na$ $[M+Na]^+$ 393.2981, found 393.2986.

*4.2.2.14. (R) 3-Acetoxy-eicosanoic acid (**7**, m=15).* Yield 89%. $[\alpha]_{20}^{D}$=−1.3 (*c*=2.5, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=9.20 (br s, COOH), 5.28–5.13 (m, 1H, CH–O), 2.72–2.53 (m, 2H, $COCH_2$), 2.05 (s, 3H, $COCH_3$), 1.72–1.52 (m, 2H, $CH–CH_2$), 1.41–1.15 (m, 32H, $(CH_2)_{16}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.6, 171.1, 70.6, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.2, 22.8, 21.2, 14.3 ppm. IR (film): ν_{max}=3385, 3019, 2926, 2854, 1737, 1714, 1467, 1375, 1215, 1022, 757 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{23}H_{44}O_4Na$ $[M+Na]^+$ 407.3137, found 407.3134.

*4.2.2.15. (R) 3-Acetoxy-docosanoic acid (**7**, m=16).* Yield 89%. $[\alpha]_{20}^{D}$=−0.9 (*c*=2.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=9.10 (br s, COOH), 5.29–5.12 (m, 1H, CH–O), 2.68–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.52 (m, 2H, $CH–CH_2$), 1.41–1.18 (m, 34H, $(CH_2)_{17}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.5, 170.8, 70.5, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.2, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3358, 3021, 2925, 2854, 1736, 1716, 1465, 1376, 1215, 1028, 758 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{24}H_{46}O_4Na$ $[M+Na]^+$ 421.3294, found 421.3297.

*4.2.2.16. (R) 3-Acetoxy-tricosanoic acid (**7**, m=17).* Yield 85%. $[\alpha]_{20}^{D}$=−1.7 (*c*=1.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.60 (br s, COOH), 5.27–5.12 (m, 1H, CH–O), 2.69–2.52 (m, 2H, $COCH_2$), 2.04 (s, 3H, $COCH_3$), 1.72–1.53 (m, 2H, $CH–CH_2$), 1.41–1.15 (m, 34H, $(CH_2)_{17}CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.3, 170.8, 70.5, 39.0, 34.1, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 25.3, 22.8, 21.2, 14.2 ppm. IR (film): ν_{max}=3358, 3020, 2926, 2854, 1740, 1716, 1464, 1376, 1215, 1030, 757 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{25}H_{48}O_4Na$ $[M+Na]^+$ 435.3450, found 435.3454.

*4.2.3. Transformation of alcohol **1** (**R**) to **3** (**S**) with a Mitsunobu reaction.* To a solution of alcohol **1** (**R**) (1.21 g, 7.03 mmol) in toluene (60 mL) were added PPh_3 (2.75 g, 10.5 mmol, 1.5 equiv) and acetic acid (1.2 mL, 1.26 g, 21 mmol, 3 equiv) at room temp. After 10 min, the reaction mixture was cooled to—30 °C and diethyl azodicarboxylate (1.66 mL, 1.83 g, 10.5 mmol, 1.5 equiv) was added dropwise over a period of 10 min. The reaction mixture was slowly warmed to room temp and stirred for 45 min. It was then filtered and the solvent removed under reduced pressure. The mixture was diluted with saturated $NaHCO_3$ and hexane with vigorous stirring. The layers were separated and the aqueous layer extracted twice with hexane. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue which was purified by silica gel column chromatography (EtOAc/Petroleum ether 1:9) to afford **3** (**S**) (1.02 g, 4.77 mmol, 68%).

3 (**S**): $[\alpha]_{20}^{D}$=−5.8 (*c*=1.2, $CHCl_3$).

