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Synthesis and Olfactory Properties of Regioisomeric Alkynolides and (*Z*)-Alkenolides

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Abstract

A general approach to the title compounds (*Z*)-**9a-d** via **8a-d** from easily available starting materials is presented. The olfactory properties of these macrolides are discussed. A new synthesis of the precursor **7e** of (*Z*)-ambrettolide (**1**) is also described.

Keywords: ω-Hydroxy alkyne carboxylic acids; Cyclization; Macrolides; Odour and structure.

Introduction

There is a need for the development of new nature-like, biodegradable non-toxic odorants with the aim to substitute problematic compounds [1] and to stimulate new creations in perfumery [2]. In previous work [3] we have shown that the olfactory properties especially the musk notes of isomeric macrolides strongly depend on their constitution and on the absolute configuration of the corresponding stereogenic centers. In this context we were interested in the relationship between odour and structure of regioisomeric (*Z*)-alkenolides, because the naturally occurring expensive macrolide (*Z*)-ambrettolide (**1**) possesses a very attractive musk note [4]. Here we describe a general approach to regioisomeric (*Z*)-alkenolides [(*Z*)-**9a-d**] with a sixteen-membered ring via the corresponding alkyne derivatives **8a-d**. A comparison of these eight odorants is also presented.

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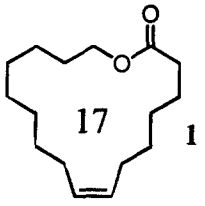
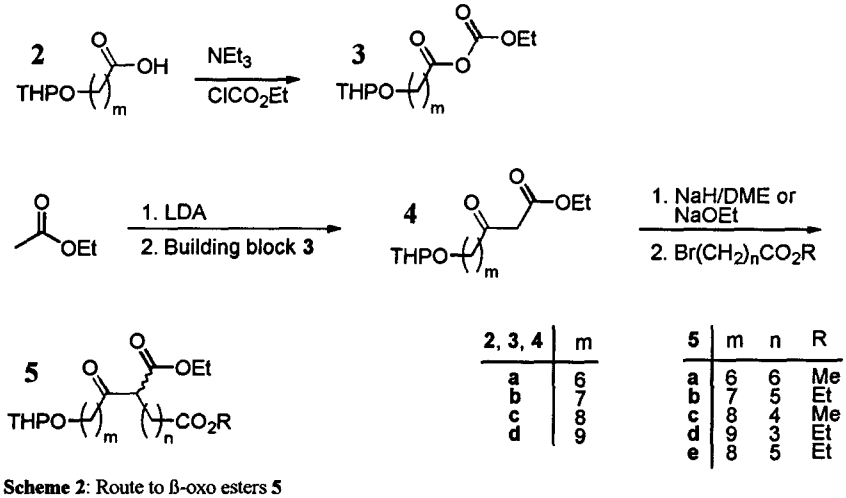


Scheme 1: (*Z*)-ambrettolide (**1**)

Results

Our synthesis started from tetrahydropyranyl protected ω-hydroxycarboxylic acids **2*** which were prepared from commercially available or known compounds via standard procedures (see Experimental) as are Grignard reaction, alkylation of diethyl malonate or ozonolysis and subsequent protection. For our project we needed a mild method for the introduction of a carbon carbon triple bond without isomerisation problems. The procedure of Boivin, Elkaim, Ferro and Zard [5] who synthesized alkynes from ß-oxo esters via nitrosation of isoxazolone derivatives proved to suitable in our case. The sequence described in scheme 2 and scheme 3 allows the possibility to introduce the multiple bond in various positions of the target molecules **8** and (*Z*)-**9**.



2, 3, 4	m
a	6
b	7
c	8
d	9

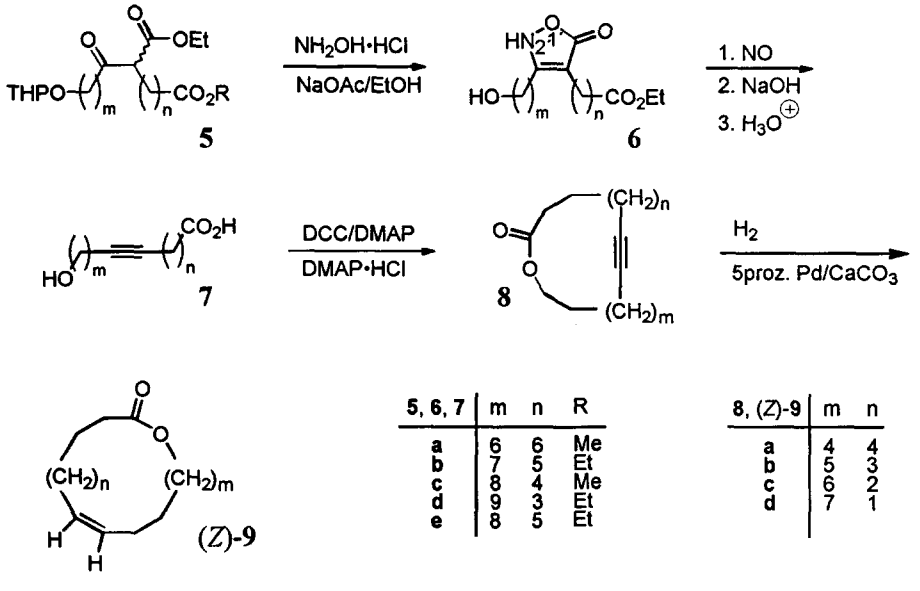
5	m	n	R
a	6	6	Me
b	7	5	Et
c	8	4	Me
d	9	3	Et
e	8	5	Et

Scheme 2: Route to ß-oxo esters **5**

The desired α-branched ß-oxo esters **5** were obtained in three steps from **2** by published procedures. At first the carboxylic groups of **2a-d** were activated as mixed anhydrides **3** [6] which were converted to the ß-oxo esters **4a-d** with the lithium enolate [7] of ethyl acetate. Treatment of the deprotonated compounds **4a-d** with ω-bromo esters led to the α-alkylated ß-oxo esters **5a-e** [8]. **5a-e** were transformed to the heterocyclic precursors **6** of the functionalized alkynes **7** with

*Chiral compounds are racemic or mixtures of diastereomers in the case of **5**.

hydroxylamine hydrochloride in the presence of sodium acetate [9]. According to the NMR spectra the isoxazolones **6** contain a small amount of the CH tautomer. The decomposition of the heterocyclic ring was achieved following the protocol of Boivin, Zard and co-worker [5]. The N-nitroso derivatives of **6** undergo a ring opening fragmentation reaction with elimination of dinitrogen monoxide and carbon dioxide to yield directly after work up the deprotected ω-hydroxy alkyne carboxylic acids **7a-e**. The cyclization of **7a-d** to the sixteen-membered rings **8** were achieved in 60-70 % yield with 4-(dimethylamino)pyridine (DMAP), 4-(dimethylamino)pyridine hydrochloride (DMAP·HCl) and dicyclohexylcarbodiimide (DCC) in chloroform [10]. Finally the (*Z*)-selective hydrogenation of **8** to (*Z*)-**9** with palladium on calcium carbonate in the presence of quinoline occurred with high stereoselectivity. The amount of (*E*)-isomer was in the range between 0.9-2.4% (see Experimental) according to GC analysis. The target compounds were characterized by their ^{1}H and ^{13}C NMR spectra, elemental analyses or high resolution mass spectra. In summary the above described sequence leads to (*Z*)-configurated alkenolides [11] in high purity from easily available starting materials.



5, 6, 7	m	n	R
a	6	6	Me
b	7	5	Et
c	8	4	Me
d	9	3	Et
e	8	5	Et

8, (Z)-9	m	n
a	4	4
b	5	3
c	6	2
d	7	1

Scheme 3: Synthesis of macrolides **8** and (*Z*)-**9**

In order to demonstrate that our procedure is not limited to sixteen-membered rings we finally prepared the hydroxy alkyne carboxylic acid **7e** in a similar way (see Experimental). **7e** is the intermediate of the (*Z*)-ambrettolide synthesis of Voss and Gerlach [12]. Therefore the conversion of **2c** to **7e** represents a new approach to **1** [13].

Table 1
Olfactory properties of musk macrolides

Compound	Position of the multiple bond	Olfactory properties of **8** and (*Z*)-**9***
8a	8	relative weak musk, somewhat camphoraceous, woody, fruity
8b	7	slightly musky, woody, fruity, earthy
8c	6	slightly musky, fruity, earthy
8d	5	slightly musky, fruity, fresh, earthy
(*Z*)-**9a**	8	strong musk, somewhat fruity, woody, and fresh
(*Z*)-**9b**	7	strong musk, clear woody, somewhat fresh, sweet
(*Z*)-**9c**	6	strong musk, erogenous, slightly sweet, less fresh
(*Z*)-**9d**	5	strong musk, somewhat fresh, slightly animalic-fatty

Discussion

Table 1 shows that all isomeric (*Z*)-macrolides (*Z*)-**9** have strong musk notes with different tonalities. (*Z*)-**9b** with its woody note is especially conspicuous. The characteristics of (*Z*)-**9a** are similar to the macrolides (*Z*)-**9c** and (*Z*)-**9d** which provide the natural animalic-fatty musk. The alkynolides **8** only have the characteristic fruity-earthy note in common. Their musk notes are only weak and less pleasant than those of the macrolides (*Z*)-**9a-d**. Therefore they are not interesting as fragrances. In all cases the unsaturated macrolides (*Z*)-**9** are superior to alkynolides **8** with regard to their olfactory properties.

Conclusion

In summary we presented a versatile reaction sequence to the title compounds that allows to introduce multiple bonds regioselectively into different positions of the macrocyclic ring.** Our procedure has also the advantage to give the interesting (*Z*)-isomers [14] with high stereoselectivity.

*Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.
**A german patent was applied for part of this work.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1600 FTIR spectrometer. Raman spectra were scanned on a Bruker IFS 66/CS FT spectrometer (FRA 106) with 350 mW Nd/YAG laser excitation. UV spectra were measured with a Zeiss DMR 10 spectrometer. $^1H/^{13}C$ NMR spectra (reference: TMS int) were taken in $CDCl_3$ on Bruker AC 200 P, Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. The assignment of data marked with * or ** may be exchanged. EI (70 eV) and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Column chromatography was performed on Baker Silicagel 30-60 µm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates. Ozonization was performed with Sander 301 (0.45 A, 30 l/h O_2). Sonications (degasified solutions) were carried out in a Bandelin Sonorex TK 52 bath. Gas chromatography (GC) was performed on a Varian 3400 CX gas chromatograph equipped with a capillary column, MN Permabond® SE 50, using nitrogen as carrier gas. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach. Reactions with organometallic compounds and hydrides were performed under nitrogen.

Synthesis of Protected ω-Hydroxy Acids **2a-d**

Procedure: To a suspension of magnesium turnings (948 mg, 39.0 mmol) in dry THF (50 ml) was added a single crystal of iodine. To this mixture was added approximately 10% of 1-bromo-6-(tetrahydro-2′H-pyran-2′-yl-oxy)hexane [15] (10.26 g, 38.68 mmol). After initiation of the reaction, as signified by the disappearance of the iodine colour, the mixture was stirred and the remaining bromide was added dropwise by a syringe while the reaction temp. was maintained at 45 °C. After 1 h at 40 °C, the solution was cooled to -70 °C and then dry ice (3 g) was added. The suspension was stirred 1 h, then warmed to room temp. and poured into 2 N NaOH. The by-products were separated by one extraction with ether. The ice-cooled aqueous layer was acidified with 2 N HCl and then extracted four times with ether. The combined organic extracts were dried (Na_2SO_4), and evaporated under reduced pressure, providing 8.02 g (90%) of **2a** as a colourless liquid, which was used directly in the next reaction.

7-(Tetrahydro-2′H-pyran-2′-yl-oxy)-1-heptanoic acid (**2a**). IR (film, cm^{-1}) $\tilde{\nu}$ 3650 - 2380 (OH), 1709 (C=O), 1120, 1077 and 1023 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.25 - 1.90 (m, 14 H), 2.36 (t, J = 7.5 Hz, 2 H, CH_2CO_2H), 3.38 (td, J = 6.5 and 9.6 Hz, 1 H, CH_2OTHP), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 3.7, 7.5 and 11.2 Hz, 1 H, CH_2O), 4.58 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), (OH was not detectable); ^{13}C NMR ($CDCl_3$, ppm) δ 19.43, 24.53, 25.34, 25.80, 28.77, 29.38, 30.58 (7 t, CH_2), 33.87 (t, C-2), 62.09 (t, CH_2O), 67.36 (t, C-7), 98.63 (d, *C*H), 179.32 (s, C-1); MS (CI, %) *m/z* 231 (94.1) [$M^{\oplus}$ + H], 213 (2.5) [$M^{\oplus}$ - H_2O], 147 (49.1) [$M^{\oplus}$ - C_5H_8O], 129 (6.7) [$M^{\oplus}$ - C_5H_8O - H_2O], 85 (100.0) [$C_5H_9O^{\oplus}$].

Procedure: 3,4-Dihydropyran (17.2 ml, 189 mmol) was added to a cooled solution (0 °C) of 8-hydroxyoctanoic acid [16] (20.37 g, 127.1 mmol) in ether (300 ml) containing *p*-toluenesulfonic acid monohydrate (242 mg, 1.27 mmol). After 16 h at room temp., the reaction mixture was washed twice with saturated sodium hydrogencarbonate solution and once with water. Ether was removed under reduced pressure and the remaining oil was dissolved in 5 N NaOH (30 ml). 3,4-Dihydropyran was separated by three extractions with ether. The ice-cooled aqueous layer was acidified with 2 N HCl and then extracted three times with ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo, providing 23.67 g (76%) of **2b** as yellow oil, which was used directly in the next reaction. Further purification by silicagel column chromatography (Et_2O, R_f 0.56) provided **2b** as a colourless oil.

8-(Tetrahydro-2′H-pyran-2′-yl-oxy)-1-octanoic acid (**2b**). IR (film, cm^{-1}) $\tilde{\nu}$ 3650 - 2380 (OH), 1709 (C=O), 1120, 1077 and 1023 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.20 - 1.90 (m, 16 H), 2.35 (t, J = 7.5 Hz, 2 H, CH_2CO_2H), 3.38 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.51 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 4.1, 7.2 and 11.3 Hz, 1 H, CH_2O), 4.58 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), (OH was not detectable); ^{13}C NMR ($CDCl_3$, ppm) δ 19.61, 24.63, 25.47, 26.04, 29.00, 29.08, 29.64, 30.73 (8 t, CH_2), 34.04 (t, C-2), 62.29 (t, CH_2O), 67.60 (t, C-8), 98.81 (d, *C*H), 179.67 (s, C-1); MS (CI, %) *m/z* 245 (7.1) [$M^{\oplus}$ + H], 161 (65.5) [$M^{\oplus}$ - C_5H_8O], 143 (5.8) [$M^{\oplus}$ - C_5H_8O - H_2O], 85 (100.0) [$C_5H_9O^{\oplus}$].

Procedure: To a solution of methyl 9-hydroxynonanoate [17] (11.14 g, 59.17 mmol) in ether (50 ml) was added *p*-toluenesulfonic acid monohydrate (112 mg, 589 μmol) followed by 3,4-dihydropyran (5.95 ml, 65.2 mmol). After stirring this homogeneous reaction mixture for 6 h at room temp., sodium hydrogencarbonate was added and the suspension was filtered with ether through silicagel. The filtrate was concentrated under reduced pressure and the residue (16.01 g) was dissolved in EtOH (50 ml). To this solution was added NaOH (15.17 g, 379.3 mmol) in water (50 ml) and the reaction mixture was stirred at ambient temp. for 20 h. Then the ice-cooled solution was acidified with 2 N HCl and then extracted five times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo, providing 12.45 g (81%) of **2c** as an yellow oil, which was used directly in the next reaction. Further purification by silicagel column chromatography (Et_2O, R_f 0.58) provided **2c** as colourless oil.

9-(Tetrahydro-2′H-pyran-2′-yl-oxy)-1-nonanoic acid (**2c**). IR (film, cm^{-1}) $\tilde{\nu}$ 3650 - 2380 (OH), 1710 (C=O), 1120, 1078 and 1023 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.17 - 1.98 (m, 18 H), 2.35 (t, J = 7.4 Hz, 2 H, CH_2CO_2H), 3.38 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.88 (m, 1 H, CH_2O), 4.58 (dd, J = 2.7 and 4.2 Hz, 1 H, OC*H*O), (OH was not detectable); ^{13}C NMR ($CDCl_3$, ppm) δ 19.57, 24.61, 25.42, 26.11, 28.95, 29.12, 29.20, 29.63, 30.69 (9 t, CH_2), 34.00 (t, C-2), 62.24 (t, CH_2O), 67.60 (t, C-9), 98.76 (d, *C*H), 179.72 (s, C-1); MS (CI, %) *m/z* 259 (1.2) [$M^{\oplus}$ + H], 175 (47.1) [$M^{\oplus}$ - C_5H_8O], 157 (4.1) [$M^{\oplus}$ - C_5H_8O - H_2O], 85 (100.0) [$C_5H_9O^{\oplus}$].

10-(Tetrahydro-2'H-pyran-2'-yl-oxy)-1-decanoic acid (**2d**). Scale 48.2 mmol of 10-hydroxydecanoic acid [17], dry THF (150 ml), 59.6 mmol of 3,4-dihydropyran, 0.48 mmol of *p*-toluenesulfonic acid monohydrate. After 14 h at room temp., the reaction mixture was poured into saturated sodium hydrogencarbonate solution, the organic layer was separated, and the aqueous layer was extracted five times with dichloromethane. Usual work, acidification followed by five extractions with dichloromethane, yield 82% (10.73 g), R_f 0.61; IR (film, cm^{-1}) $\tilde{\nu}$ 3650 - 2380 (OH), 1709 (C=O), 1120, 1078 and 1033 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.15 - 1.92 (m, 20 H), 2.34 (t, J = 7.4 Hz, 2 H, CH_2CO_2H), 3.38 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.88 (m, 1 H, CH_2O), 4.59 (m, 1 H, OC*H*O), (OH was not detectable); ^{13}C NMR ($CDCl_3$, ppm) δ 19.50, 24.64, 25.41, 26.14, 28.99, 29.13, 29.30, 29.34, 29.63, 30.65 (10 t, CH_2), 34.02 (t, C-2), 62.13 (t, CH_2O), 67.61 (t, C-10), 98.68 (d, *C*H), 179.53 (s, C-1); MS (CI, %) *m/z* 273 (12.5) [$M^{\oplus}$ + H], 189 (68.1) [$M^{\oplus}$ - C_5H_8O], 171 (3.5) [$M^{\oplus}$ - C_5H_8O - H_2O], 85 (100.0) [$C_5H_9O^{\oplus}$].

Synthesis of Mixed Carboxylic Anhydrides ***3a-d***

General procedure: A solution of **2a** (4.20 g, 18.2 mmol) and of triethylamine (2.55 ml, 18.3 mmol) in ether (70 ml) is placed in a round-bottom flask fitted with a stirrer and a dropping funnel protected by a drying tube. The solution was cooled to 0 °C, and ethyl chlorocarbonate (1.79 ml, 18.7 mmol) was added in one portion. The stirring was continued further 0.5 h while triethylamine hydrochloride precipitated. Water was added, the organic layer was separated, once washed with water, dried (Na_2SO_4) and evaporated under reduced pressure below 30 °C to yield **3a** (5.14 g, 93%) as colourless oil.

Carboxylic anhydride **3a**. IR (film, cm^{-1}) $\tilde{\nu}$ 1822 and 1760 (C=O), 1237, 1121, 1078 and 1034 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.35 - 1.41 (m, 4 H), 1.36 (t, J = 7.15 Hz, 3 H, CH_3), 1.51 - 1.62 (m, 6 H), 1.65 - 1.74 (m, 3 H), 1.79 - 1.87 (m, 1 H), 2.46 (t, J = 7.5 Hz, 2 H, $CH_2CO_2CO_2Et$), 3.38 (td, J = 6.5 and 9.6 Hz, 1 H, CH_2OTHP), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.86 (ddd, J = 3.6, 7.6 and 11.2 Hz, 1 H, CH_2O), 4.32 (q, J = 7.15 Hz, 2 H, OCH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O); ^{13}C NMR ($CDCl_3$, ppm) δ 13.94 (q, CH_3), 19.70, 24.17, 25.51, 25.87, 28.65, 29.50, 30.78 (7 t, CH_2), 34.14 (t, C-2), 62.35 (t, CH_2O), 65.57 (t, CH_2CH_3), 67.39 (t, C-7), 98.87 (d, *C*H), 149.14 (s, CO_2Et), 167.98 (s, C-1); MS (CI, %) *m/z* 303 (1.7) [$M^{\oplus}$ + H], 259 (1.7) [$M^{\oplus}$ - CO_2], 213 (21.7) [$M^{\oplus}$ -CO_2 - C_2H_6O], 175 (56.6) [$M^{\oplus}$ - CO_2 - C_5H_8O], 129 (100) [$M^{\oplus}$ - CO_2 - C_5H_8O - C_2H_6O], 85 (86.5) [$C_5H_9O^{\oplus}$].