*4.2.3.1. (S) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)pent-4-enoate **8** (m=2).* To a solution of alcohol **1** (**R**) (313 mg, 1.82 mmol) in

toluene (12 mL) were added PPh_3 (908 mg, 3.47 mmol, 1.9 equiv) and acid **7** (m=2) (460 mg, 2.28 mmol, 1.25 equiv). The reaction mixture was stirred at room temperature. After 15 min, the mixture was cooled down to—30 °C and diethyl azodicarboxylate (0.57 mL, 604 mg, 3.47 mmol, 1.9 equiv) was added dropwise over a period of 20 min. After complete addition, the reaction mixture was slowly warmed to room temp and stirred for 2 h. The reaction mixture was monitored by TLC. The mixture was filtered and washed with Et_2O. The solvent was concentrated under reduced pressure, to give a residue which was purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:9) to afford **8** (m=2) (375 mg, 1.05 mmol, 58%).

Yield 58%. $[\alpha]_{20}^{D}$=−0.5 (c=1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.87–5.70 (m, 2H, 2CH=CHaHb), 5.64–5.56 (m, 2H, 2CH–OCO), 5.33–5.13 (m, 4H, 2CH=CH_2), 2.65–2.45 (m, 4H, 2$COCH_2$), 2.01 (s, 3H, $OCOCH_3$), 1.75–1.50 (m, 2H, CH–CH_2), 1.43 (s, 9H, *t*-Bu), 1.36–1.20 (m, 6H, $(CH_2)_3CH_3$), 0.87 (t, 3H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=170.4, 169.3, 168.9, 135.1, 117.8, 81.2, 71.5, 70.6, 40.7, 39.3, 34.0, 28.1, 24.9, 22.6, 21.2, 14.1 ppm. IR (film): ν_{max}=3020, 2983, 2926, 2854, 1719, 1597, 1467, 1370, 1292, 1216, 1155, 1107, 1024, 935, 837, 755 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{19}H_{32}O_6Na$ $[M+Na]^+$ 379.2097, found 379.2088.

4.2.4. General procedure for the cross-metathesis and hydrogenation, access to ***9a–e*** *(n=2 to n=6).* To a solution of **8** (m=2) (0.2 mmol) in anhydrous ethyl ether (5 mL) were added Grubbs2 catalyst (10.2 mg, 12 μmol, 6 mol %), CuI (3.4 mg, 18 μmol, 9% eq) and alkene (1.2 mmol, 6 equiv) under an Ar atmosphere. The mixture was heated to 40 °C for 2 h until the color of the reaction mixture turned from brown to dark green, corresponding to disappearance of starting material by TLC. After cooling to room temperature, the mixture was filtered through a short column of sand and $MgSO_4$. The solid was washed with ethyl ether and the solvent was evaporated under reduced pressure. The obtained residue was used for the next step without further purification. To a solution of residue in dry EtOAc (5 mL) at room temperature, a catalytic amount of PtO_2 was added. The flask was purged and filled with H_2 gas. The mixture was stirred vigorously at room temperature for 2 h. The reaction was filtered through a Celite pad and washed with EtOAc. The solvent was removed and the crude product was purified by silica gel column chromatography (EtOAc/Petroleum ether as eluent, 1:19) to afford the corresponding adduct **9a–e** (n=2 to n=6) (48–60% yield for two steps).

4.2.4.1. (R) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)octanoate ***9a*** *(n=2).* Yield 60%. $[\alpha]_{20}^{D}$=−1.2 (c=1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.22–5.17 (m, 2H, 2 CH–O), 2.59–2.41 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.65–1.51 (m, 4H, 2 CH_2), 1.43 (s, 9H, *t*-Bu), 1.35–1.20 (m, 12H, 6 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.5, 169.8, 169.7, 81.0, 71.3, 70.7, 40.6, 39.3, 34.2, 34.0, 31.7, 31.7, 28.2, 25.2, 24.9, 22.8, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=3020, 2928, 2856, 1738, 1463, 1369, 1242, 1159, 1026, 757 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{22}H_{40}O_6Na$ $[M+Na]^+$ 423.2723, found 423.2729.