Carboxylic anhydride **3b**. Scale 95.65 mmol of **2b**, ether (250 ml), yield 95% (28.71 g); IR (film, cm^{-1}) $\tilde{\nu}$ 1822 and 1760 (C=O), 1237, 1121, 1079 and 1034 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.34 - 1.39 (m, 6 H), 1.36 (t, J = 7.15 Hz, 3 H, CH_3), 1.49 - 1.61 (m, 6 H), 1.65 - 1.74 (m, 3 H), 1.78 - 1.88 (m, 1 H), 2.46 (t, J = 7.5 Hz, 2 H, $CH_2CO_2CO_2Et$), 3.38 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J =

3.6, 7.6 and 11.2 Hz, 1 H, C*H*$_2$O), 4.32 (q, *J* = 7.15 Hz, 2 H, OC*H*$_2$CH$_3$), 4.57 (dd, *J* = 2.7 and 4.5 Hz, 1 H, OC*H*O); ^{13}C NMR ($CDCl_3$, ppm) δ 13.94 (q, *C*H$_3$), 19.71, 24.15, 25.50, 26.02, 28.75, 28.99, 29.64, 30.78 (8 t, *C*H$_2$), 34.18 (t, C-2), 62.35 (t, *C*H$_2$O), 65.57 (t, *C*H$_2$CH$_3$), 67.52 (t, C-8), 98.86 (d, *C*H), 149.15 (s, *C*O$_2$Et), 168.02 (s, C-1); MS (CI, %) *m/z* 317 (1.8) [M$^{\oplus}$ + H], 227 (48.8) [M$^{\oplus}$ - CO$_2$ - C$_2$H$_6$O], 189 (21.7) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O], 143 (100) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O - C$_2$H$_6$O], 85 (90.8) [C$_5$H$_9$O$^{\oplus}$].

Carboxylic anhydride **3c**. Scale 46.49 mmol of **2c**, dichloromethane (100 ml), triethylamine hydrochloride is soluble in dichloromethane, yield 94% (14.44 g); IR (film, cm^{-1}) ṽ 1822 and 1760 (C=O), 1235, 1121, 1079 and 1033 (C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.25 - 1.39 (m, 8 H), 1.36 (t, *J* = 7.15 Hz, 3 H, C*H*$_3$), 1.49 - 1.85 (m, 10 H), 2.46 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$CO$_2$CO$_2$Et), 3.38 (td, *J* = 6.6 and 9.6 Hz, 1 H, C*H*$_2$OTHP), 3.50 (m, 1 H, C*H*$_2$O), 3.73 (td, *J* = 6.9 and 9.6 Hz, 1 H, C*H*$_2$OTHP), 3.87 (m, 1 H, C*H*$_2$O), 4.32 (q, *J* = 7.15 Hz, 2 H, OC*H*$_2$CH$_3$), 4.57 (dd, *J* = 2.7 and 4.5 Hz, 1 H, OC*H*O); ^{13}C NMR ($CDCl_3$, ppm) δ 13.95 (q, *C*H$_3$), 19.72, 24.19, 25.51, 26.16, 28.76, 29.10, 29.21, 29.71, 30.79 (9 t, *C*H$_2$), 34.21 (t, C-2), 62.37 (t, *C*H$_2$O), 65.58 (t, *C*H$_2$CH$_3$), 67.61 (t, C-9), 98.87 (d, *C*H), 149.16 (s, *C*O$_2$Et), 168.05 (s, C-1); MS (CI, %) *m/z* 331 (5.4) [M$^{\oplus}$ + H], 241 (5.2) [M$^{\oplus}$ - CO$_2$ - C$_2$H$_6$O], 203 (22.2) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O], 157 (10.2) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O - C$_2$H$_6$O], 85 (100.0) [C$_5$H$_9$O$^{\oplus}$].

Carboxylic anhydride **3d**. Scale 37.52 mmol of **2d**, dichloromethane (150 ml), triethylamine hydrochloride is soluble in dichloromethane, yield 94% (12.15 g); IR (film, cm^{-1}) ṽ 1822 and 1761 (C=O), 1241, 1122, 1080 and 1033 (C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.25 - 1.38 (m, 10 H), 1.36 (t, *J* = 7.15 Hz, 3 H, C*H*$_3$), 1.50 - 1.62 (m, 6 H), 1.64 - 1.74 (m, 3 H), 1.78 - 1.89 (m, 1 H), 2.45 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$CO$_2$CO$_2$Et), 3.38 (td, *J* = 6.7 and 9.6 Hz, 1 H, C*H*$_2$OTHP), 3.50 (m, 1 H, C*H*$_2$O), 3.73 (td, *J* = 6.9 and 9.6 Hz, 1 H, C*H*$_2$OTHP), 3.87 (ddd, *J* = 3.6, 7.5 and 11.1 Hz, 1 H, C*H*$_2$O), 4.32 (q, *J* = 7.15 Hz, 2 H, OC*H*$_2$CH$_3$), 4.57 (dd, *J* = 2.7 and 4.5 Hz, 1 H, OC*H*O); ^{13}C NMR ($CDCl_3$, ppm) δ 13.98 (q, *C*H$_3$), 19.74, 24.24, 25.57, 26.25, 28.82, 29.13, 29.34, 29.40, 29.77, 30.83 (10 t, *C*H$_2$), 34.21 (t, C-2), 62.32 (t, *C*H$_2$O), 65.57 (t, *C*H$_2$CH$_3$), 67.64 (t, C-10), 98.86 (d, *C*H), 149.19 (s, *C*O$_2$Et), 168.05 (s, C-1); MS (CI, %) *m/z* 301 (1.7) [M$^{\oplus}$ - CO$_2$], 255 (18.8) [M$^{\oplus}$ - CO$_2$ - C$_2$H$_6$O], 217 (88.3) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O], 171 (66.1) [M$^{\oplus}$ - CO$_2$ - C$_5$H$_8$O - C$_2$H$_6$O], 85 (100.0) [C$_5$H$_9$O$^{\oplus}$].

Synthesis of β-Oxo Esters ***4a-d***

General procedure: To a cooled and stirred solution (0 °C) of diisopropylamine (4.78 ml, 34.0 mmol) in dry THF (60 ml) was added *n*-butyllithium (21.2 ml of a 1.6 M solution in *n*-hexane, 33.9 mmol). After 50 min the solution was cooled to -70 °C and treated dropwise with ethyl acetate (1.8 ml, 18 mmol), keeping the temp. below -65 °C. The solution was stirred additional 50 min, then **3a** (4.97 g, 16.4 mmol) in dry THF (10 ml) was added by means of a syringe, keeping the temp. below -65 °C. After 1.5 h of stirring at -70 °C the reaction solution was quenched with water and allowed

to reach room temp.. Then it was neutralized (development of gas) with 2 N HCl. The organic layer was separated and the aqueous solution was extracted twice with ether. The combined organic extracts were washed once with 1 N HCl, water, satd. aqueous $NaHCO_3$, water, dried (Na_2SO_4), filtered, and evaporated to give **4a** (4.79 g, 97%) as colourless oil. Further purification is possible by silicagel column chromatography (Et_2O/*n*-pentane, 1:1, R_f 0.42).

Ethyl 3-oxo-9-(tetrahydro-2′H-pyran-2′-yl-oxy)nonanate (**4a**). IR (film, cm^{-1}) $\tilde{\nu}$ 1745 (ester C=O), 1716 (C=O), 1643 and 1630 (C=C), 1236, 1077 and 1034 (C-O); UV (EtOH, nm) λ_{max}(lgε) 246 (3.05); ^{1}H NMR ($CDCl_3$, ppm) δ 1.23 - 1.87 (m, 14 H), 1.28 (t, J = 7.14 Hz, 2.625 H, CH_3), 1.29 (t, J = 7.1 Hz, 0.375 H, CH_3 enol tautomer), 2.20 (dd, J = 7.3 and 7.8 Hz, 0.25 H, CH_2CO enol tautomer), 2.54 (t, J = 7.4 Hz, 1.75 H, $CH_2COCH_2CO_2Et$), 3.38 (td, J = 6.5 and 9.6 Hz, 1 H, CH_2OTHP), 3.43 (s, 1.75 H, CH_2CO_2Et), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.86 (ddd, J = 3.9, 7.2 and 11.1 Hz, 1 H, CH_2O), 4.19 (q, J = 7.1 Hz, 0.25 H, OCH_2CH_3 enol tautomer), 4.20 (q, J = 7.14 Hz, 1.75 H, CH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), 4.97 (s, 0.125 H, $CHCO_2Et$ enol tautomer), 12.11 (s, 0.125 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.11 (q, CH_3), 19.71 (t, CH_2), 23.38 (C-5), 25.49, 26.04, 28.84, 29.55, 30.77 (5 t, CH_2), 42.94 (t, C-4) 49.31 (t, C-2), 61.32 (t, CH_2CH_3), 62.37 (t, CH_2O), 67.46 (t, C-9), 98.86 (d, *C*H), 167.26 (s, C-1), 202.91 (s, C-3), enol tautomer δ 14.28 (q, CH_3), 34.96 (t, C-4), 59.91 (t, CH_2CH_3), 89.02 (d, C-2), 172.77 (s, C-1), 178.87 (s, C-3); MS (CI, %) *m/z* 301 (0.9) [$M^{\oplus}$ + H], 283 (0.8) [$M^{\oplus}$ - H_2O], 255 (0.6) [$M^{\oplus}$ - C_2H_6O], 217 (10.5) [$M^{\oplus}$ - C_5H_8O], 199 (100) [$M^{\oplus}$ - C_5H_8O - H_2O], 171 (0.7) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 153 (0.7) [$M^{\oplus}$ - C_5H_8O - C_2H_6O - H_2O], 85 (42.7) [$C_5H_9O^{\oplus}$].

Ethyl 3 oxo-10-(tetrahydro-2′H-pyran-2′-yl-oxy)decanoate (**4b**). Scale 90.76 mmol of **3b**, dry THF (350 ml), yield 99% (28.38 g), R_f 0.50; IR (film, cm^{-1}) $\tilde{\nu}$ 1745 (ester C=O), 1716 (C=O), 1644 and 1630 (C=C), 1235, 1078 and 1034 (C-O); UV (EtOH, nm) λ_{max}(lgε) 246 (3.14); ^{1}H NMR ($CDCl_3$, ppm) δ 1.23 - 1.43 (m, 6 H), 1.28 (t, J = 7.14 Hz, 2.58 H, CH_3), 1.29 (t, J = 7.1 Hz, 0.42 H, CH_3 enol tautomer), 1.48 - 1.89 (m, 10 H), 2.19 (dd, J = 7.3 and 7.8 Hz, 0.28 H, CH_2CO enol tautomer), 2.53 (t, J = 7.4 Hz, 1.72 H, $CH_2COCH_2CO_2Et$), 3.37 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.43 (s, 1.72 H, CH_2CO_2Et), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 4.1, 7.2 and 11.3 Hz, 1 H, CH_2O), 4.19 (q, J = 7.1 Hz, 0.28 H, OCH_2CH_3 enol tautomer), 4.20 (q, J = 7.14 Hz, 1.72 H, CH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), 4.97 (s, 0.14 H, $CHCO_2Et$ enol tautomer), 12.10 (s, 0.14 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.12 (q, CH_3), 19.72 (t, CH_2), 23.39 (t, C-5), 25.51, 26.07, 28.95, 29.20, 29.68, 30.79 (6 t, CH_2), 43.01 (t, C-4) 49.32 (t, C-2), 61.33 (t, CH_2CH_3), 62.37 (t, CH_2O), 67.58 (t, C-10), 98.87 (d, *C*H), 167.28 (s, C-1), 202.96 (s, C-3), enol tautomer δ 14.28 (q, CH_3), 35.02 (t, C-4), 59.91 (t, CH_2CH_3), 89.01 (d, C-2), 172.79 (s, C-1), 178.95 (s, C-3); MS (CI, %) *m/z* 315 (1.2) [$M^{\oplus}$ + H], 231 (100.0) [$M^{\oplus}$ - C_5H_8O], 213 (22.9) [$M^{\oplus}$ - C_5H_8O - H_2O], 85 (40.0) [$C_5H_9O^{\oplus}$].

Ethyl 3-oxo-11-(tetrahydro-2′H-pyran-2′-yl-oxy)undecanoate (**4c**). Scale 43.70 mmol of **3c**, dry THF (150 ml), yield 91% (13.04 g), R_f 0.54; IR (film, cm^{-1}) $\tilde{\nu}$ 1745 (ester C=O), 1717 (C=O),

1643 and 1630 (C=C), 1234, 1077 and 1032 (C-O); UV (EtOH, nm) λ_{max}(lgε) 246 (3.14); ^{1}H NMR ($CDCl_3$, ppm) δ 1.24 - 1.36 (m, 8 H), 1.28 (t, J = 7.15 Hz, 2.49 H, CH_3), 1.29 (t, J = 7.1 Hz, 0.51 H, CH_3 enol tautomer), 1.50 - 1.62 (m, 8 H), 1.69 - 1.74 (m, 1 H), 1.78 - 1.87 (m, 1 H), 2.18 (dd, J = 7.5 and 7.8 Hz, 0.34 H, CH_2CO enol tautomer), 2.53 (t, J = 7.4 Hz, 1.66 H, $CH_2COCH_2CO_2Et$), 3.38 (td, J = 6.7 and 9.6 Hz, 1 H, CH_2OTHP), 3.43 (s, 1.66 H, CH_2CO_2Et), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 3.5, 7.6 and 11.1 Hz, 1 H, CH_2O), 4.19 (q, J = 7.1 Hz, 0.34 H, OCH_2CH_3 enol tautomer), 4.20 (q, J = 7.15 Hz, 1.66 H, CH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), 4.97 (s, 0.17 H, $CHCO_2Et$ enol tautomer), 12.11 (s, 0.17 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.11 (q, CH_3), 19.71 (t, CH_2), 23.41 (t, C-5), 25.50 (t, CH_2), 26.18 (t, C-9), 28.95, 29.27, 29.30 (3 t, CH_2), 29.71 (C-10), 30.78 (t, CH_2), 43.02 (t, C-4) 49.31 (t, C-2), 61.32 (t, CH_2CH_3), 62.36 (t, CH_2O), 67.62 (t, C-11), 98.85 (d, CH), 167.29 (s, C-1), 203.01 (s, C-3), enol tautomer δ 14.28 (q, CH_3), 35.03 (t, C-4), 59.90 (t, CH_2CH_3), 88.97 (d, C-2); MS (CI, %) *m/z* 329 (2.0) [$M^{\oplus}$ + H], 245 (100.0) [$M^{\oplus}$ - C_5H_8O], 227 (9.2) [$M^{\oplus}$ - C_5H_8O - H_2O], 199 (1.3) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 85 (28.7) [$C_5H_9O^{\oplus}$].

Ethyl 3-oxo-12-(tetrahydro-2′H-pyran-2′-yl-oxy)dodecanoate (**4d**). Scale 34.20 mmol of **3d**, dry THF (100 ml), yield 96% (11.24 g), R_f 0.48; IR (film, cm^{-1}) $\tilde{\nu}$ 1746 (ester C=O), 1717 (C=O), 1644 and 1630 (C=C), 1234, 1078 and 1033 (C-O); UV (EtOH, nm) λ_{max}(lgε) 246 (3.14); ^{1}H NMR ($CDCl_3$, ppm) δ 1.26 - 1.39 (m, 10 H), 1.28 (t, J = 7.14 Hz, 2.19 H, CH_3), 1.29 (t, J = 7.1 Hz, 0.81 H, CH_3 enol tautomer), 1.49 - 1.87 (m, 10 H), 2.18 (dd, J = 7.5 and 7.8 Hz, 0.54 H, CH_2CO enol tautomer), 2.53 (t, J = 7.4 Hz, 1.46 H, $CH_2COCH_2CO_2Et$), 3.38 (td, J = 6.7 and 9.6 Hz, 1 H, CH_2OTHP), 3.43 (s, 1.46 H, CH_2CO_2Et), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 3.8, 7.2 and 11.0 Hz, 1 H, CH_2O), 4.19 (q, J = 7.1 Hz, 0.54 H, OCH_2CH_3 enol tautomer), 4.20 (q, J = 7.14 Hz, 1.46 H, CH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, OC*H*O), 4.97 (s, 0.27 H, $CHCO_2Et$ enol tautomer), 12.11 (s, 0.27 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.12 (q, CH_3), 19.72 (t, CH_2), 23.44 (t, C-5), 25.51, 26.22, 29.00, 29.31, 29.38, 29.41, 29.74, 30.79 (8 t, CH_2), 43.05 (t, C-4) 49.32 (t, C-2), 61.34 (t, CH_2CH_3), 62.36 (t, CH_2O), 67.66 (t, C-12), 98.86 (d, CH), 167.29 (s, C-1), 203.02 (s, C-3), enol tautomer δ 14.29 (q, CH_3), 35.05 (t, C-4), 59.91 (t, CH_2CH_3), 88.97 (d, C-2), 172.80 (s, C-1), 179.01 (s, C-3); MS (CI, %) *m/z* 259 (100.0) [$M^{\oplus}$ - C_5H_8O], 241 (12.1) [$M^{\oplus}$ - C_5H_8O - H_2O], 213 (11.6) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 195 (2.7) [$M^{\oplus}$ - C_5H_8O - C_2H_6O - H_2O], 85 (91.1) [$C_5H_9O^{\oplus}$].

Synthesis of α-Alkylated ß-Oxo Esters ***5a-e***

General procedure, method A: To a solution of sodium ethoxide (481 mg, 20.9 mmol of sodium in 60 ml of anhydrous ethanol) cooled to 0 °C, ß-oxo ester **4a** (6.67 g, 22.2 mmol) was added dropwise, followed by NaI (30 mg). Then methyl 7-bromoheptanoate[#] (4.52 g, 20.2 mmol) was

[#]This compound was prepared from **2a** by esterification and subsequent reaction with triphenylphosphine and bromine [18], yield 86%.

added in one portion and the mixture was refluxed under stirring for 24 h. The ethanol was removed under reduced pressure, the residue was acidified (pH~6) with a few drops of 2 N HCl and then extracted twice with ether. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to yield **5a** as a pale yellow oil. It was used directly in the next reaction. Purification by silicagel column chromatography (Et_2O/*n*-pentane, 1:1, R_f 0.33) provided **5a** as colourless oil.

Methyl 8-ethoxycarbonyl-9-oxo-15-(tetrahydro-2′H-pyran-2′-yl-oxy)pentadecanoate (**5a**). IR (film, cm^{-1}) $\tilde{\nu}$ 1740 (ester C=O), 1715 (C=O), 1638 (C=C), 1077 and 1034 (C-O); UV (EtOH, nm) λ_{max}(lgε) 251 (2.65); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20 - 1.90 (m, 24 H), 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 2.30 (t, J = 7.5 Hz, 2 H, CH_2CO_2Me), 2.46 (td, J = 7.2 and 17.4 Hz, 1 H, CH_2COCH), 2.55 (td, J = 7.4 and 17.4 Hz, 1 H, CH_2COCH), 3.37 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.40 (t, J = 7.4 Hz, 1 H, $COCHCO_2Et$), 3.50 (m, 1 H, CH_2O), 3.67 (s, 3 H, OCH_3), 3.72 (td, J = 6.8 and 9.6 Hz, 1 H, CH_2OTHP), 3.86 (ddd, J = 4.0, 7.1 and 11.1 Hz, 1 H, CH_2O), 4.18 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, $OCHO$), 12.83 (s, 0.04 H, OH enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.14 (q, CH_3), 19.71, 23.41, 24.79, 25.49, 26.07, 27.27, 28.09, 28.80, 28.90, 29.00, 29.57, 30.77 (12 t, CH_2), 33.98, (t, C-2), 41.79 (t, C-10), 51.47 (q, OCH_3), 59.12 (d, C-8), 61.24 (t, CH_2CH_3), 62.37 (t, CH_2O), 67.49 (t, C-15), 98.86 (d, CH), 169.92 (s, CO_2Et), 174.18 (s, C-1), 205.42 (s, C-9); MS (CI, %) *m/z* 443 (0.9) [$M^{\oplus}$ + H], 397 (3.2) [$M^{\oplus}$ - C_2H_6O], 359 (100.0) [$M^{\oplus}$ - C_5H_8O], 341 (33.0) [$M^{\oplus}$ - C_5H_8O - H_2O], 313 (1.5) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 295 (2.2) [$M^{\oplus}$ - C_5H_8O - C_2H_6O - H_2O], 85 (15.1) [$C_5H_9O^{\oplus}$].