4.2.4.2. (R) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)nonanoate ***9b*** *(n=3).* Yield 53%. $[\alpha]_{20}^{D}$=+2.2 (c=1.75, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=5.22–5.15 (m, 2H, 2 CH–O), 2.59–2.40 (m, 4H, α-CH_2, α′-CH_2), 2.01 (s, 3H, $COCH_3$), 1.63–1.51 (m, 4H, 2 CH_2), 1.42 (s, 9H, *t*-Bu), 1.35–1.20 (m, 14H, 7 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.4, 169.8, 169.7, 80.9, 71.3, 70.6, 40.6, 39.3, 34.1, 33.9, 31.8, 31.7, 29.2, 28.1, 25.2, 24.9, 22.7, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=3023, 2961, 2861, 1736, 1461, 1369, 1244, 1161, 1027, 972, 758 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{23}H_{42}O_6Na$ $[M+Na]^+$ 437.2879, found 437.2873.

4.2.4.3. (R) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)decanoate ***9c*** *(n=4).* Yield 48%. $[\alpha]_{20}^{D}$=+2.9 (c=1.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.22–5.17 (m, 2H, 2 CH–O), 2.59–2.40 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.63–1.52 (m, 4H, 2 CH_2), 1.43 (s, 9H, *t*-Bu), 1.34–1.22 (m, 16H, 8 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.5, 169.8, 169.7, 81.0, 71.3, 70.7, 40.6, 39.4, 34.1, 34.0, 31.9, 31.7, 29.5, 29.3, 28.2, 25.2, 24.9, 22.8, 22.6, 21.3, 14.2, 14.1 ppm IR (film): ν_{max}=3022, 2928, 2857, 1736, 1458, 1368, 1243, 1157, 1026, 757 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{24}H_{44}O_6Na$ $[M+Na]^+$ 451.3036, found 451.3028.

4.2.4.4. (R) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)undecanoate ***9d*** *(n=5).* Yield 54%. $[\alpha]_{20}^{D}$=+2.6 (c=2.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=5.21–5.16 (m, 2H, 2 CH–O), 2.59–2.40 (m, 4H, α-CH_2, α′-CH_2), 2.01 (s, 3H, $COCH_3$), 1.62–1.52 (m, 4H, 2 CH_2), 1.42 (s, 9H, *t*-Bu), 1.34–1.20 (m, 18H, 9 CH_2), 0.86 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=170.4, 169.8, 169.7, 80.9, 71.2, 70.6, 40.6, 39.3, 34.1, 34.0, 32.0, 31.7, 29.6, 29.5, 29.3, 28.1, 25.2, 24.9, 22.8, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=3022, 2928, 2856, 1735, 1458, 1369, 1246, 1216, 1156, 1027, 955, 757 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{25}H_{46}O_6Na$ $[M+Na]^+$ 465.3192, found 465.3199.

4.2.4.5. (R) t-Butyl 3-(((R)-3-acetoxy-octanoyl)oxy)dodecanoate ***9e*** *(n=6).* Yield 54%. $[\alpha]_{20}^{D}$=+3.2 (c=1.5, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.24–5.14 (m, 2H, 2 CH–O), 2.62–2.37 (m, 4H, α-CH_2, α′-CH_2), 2.01 (s, 3H, $COCH_3$), 1.67–1.50 (m, 4H, 2 CH_2), 1.42 (s, 9H, *t*-Bu), 1.36–1.19 (m, 20H, 10 CH_2), 0.86 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=170.4, 169.8, 169.7, 81.0, 71.3, 70.6, 40.6, 39.3, 34.1, 34.0, 32.0, 31.7, 29.6, 29.6, 29.5, 29.4, 28.1, 25.2, 24.9, 22.8, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=3025, 2929, 2859, 1736, 1459, 1368, 1242, 1161, 1027, 972, 757 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{26}H_{48}O_6Na$ $[M+Na]^+$ 479.3349, found 479.3340.

4.2.5. General procedure for the final deprotection, same as access to compounds ***7***

4.2.5.1. (R) 3-(((R)-3-Acetoxy-octanoyl)oxy)octanoic acid ***10a*** *(n=2).* Yield 76%. $[\alpha]_{20}^{D}$=−1.0 (c=0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=5.24–5.16 (m, 2H, 2 CH–O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.52 (m, 4H, 2 CH_2), 1.38–1.19 (m, 12H, 6 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=175.6, 170.6, 169.9, 70.8, 70.7, 39.4, 38.4, 34.0, 33.9, 31.7, 31.6, 24.9, 22.6, 21.2, 14.1 ppm. IR (film): ν_{max}=2958, 2927, 2856, 1745, 1715, 1433, 1376, 1238, 1172, 1124, 1026, 805 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{18}H_{32}O_6Na$ $[M+Na]^+$ 367.2097, found 367.2079.