Ethyl 7-ethoxycarbonyl-8-oxo-15-(tetrahydro-2′H-pyran-2′-yl-oxy)pentadecanoate (**5b**). Method A, scale 30.1 mmol of **4b**, dry EtOH (80 ml), 30.5 mmol of sodium, 30.2 mmol of ethyl 6-bromohexanoate, 50 mg of NaI, R_f 0.44; IR (film, cm^{-1}) $\tilde{\nu}$ 1737 (ester C=O), 1715 (C=O), 1078 and 1034 (C-O); UV (EtOH, nm) λ_{max}(lgε) 256 (2.52); ^{1}H NMR ($CDCl_3$, ppm) δ = 1.22 - 1.38 (m, 10 H), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.50 - 1.65 (m, 10 H), 1.68 - 1.74 (m, 1 H), 1.77 - 1.89 (m, 3 H), 2.28 (t, J = 7.5 Hz, 2 H, CH_2CO_2Et), 2.45 (td, J = 7.3 and 17.4 Hz, 1 H, CH_2COCH), 2.54 (td, J = 7.4 and 17.4 Hz, 1 H, CH_2COCH), 3.37 (td, J = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.40 (t, J = 7.4 Hz, 1 H, $COCHCO_2Et$), 3.50 (m, 1 H, CH_2O), 3.72 (td, J = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 3.6, 7.6 and 11.2 Hz, 1 H, CH_2O), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.18 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.57 (dd, J = 2.7 and 4.5 Hz, 1 H, $OCHO$), 12.83 (s, 0.03 H, OH enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.13, 14.25 (2 q, CH_3), 19.71, 23.41, 24.64, 25.49, 26.07, 27.12, 27.96, 28.84, 29.00, 29.24, 29.68, 30.78 (12 t, CH_2), 34.17, (t, C-2), 41.86 (t, C-9), 59.07 (d, C-7), 60.23, 61.26 (2 t, CH_2CH_3), 62.37 (t, CH_2O), 67.59 (t, C-15), 98.87 (d, CH), 169.88 (s, CO_2Et), 173.65 (s, C-1), 205.41 (s, C-8); MS (CI, %) *m/z* 457 (3.0) [$M^{\oplus}$ + H], 411 (15.6) [$M^{\oplus}$ - C_2H_6O], 373 (100.0) [$M^{\oplus}$ - C_5H_8O], 327 (8.1) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 85 (67.9) [$C_5H_9O^{\oplus}$].

General procedure, method B: ß-Oxo ester **4c** (6.88 g, 20.9 mmol) in dry DME (20 ml) was added slowly to a stirred suspension of sodium hydride (60% dispersion, 874 mg, 21.9 mmol) in dry DME (10 ml), and the mixture was stirred for 0.5 h at room temp.. Then methyl 5-bromovalerate (2.86 ml, 20.0 mmol) in dry DME (5 ml) was added in one portion and the mixture was stirred and refluxed for 26 h. After the mixture had cooled, water and then a few drops 2 N HCl were added to it (pH~6). The organic layer was separated and the aqueous layer was extracted once with ether. The combined organic extracts were washed once with water, dried (Na_2SO_4), and then evaporated in vacuo. The residue was purified by silicagel column chromatography (Et_2O/*n*-pentane, 1:1, R_f 0.44) to yield **5c** (5.89 g, 67%) as colourless oil.

Methyl 6-ethoxycarbonyl-7-oxo-15-(tetrahydro-2′H-pyran-2′-yl-oxy)pentadecanoate (**5c**). IR (film, cm^{-1}) $\tilde{\nu}$ 1739 (ester C=O), 1713 (C=O), 1078 and 1032 (C-O); UV (EtOH, nm) λ_{max}(lgε) 260 (2.50); ^{1}H NMR ($CDCl_3$, ppm) δ 1.25 - 1.35 (m, 10 H), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.50 - 1.74 (m, 11 H), 1.79 - 1.90 (m, 3 H), 2.18 (m, 0.1 H, enol tautomer), 2.31 (t, *J* = 7.5 Hz, 2 H, CH_2CO_2Me), 2.45 (td, *J* = 7.3 and 17.4 Hz, 1 H, CH_2COCH), 2.54 (td, *J* = 7.4 and 17.4 Hz, 1 H, CH_2COCH), 3.38 (td, *J* = 6.7 and 9.6 Hz, 1 H, CH_2OTHP), 3.42 (t, *J* = 7.3 Hz, 1 H, $COCHCO_2Et$), 3.50 (m, 1 H, CH_2O), 3.66 (s, 3 H), 3.73 (td, *J* = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, *J* = 3.5, 7.6 and 11.1 Hz, 1 H, CH_2O), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.57 (dd, *J* = 2.7 and 4.6 Hz, 1 H, OCHO), 12.85 (s, 0.05 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.04 (q, CH_3), 19.64, 23.35, 24.53, 25.42, 26.11, 26.83, 27.65, 28.91, 29.21, 29.25, 29.64, 30.70 (12 t, CH_2), 33.59, (t, C-2), 41.84 (t, C-8), 51.45 (q, OCH_3), 58.78 (d, C-6), 61.22 (t, CH_2CH_3), 62.29 (t, CH_2O), 67.55 (t, C-15), 98.78 (d, CH), 169.69 (s, CO_2Et), 173.78 (s, C-1), 205.21 (s, C-7); MS (CI, ppm) *m/z* 443 (0.4) [$M^{\oplus}$ + H], 397 (1.8) [$M^{\oplus}$ - C_2H_6O], 359 (100.0) [$M^{\oplus}$ - C_5H_8O], 313 (1.6) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 85 (12.6) [$C_5H_9O^{\oplus}$].

Ethyl 5-ethoxycarbonyl-6-oxo-15-(tetrahydro-2′H-pyran-2′-yl-oxy)pentadecanoate (**5d**). Method B, scale 21.5 mmol of **4d**, dry DME (11/22 ml), 22.6 mmol of sodium hydride, 20.7 mmol of ethyl 4-bromobutyrate, R_f 0.39; IR (film, cm^{-1}) $\tilde{\nu}$ 1736 (ester C=O), 1715 (C=O), 1638 (C=C), 1078 and 1033 (C-O); UV (EtOH, nm) λ_{max}(lgε) 259 (2.71); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20 - 1.41 (m, 10 H), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.45 - 1.91 (m, 14 H), 2.32 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Et), 2.46 (td, *J* = 7.2 and 17.4 Hz, 1 H, CH_2COCH), 2.56 (td, *J* = 7.3 and 17.4 Hz, 1 H, CH_2COCH), 3.38 (td, *J* = 6.6 and 9.6 Hz, 1 H, CH_2OTHP), 3.44 (t, *J* = 7.3 Hz, 1 H, $COCHCO_2Et$), 3.50 (m, 1 H, CH_2O), 3.73 (td, *J* = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, *J* = 3.7, 7.4 and 11.1 Hz, 1 H, CH_2O), 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.19 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.57 (dd, *J* = 2.7 and 4.5 Hz, 1 H, OCHO), 12.89 (s, 0.07 H, O*H* enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.07, 14.18 (2 q, CH_3), 19.66, 22.71, 23.38, 25.45, 26.16, 27.41, 28.98, 29.28, 29.34, 29.37, 29.69, 30.74 (12 t, CH_2), 33.86, (t, C-2), 41.91 (t, C-7), 58.73 (d, C-5), 60.33, 61.32 (2 t, CH_2CH_3), 62.30 (t, CH_2O), 67.60 (t, C-15), 98.80 (d, CH), 169.55 (s, CO_2Et), 173.00 (s, C-1), 205.02 (s, C-6); MS (CI, %) *m/z* 373 (100.0) [$M^{\oplus}$ - C_5H_8O], 327 (27.1) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 281 (23.7) [$M^{\oplus}$ - C_5H_8O - $2C_2H_6O$], 85 (84.5) [$C_5H_9O^{\oplus}$].

Ethyl 7-ethoxycarbonyl-8-oxo-16-(tetrahydro-2′H-pyran-2′-yl-oxy)hexadecanoate (**5e**). Method A, scale 5.02 mmol of **4c**, dry EtOH (14 ml), 5.18 mmol of sodium, 4.93 mmol of ethyl 6-bromohexanoate, R_f 0.44; IR (film, cm^{-1}) $\tilde{\nu}$ 1737 (ester C=O), 1715 (C=O), 1078 and 1033 (C-O); UV (EtOH, nm) λ_{max}(lgε) 260 (2.68); ^1H NMR ($CDCl_3$, ppm) δ 1.23 - 1.38 (m, 12 H), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.49 - 1.65 (m, 10 H), 1.69 - 1.76 (m, 1 H), 1.78 - 1.89 (m, 3 H), 2.28 (t, J = 7.5 Hz, 2 H, CH_2CO_2Et), 2.45 (td, J = 7.3 and 17.4 Hz, 1 H, CH_2COCH), 2.54 (td, J = 7.4 and 17.4 Hz, 1 H, CH_2COCH), 3.38 (td, J = 6.7 and 9.6 Hz, 1 H, CH_2OTHP), 3.40 (dd, J = 6.9 and 7.8 Hz, 1 H, $COCHCO_2Et$), 3.50 (m, 1 H, CH_2O), 3.73 (td, J = 6.9 and 9.6 Hz, 1 H, CH_2OTHP), 3.87 (ddd, J = 3.6, 7.6 and 11.2 Hz, 1 H, CH_2O), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.19 (dq, J = 0.9 and 7.1 Hz, 2 H, $CHCO_2CH_2CH_3$), 4.57 (dd, J = 2.7 and 4.6 Hz, 1 H, OCHO), 12.84 (s, 0.05 H, OH enol tautomer); ^{13}C NMR ($CDCl_3$, ppm) δ 14.13, 14.25 (2q, CH_3), 19.72, 23.45, 24.64, 25.51, 26.19, 27.12, 27.96, 28.84, 29.01, 29.29, 29.33, 29.72, 30.79 (13 t, CH_2), 34.17, (t, C-2), 41.87 (t, C-9), 59.07 (d, C-7), 60.22 (t, CH_2CH_3), 61.25 (t, CH_2CH_3), 62.37 (t, CH_2O), 67.64 (t, C-16), 98.87 (d, CH), 169.88 (s, CO_2Et), 173.64 (s, C-1), 205.41 (s, C-8); MS (CI, %) *m/z* 425 (1.9) [$M^{\oplus}$ - C_2H_6O], 387 (100.0) [$M^{\oplus}$ - C_5H_8O], 341 (2.1) [$M^{\oplus}$ - C_5H_8O - C_2H_6O], 295 [$M^{\oplus}$ - C_5H_8O - $2C_2H_6O$], 85 (7.7) [$C_5H_9O^{\oplus}$].

Synthesis of Heterocyclic Compounds ***6a-e***

General procedure: A mixture of ester **5a** (10.43 g), hydroxylamine hydrochloride (2.78 g, 40.0 mmol), sodium acetate (33 mg, 0.40 mmol), and ethanol (100 ml) was heated at reflux for 2.5 h. Volatile compounds were evaporated, water was added and the emulsion was extracted four times with ether. Evaporation of the dried (Na_2SO_4) combined extracts was followed by filtration with ether through silicagel. The filtrate was concentrated under reduced pressure to give isoxazol-5-one **6a** as pale yellow oil, which was used directly in the next reaction. Purification by silicagel column chromatography (Et_2O/MeOH, 9:1, R_f 0.44) provided **6a** as colourless oil. The protecting group was cleaved under these reaction conditions.

Ethyl 7-[3′-(6′′-hydroxyhexyl)-5′oxo-2′,5′-dihydroisoxazol-4′-yl]heptanoate (**6a**). IR (film, cm^{-1}) $\tilde{\nu}$ 3405 (OH, NH), 1798 (C=O), 1732 (ester C=O), 1614 (C=C), 1194 and 1033 (C-O); UV (EtOH, nm) λ_{max}(lgε) 210 (3.46) and 259 (3.51); ^1H NMR ($CDCl_3$, ppm) δ 1.11 - 1.23 (m, 2 H, 6-H), 1.25 (t, J = 7.14 Hz, 3 H, CH_3), 1.29 - 1.35 (m, 4 H, 4-H and 5-H), 1.38 - 1.50 (m, 4 H, 12-H and 13-H), 1.55 - 1.62 (m, 4 H, 3-H and 14-H), 1.72 - 1.78 (m, 2 H, 11-H), 1.78 (ddd, J = 5.3, 11.6 and 13.3 Hz, 1 H, 7-H), 1.84 (br. s, 2 H, OH and NH), 1.89 (ddd, J = 5.3, 11.7 and 13.3 Hz, 1 H, 7-H), 2.28 (t, J = 7.4 Hz, 2 H, CH_2CO_2Et), 2.38 (ddd, J = 7.1, 8.0 and 16.6 Hz, 1 H, 10-H), 2.47 (ddd, J = 6.6, 8.2 and 16.6 Hz, 1 H, 10-H), 3.32 (dd, J = 5.1 and 6.2 Hz, < 0.1 H, CH-tautomer), 3.65 (t, J = 6.4 Hz, 2 H, CH_2OH), 4.12 (q, J = 7.14 Hz, 2 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, ppm) δ 14.20 (q, CH_3), 22.02 (t, C-6), 24.16 (t, C-11), 24.58 (t, C-3), 25.13 (t, C-13), 25.95 (t, C-10), 28.57 (C-4), 28.60 (C-12), 28.88 (C-5), 32.01 (C-14), 34.12 (t, C-2), 35.82 (t, C-7), 60.39 (t,

CH_2CH_3), 62.72 (t, C-15), 77.71 (s, C-8), 170.19 (s, C-9), 173.93 (s, C-1), 177.94 (s, *C*O_2NH); MS (CI, %) *m/z* 342 (2.5) [$M^{\oplus}$ + H], 300 (6.2) [$M^{\oplus}$ - 42], 298 (1.7) [$M^{\oplus}$ - CO_2], 231 (62.9) [$M^{\oplus}$ - 111], 185 (4.2) [$M^{\oplus}$ - 111 -C_2H_6O], 128 (100.0) [$C_7H_{14}NO^{\oplus}$], 110 (13.3) [$C_7H_{14}NO^{\oplus}$ - H_2O].

Ethyl 6-[3′-(7′′-hydroxyheptyl)-5′oxo-2′,5′-dihydroisoxazol-4′-yl]hexanoate (**6b**). Scale 13.25 g of **5b**, EtOH (50 ml), 58.0 mmol of hydroxylamine hydrochloride, 0.59 mmol of sodium acetate, R_f 0.46; IR (film, cm^{-1}) $\tilde{\nu}$ 3403 (OH, NH), 1798 (C=O), 1732 (ester C=O), 1619 (C=C), 1188 and 1035 (C-O); UV (EtOH, nm) λ_{max}(lgε) 205 (3.57) and 259 (3.29); ^{1}H NMR ($CDCl_3$, ppm) δ 1.15 - 1.79 (m, 16 H and 2 H, O*H* and N*H*), 1.25 (t, *J* = 7.14 Hz, 3 H, CH_3), 1.79 (ddd, *J* = 5.2, 11.6 and 13.4 Hz, 1 H, 6-H), 1.90 (ddd, *J* = 5.4, 11.7 and 13.4 Hz, 1 H, 6-H), 2.28 (t, *J* = 7.5 Hz, 2 H, C$H_2$$CO_2$Et), 2.37 (ddd, *J* = 7.1, 8.2 and 16.7 Hz, 1 H, 9-H), 2.46 (ddd, *J* = 6.8, 8.4 and 16.7 Hz, 1 H, 9-H), 3.32 (dd, *J* = 5.2 and 6.2 Hz, < 0.1 H, C*H*-tautomer), 3.65 (t, *J* = 6.5 Hz, 2 H, CH_2OH), 4.12 (q, *J* = 7.14 Hz, 2 H, C$H_2$$CH_3$); ^{13}C NMR ($CDCl_3$, ppm) δ 14.24 (q, *C*$H_3$), 21.95, 24.19, 24.37, 25.40, 26.14, 28.58, 28.69, 28.89, 32.44, 33.95, 35.90 (11 t, *C*H_2), 60.42 (t, *C*$H_2$$CH_3$), 62.90 (t, C-15), 77.66 (s, C-7), 170.02 (s, C-8), 173.59 (s, C-1), 177.80 (s, *C*O_2NH); MS (CI, %) *m/z* 342 (64.7) [$M^{\oplus}$ + H], 300 (61.8) [$M^{\oplus}$ - 42], 298 (15.9) [$M^{\oplus}$ - CO_2], 217 (72.9) [$M^{\oplus}$ - 125], 171 (5.6) [$M^{\oplus}$ - 125 - C_2H_6O], 142 (100.0) [$C_8H_{16}NO^{\oplus}$], 124 (15.8) [$C_8H_{16}NO^{\oplus}$ - H_2O].

Ethyl 5-[3′-(8′′-hydroxyoctyl)-5′oxo-2′,5′-dihydroisoxazol-4′-yl]pentanoate (**6c**). Scale 11.4 mmol of **5c**, EtOH (50 ml), 24.9 mmol of hydroxylamine hydrochloride, 0.11 mmol of sodium acetate, R_f 0.44; IR (film, cm^{-1}) $\tilde{\nu}$ 3386 (OH, NH), 1797 (C=O), 1732 (ester C=O), 1629 (C=C), 1193 and 1027 (C-O); UV (EtOH, nm) λ_{max}(lgε) 208 (3.50) and 264 (3.06); ^{1}H NMR ($CDCl_3$, ppm) δ 1.23 - 1.49 (m, 10 H), 1.25 (t, *J* = 7.14 Hz, 3 H, CH_3), 1.50 - 1.78 (m, 6 H and 1 O*H*), 1.81 (ddd, *J* = 6.3, 10.9 and 13.5 Hz, 1 H, 5-H), 1.91 (ddd, *J* = 6.1, 10.9 and 13.5 Hz, 1 H, 5-H), 2.30 (t, *J* = 7.4 Hz, 2 H, C$H_2$$CO_2$Et), 2.38 (ddd, *J* = 7.0, 8.4 and 16.7 Hz, 1 H, 8-H), 2.46 (ddd, *J* = 6.4, 8.6 and 16.7 Hz, 1 H, 8-H), 3.33 (dd, *J* = 5.2 and 6.3 Hz, < 0.1 H, C*H*-tautomer), 3.65 (t, *J* = 6.5 Hz, 2 H, CH_2OH), 3.67 (br. s, 1 N*H*), 4.12 (q, *J* = 7.14 Hz, 2 H, C$H_2$$CH_3$); ^{13}C NMR ($CDCl_3$, ppm) δ 14.19 (q, *C*$H_3$), 21.66, 24.29, 24.46, 25.42, 26.14, 28.87, 28.89, 28.94, 32.46 (9 t, *C*H_2), 33.65 (t, C-2), 35.71 (t, C-5), 60.55 (t, *C*$H_2$$CH_3$), 62.95 (t, C-15), 77.50 (s, C-6), 170.06 (s, C-7), 173.25 (s, C-1), 177.66 (s, *C*O_2NH); MS (CI, %) *m/z* 342 (28.0) [$M^{\oplus}$ + H], 300 (37.8) [$M^{\oplus}$ - 42], 298 (19.2) [$M^{\oplus}$ - CO_2], 203 (90.2) [$M^{\oplus}$ - 139], 157 (87.9) [$M^{\oplus}$ - 139 - C_2H_6O], 156 (52.9) [$C_9H_{18}NO^{\oplus}$], 138 (100.0) [$C_9H_{18}NO^{\oplus}$ - H_2O].