4.2.5.2. (R) 3-(((R)-3-Acetoxy-octanoyl)oxy)nonanoic acid ***10b*** *(n=3).* Yield 86%. $[\alpha]_{20}^{D}$=+1.1 (c=0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.75 (br s, 1H, OH), 5.26–5.15 (m, 2H, 2 CH–O), 2.66–2.49 (m, 4H, α-CH2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.69–1.50 (m, 4H, 2 CH_2), 1.38–1.18 (m, 14H, 7 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=175.3, 170.6, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 31.8, 31.7, 29.1, 25.2, 24.9, 22.7, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=2965, 2928, 2859, 1745, 1714, 1435, 1378, 1240, 1172, 1121, 1027, 806, 725 cm^{-1}. HRMS (ESI+) m/z calcd for $C_{19}H_{34}O_6Na$ $[M+Na]^+$ 381.2253, found 381.2249.

4.2.5.3. (R) 3-(((R)-3-Acetoxy-octanoyl)oxy)decanoic acid ***10c*** *(n=4).* Yield 70%. $[\alpha]_{20}^{D}$=−1.4 (c=0.85, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.38 (br s, 1H, OH), 5.25–5.15 (m, 2H, 2 CH–O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.50 (m, 4H, 2 CH_2), 1.38–1.20 (m, 16H, 8 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=175.9, 170.8, 170.0, 70.9, 70.8, 39.4, 38.8, 34.0, 31.9, 31.7, 29.4, 29.3, 25.2, 24.9, 22.7, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=2963, 2928, 2858, 1744, 1712, 1434, 1377, 1240, 1171,

1123, 1027, 953, 725 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{20}H_{36}O_6Na$ $[M+Na]^+$ 395.2410, found 395.2404.

4.2.5.4. (R) 3-(((R)-3-Acetoxy-octanoyl)oxy)undecanoic acid ***10d*** *(n=5).* Yield 73%. $[\alpha]_{20}^{D}$=+2.2 (*c*=1.25, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ=8.0 (br s, 1H, OH), 5.25–5.16 (m, 2H, 2 CH–O), 2.66–2.50 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.51 (m, 4H, 2 CH_2), 1.38–1.19 (m, 18H, 9 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=175.9, 170.7, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 31.9, 31.7, 29.6, 29.5, 29.3, 25.2, 24.8, 22.8, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=2961, 2926, 2856, 1743, 1710, 1457, 1377, 1240, 1172, 1123, 1027, 801 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{21}H_{38}O_6Na$ $[M+Na]^+$ 409.2566, found 409.2570.

4.2.5.5. (R) 3-(((R)-3-Acetoxy-octanoyl)oxy)dodecanoic acid ***10e*** *(n=6).* Yield 88%. $[\alpha]_{20}^{D}$=−1.6 (*c*=0.65, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ=5.25–5.16 (m, 2H, 2 CH–O), 2.66–2.49 (m, 4H, α-CH_2, α′-CH_2), 2.02 (s, 3H, $COCH_3$), 1.68–1.50 (m, 4H, 2 CH_2), 1.38–1.19 (m, 20H, 10 CH_2), 0.87 (t, 6H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ=175.4, 170.6, 169.9, 70.9, 70.7, 39.4, 38.8, 34.0, 32.0, 31.7, 29.7, 29.6, 29.5, 29.4, 25.2, 24.9, 22.8, 22.6, 21.2, 14.2, 14.1 ppm. IR (film): ν_{max}=2960, 2925, 2855, 1742, 1709, 1457, 1375, 1239, 1171, 1123, 1026, 799 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{22}H_{40}O_6Na$ $[M+Na]^+$ 423.2712, found 423.2723.

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Supplementary data

Supplementary data (Copies of the ^1H and ^{13}C NMR spectra, FTIR and HRMS spectra for all new compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.09.065.

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