Ethyl 4-[3′-(9′′-hydroxynonyl)-5′oxo-2′,5′-dihydroisoxazol-4′-yl]butanoate (**6d**). Scale 6.07 g of **5d**, EtOH (60 ml), 35.6 mmol of hydroxylamine hydrochloride, 0.18 mmol of sodium acetate, R_f 0.43; IR (film, cm^{-1}) $\tilde{\nu}$ 3389 (OH, NH), 1798 (C=O), 1732 (ester C=O), 1624 (C=C), 1204 and 1033 (C-O); UV (EtOH, nm) λ_{max}(lgε) 209 (3.49) and 260 (2.96); ^{1}H NMR ($CDCl_3$, ppm) δ 1.25 - 1.50 (m, 10 H), 1.26 (t, *J* = 7.15 Hz, 3 H, CH_3), 1.53 - 1.83 (m, 7 H and 2 H, O*H* and N*H*), 1.90 (m, 1 H, 4-H), 2.32 - 2.49 (m, 4 H, C$H_2$$CO_2$Et and C$H_2$CNH), 3.34 (dd, *J* = 5.4 and 6.0 Hz, ~0.17 H, C*H*-tautomer), 3.65 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 4.14 (q, *J* = 7.15 Hz, 2 H, C$H_2$$CH_3$); ^{13}C NMR ($CDCl_3$, ppm) δ 14.11 (q, *C*$H_3$), 17.47 (t, C-3), 24.26, 25.55, 26.06, 29.12, 29.14, 29.17, 29.18

(7 t, CH_2), 32.43 (t, C-14), 33.28 (t, C-2), 34.81 (t, C-4), 60.73 (t, CH_2CH_3), 62.87 (t, C-15), 77.24 (s, C-5), 170.66 (s, C-6), 172.96 (s, C-1), 177.88 (s, CO_2NH); MS (CI, %) *m/z* 342 (14.7) [$M^{\oplus}$ + H], 300 (44.4) [$M^{\oplus}$ - 42], 298 (29.8) [$M^{\oplus}$ - CO_2], 189 (60.9) [$M^{\oplus}$ - 153], 170 (66.7) [$C_{10}H_{20}NO^{\oplus}$], 152 (100.0) [$C_{10}H_{20}NO^{\oplus}$ - H_2O], 143 (41.7) [$M^{\oplus}$ - 153 - C_2H_6O].

Ethyl 6-[3′-(8′′-hydroxyoctyl)-5′oxo-2′,5′-dihydroisoxazol-4′-yl]hexanoate (**6e**). Scale 2.12 g of **5e**, EtOH (22 ml), 10.0 mmol of hydroxylamine hydrochloride, 0.05 mmol of sodium acetate, R_f 0.46; IR (film, cm^{-1}) $\tilde{\nu}$ 3379 (OH, NH), 1798 (C=O), 1732 (ester C=O), 1615 (C=C), 1187 and 1034 (C-O); UV (EtOH, nm) λ_{max}(lgε) shoulder at 206 (3.43) and 260 (3.45); UV (cyclohexane, nm) λ_{max}(lgε) shoulder at 208 (2.90) and 255 (2.46); ^{1}H NMR ($CDCl_3$, ppm) δ 1.15 - 1.49 (m, 12 H), 1.25 (t, *J* = 7.14 Hz, 3 H, CH_3), 1.50 - 1.95 (m, 6 H and 2 H, O*H* and N*H*), 1.80 (ddd, *J* = 5.3, 11.6 and 13.4 Hz, 1 H, 6-H), 1.90 (ddd, *J* = 5.4, 11.6 and 13.4 Hz, 1 H, 6-H), 2.28 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Et), 2.37 (ddd, *J* = 7.0, 8.3 and 16.7 Hz, 1 H, 9-H), 2.46 (ddd, *J* = 6.6, 8.5 and 16.7 Hz, 1 H, 9-H), 3.32 (dd, *J* = 5.1 and 6.1 Hz, ~ 0.21 H, C*H*-tautomer), 3.65 (t, *J* = 6.5 Hz, 2 H, CH_2OH), 4.12 (q, *J* = 7.14 Hz, 2 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, ppm) δ 14.22 (q, CH_3), 21.97, 24.33, 24.43, 25.53, 26.09, 28.74, 29.00, 29.03, 29.04, 32.45, 34.00, 35.55 (12 t, CH_2), 60.46 (t, CH_2CH_3), 62.80 (t, C-16), 77.61 (s, C-7), 170.67 (s, C-8), 173.81 (s, C-1), 178.23 (s, CO_2NH); MS (CI, %) *m/z* 356 (100.0) [$M^{\oplus}$ + H], 314 (33.2) [$M^{\oplus}$ - 42], 312 (19.3) [$M^{\oplus}$ - CO_2], 217 (75.3) [$M^{\oplus}$ - 139], 171 (25.0) [$M^{\oplus}$ - 139 - C_2H_6O], 156 (31.5) [$C_9H_{18}NO^{\oplus}$], 138 (29.1) [$C_9H_{18}NO^{\oplus}$ - H_2O].

Synthesis of ω-Hydroxy Alkynoic Acids ***7a-e***

General procedure: To a suspension of ferrous(II)-sulfate (30.62 g, 110.1 mmol) in acetic acid (265 ml) was added half of a solution of sodium nitrite (13.95 g, 202.2 mmol) in water (142 ml) under nitrogen atmosphere. After stirring for 10 min the remaining solution was added simultaneously with a solution of the isoxazolone **6a** (9.23 g) in acetic acid (71 ml) over 0.5 h. All solutions must be thoroughly degassed before. The apparatus, a three-necked flask, was flushed for an additional hour with nitrogen to eliminate gaseous nitric oxides. Water was added to solve ferrous(II)-sulfate and the mixture was extracted twice with ether. The combined ether extracts were washed four times with water and saturated sodium hydrogencarbonate solution. Concentration provided an oil (5.91 g) which was treated with NaOH (2.0 g, 50 mmol) in water (30 ml) and MeOH (5 ml). This solution was stirred at ambient temp. for 16 h and then twice extracted with ether to separate by-products. Then the aqueous layer was acidified with 5 N HCl, extracted three times with ether, dried (Na_2SO_4) and evaporated. Purification by filtration with ether through silicagel and recrystallization (Et_2O) gave **7a** (1.92 g, 37% from methyl 7-bromoheptanoate) as colourless solid, mp 55.5 to 57 °C.

15-Hydroxy-pentadec-8-ynoic acid (**7a**). IR (KBr, cm^{-1}) $\tilde{\nu}$ 3650 - 2380 (OH), 3406 (OH), 3336 (OH), 1699 (C=O), 1059 (C-O); Raman (cm^{-1}) $\tilde{\nu}$ 2290 and 2226 (C≡C); ^{1}H NMR ($CDCl_3$, ppm) δ 1.32 - 1.52 (m, 12 H), 1.59 (tdd, *J* = 6.7, 6.8 and 8.0 Hz, 2 H, CH_2CH_2OH), 1.65 (tt, *J* = 7.5 and

7.5 Hz, 2 H, $CH_2CH_2CO_2H$), 2.14 - 2.17 (m, 4 H, $CH_2C{\equiv}C$), 2.35 (t, J = 7.5 Hz, 2 H, CH_2CO_2H), 3.66 (t, J = 6.7 Hz, 2 H, CH_2OH, 4 - 6 (br. s, 2 H, CO_2H and OH); ^{13}C NMR ($CDCl_3$, ppm) δ 18.64, 18.66 (2 t, $CH_2C{\equiv}C$), 24.65 (t, C-3), 25.25 (t, C-13), 28.34, 28.55, 28.55, 28.79, 28.98 (5 t, CH_2), 32.54 (t, C-14), 33.87 (t, C-2), 62.96 (t, C-15), 80.19 (s, C-8)*, 80.29 (s, C-9)*, 178.85 (s, C-1); MS (CI, %) *m/z* 255 (47.2) [$M^{\oplus}$ + H], 237 (100.0) [$M^{\oplus}$ - H_2O], 219 (22.9) [$M^{\oplus}$ - $2H_2O$]; Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.79, H 10.30.

15-Hydroxy-pentadec-7-ynoic acid (**7b**). Scale 11.10 g of **6b** in acetic acid (80 ml), 154.2 mmol of ferrous(II)-sulfate in acetic acid (296 ml), 283.0 mmol of sodium nitrite in water (160 ml); then 70 mmol of NaOH in water (50 ml) and MeOH (10 ml), yield from **4b** 31% (2.38 g), mp 54.5 to 55.5 °C; IR (KBr, cm^{-1}) ν̃ 3630 - 2380 (OH), 3421 (OH), 3354 (OH), 1689 (C=O), 1065 (C-O); Raman (cm^{-1}) ν̃ 2291 and 2225 (C≡C), 1090 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.32 - 1.53 (m, 12 H), 1.58 (tdd, J = 6.5, 6.5 and 8.1 Hz, 2 H, CH_2CH_2OH), 1.66 (tt, J = 7.4 and 7.4 Hz, 2 H, $CH_2CH_2CO_2H$), 2.15 (tt, J = 2.4 and 6.9 Hz, 2 H, $CH_2C{\equiv}C$), 2.17 (tt, 2.4 and 6.6 Hz, 2 H, $CH_2C{\equiv}C$), 2.36 (t, J = 7.3 Hz, 2 H, CH_2CO_2H), 3.67 (t, J = 6.5 Hz, 2 H, CH_2OH, 6.47 (br. s, 2 H, CO_2H and OH); ^{13}C NMR ($CDCl_3$, ppm) δ 18.59, 18.69 (2 t, $CH_2C{\equiv}C$), 24.31 (t, C-3), 25.65 (t, C-13), 28.24, 28.67, 28.73, 28.91, 28.97 (5 t, CH_2), 32.47 (t, C-14), 34.01 (t, C-2), 62.89 (t, C-15), 79.91 (s, C-7)*, 80.47 (s, C-8)*, 178.94 (s, C-1); MS (CI, %) *m/z* 255 (57.4) [$M^{\oplus}$ + H], 237 (100.0) [$M^{\oplus}$ - H_2O], 219 (31.0) [$M^{\oplus}$ - $2H_2O$]; Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.83, H 10.34.

15-Hydroxy-pentadec-6-ynoic acid (**7c**). Scale 4.2 g of **6c** in acetic acid (45 ml), 68 mmol of ferrous(II)-sulfate in acetic acid (150 ml), 128 mmol of sodium nitrite in water (90 ml); then 22 mmol of NaOH in water (20 ml) and MeOH (5 ml), yield from **5c** 51% (1.48 g), mp 48.5 to 50 °C; IR (KBr, cm^{-1}) ν̃ 3630 - 2380 (OH), 3288 (OH), 3142 (OH), 1690 (C=O), 1060 (C-O); Raman (cm^{-1}) ν̃ 2295 and 2228 (C≡C), 1060 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.27 - 1.42 (m, 8 H), 1.44 - 1.60 (m, 6 H), 1.76 (tt, J = 7.7 and 7.7 Hz, 2 H, $CH_2CH_2CO_2H$), 2.15 (tt, J = 2.4 and 6.8 Hz, 2 H, $CH_2C{\equiv}C$), 2.19 (tt, 2.4 and 6.9 Hz, 2 H, $CH_2C{\equiv}C$), 2.37 (t, J = 7.6 Hz, 2 H, CH_2CO_2H), 3.67 (t, J = 6.4 Hz, 2 H, CH_2OH), not detectable (2 H, CO_2H and OH); ^{13}C NMR ($CDCl_3$, ppm) δ 18.44, 18.67 (2 t, $CH_2C{\equiv}C$), 23.90 (t, C-3), 25.61 (t, C-13), 28.35, 28.67, 28.98, 29.10, 29.29 (5 t, CH_2), 32.49 (t, C-14), 33.65 (t, C-2), 62.83 (t, C-15), 79.44 (s, C-6)*, 80.80 (s, C-7)*, 178.85 (s, C-1); MS (CI, %) *m/z* 255 (62.0) [$M^{\oplus}$ + H], 237 (100.0) [$M^{\oplus}$ - H_2O], 219 (30.6) [$M^{\oplus}$ - $2H_2O$]; Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.82, H 10.22.

15-Hydroxy-pentadec-5-ynoic acid (**7d**). Scale 4.9 g of **6d** in acetic acid (46 ml), 70 mmol of ferrous(II)-sulfate in acetic acid (155 ml), 132 mmol of sodium nitrite in water (96 ml); then 23 mmol of NaOH in water (21 ml) and MeOH (5 ml), yield from ethyl 4-bromobutyrate 32% (1.69 g), mp 57.5 to 60 °C; IR (KBr, cm^{-1}) ν̃ 3580 - 2380 (OH), 3264 (OH), 1689 (C=O), 1058 (C-O); Raman (cm^{-1}) ν̃ 2282 and 2224 (C≡C), 1062 (C-O); ^1H NMR ($CDCl_3$, ppm) δ 1.24 - 1.40 (m, 10 H), 1.47 (tdd, J = 6.8, 7.1 and 8.1 Hz, 2 H), 1.57 (tdd, J = 6.7, 6.7 and 7.9 Hz, 2 H, CH_2CH_2OH), 1.81 (tt, J = 7.2 and 7.2 Hz, 2 H, $CH_2CH_2CO_2H$), 2.14 (tt, J = 2.4 and 6.9 Hz, 2 H, $CH_2C{\equiv}C$), 2.25

(tt, 2.4 and 6.8 Hz, 2 H, $CH_2C{\equiv}C$), 2.50 (t, J = 7.5 Hz, 2 H, CH_2CO_2H), 3.65 (t, J = 6.6 Hz, 2 H, CH_2OH, not detectable (2 H, CO_2H and OH); ^{13}C NMR ($CDCl_3$, ppm) δ 18.16, 18.67 (2 t, $CH_2C{\equiv}C$), 24.03 (t, C-3), 25.66 (t, C-13), 28.76, 28.94, 29.02, 29.29, 29.44 (5 t, CH_2), 32.44 (t, C-14), 32.84 (t, C-2), 62.84 (t, C-15), 78.72 (s, C-5)*, 81.42 (s, C-6)*, 178.68 (s, C-1); MS (CI, %) *m/z* 255 (74.9) [$M^{\oplus}$ + H], 237 (100.0) [$M^{\oplus}$ - H_2O], 219 (18.6) [$M^{\oplus}$ - $2H_2O$]; Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.88, H 10.32.

16-Hydroxy-hexadec-7-ynoic acid (**7e**). Scale 1.1 g of **6e** in acetic acid (11 ml), 17 mmol of ferrous(II)-sulfate in acetic acid (41 ml), 31 mmol of sodium nitrite in water (22 ml); then 12.5 mmol of NaOH in water (10 ml) and MeOH (5 ml), yield from ethyl 6-bromohexanoate 37% (490 mg), mp 58 to 60 °C, the mp and the ^1H NMR spectrum are in agreement with ref. 12.

Synthesis of Macrocyclic Alkynolides ***8a-d***

General procedure: The cyclization was performed as described in ref. 10, purification by silicagel column chromatography (300 ml *n*-pentane, then Et_2O/*n*-pentane, 1:9) provided **8a** as colourless oil, GC (t_{ret} 16.52), temperature-program 150(5)-10-250(15).

8-Pentadecyn-15-olide (**8a**). Scale 3.50 mmol of **7a** in dry and ethanol-free $CHCl_3$ (40 ml), 10.4 mmol of DMAP, 6.86 mmol of 4-(dimethylamino)pyridine hydrochloride, 7.12 mmol of DCC, dry and ethanol-free $CHCl_3$ (100 ml), yield 60% (493 mg), R_f 0.33; IR (film, cm^{-1}) $\tilde{\nu}$ 1734 (C=O), 1235 (C-O); Raman (cm^{-1}) $\tilde{\nu}$ 2285 and 2232 (C≡C), 1732 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.26 - 1.53 (m, 12 H), 1.67 - 1.77 (m, 4 H), 2.16 - 2.23 (m, 4 H, $CH_2C{\equiv}C$), 2.37 (m, 2 H, CH_2CO), 4.13 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, ppm) δ 17.88 (t, C-7)*, 18.05 (t, C-10)*, 24.94, 25.85, 26.97, 27.27, 27.70, 28.33, 28.36, 28.60 (8 t, CH_2), 33.69 (t, C-2), 63.79 (t, C-15), 80.30 (s, C-8)**, 80.43 (s, C-9)**, 173.98 (s, C-1); MS (EI, %) *m/z* 236 (12.4) [$M^{\oplus}$], 218 (2.0) [$M^{\oplus}$ - H_2O], 79 (100.0); Anal calcd for $C_{15}H_{24}O_2$ (236.35), C 76.23, H 10.23; found C 75.08, H 10.11.

7-Pentadecyn-15-olide (**8b**). Scale 3.46 mmol of **7b** in dry and ethanol-free $CHCl_3$ (40 ml), 10.4 mmol of DMAP, 6.86 mmol of 4-(dimethylamino)pyridine hydrochloride, 7.19 mmol of DCC, dry and ethanol-free $CHCl_3$ (100 ml), yield 60% (488 mg), R_f 0.30, GC (t_{ret} 16.56); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (C=O), 1251 (C-O); Raman (cm^{-1}) $\tilde{\nu}$ 2287 and 2231 (C≡C), 1733 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.25 - 1.34 (m, 2 H), 1.38 - 1.53 (m, 10 H), 1.64 - 1.73 (m, 4 H), 2.17 - 2.22 (m, 4 H, $CH_2C{\equiv}C$), 2.36 (m, 2 H, CH_2CO), 4.17 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, ppm) δ 17.75 (t, C-6)*, 18.81 (t, C-9)*, 25.19, 25.56, 26.12, 27.12, 27.36, 27.77, 28.26, 28.83 (8 t, CH_2), 34.87 (t, C-2), 62.99 (t, C-15), 80.13 (s, C-7)**, 80.66 (s, C-8)**, 173.96 (s, C-1); MS (EI, %) *m/z* 236 (9.3) [$M^{\oplus}$], 218 (2.0) [$M^{\oplus}$ - H_2O], 94 (100.0); Anal calcd for $C_{15}H_{24}O_2$ (236.35), C 76.23, H 10.23; found C 75.80, H 10.09.

6-Pentadecyn-15-olide (**8c**). Scale 3.46 mmol of **7c** in dry and ethanol-free $CHCl_3$ (40 ml), 10.4 mmol of DMAP, 7.08 mmol of 4-(dimethylamino)pyridine hydrochloride, 6.91 mmol of DCC, dry

and ethanol-free $CHCl_3$ (100 ml), yield 70% (526 mg)#, purification by silicagel column chromatography (300 ml *n*-pentane, then Et_2O/*n*-pentane, 1:10, R_f 0.22), GC (t_{ret} 16.81); IR (film, cm^{-1}) $\tilde{\nu}$ 1734 (C=O), 1229 (C-O); Raman (cm^{-1}) $\tilde{\nu}$ 2285 and 2230 (C≡C), 1732 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.35 - 1.54 (m, 12 H), 1.62 (m, 2 H, CH_2CH_2O), 1.84 (tt, J = 8.1 and 8.1 Hz, 2 H, CH_2CH_2CO), 2.21 (m, 2 H, $CH_2C{\equiv}C$), 2.22 (m, 2 H, $CH_2C{\equiv}C$), 2.33 (m, 2 H, CH_2CO), 4.14 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, ppm) δ 18.51 (t, C-5), 18.65 (t, C-8), 24.43 (t, C-13), 25.08 (t, C-3), 26.64 (t, C-11), 27.26 (t, C-12)*, 27.44 (t, C-10)*, 27.91 (t, C-9), 27.95 (t, C-14), 28.29 (t, C-4), 35.15 (t, C-2), 64.17 (t, C-15), 79.80 (s, C-6), 81.00 (s, C-7), 173.60 (s, C-1); MS (EI, %) *m/z* 236 (7.8) [$M^{\oplus}$], 218 (2.0) [$M^{\oplus}$ - H_2O], 79 (100.0); HRMS: calcd for $C_{15}H_{24}O_2$ (236.35), 236.17763, found 236.1774 (100.00); HRMS: calcd for $^{12}C_{14}{}^{13}CH_{24}O_2$, 237.18098, found 237.1817 (16.76).

5-Pentadecyn-15-olide (**8d**). Scale 2.00 mmol of **7d** in dry and ethanol-free $CHCl_3$ (30 ml), 6.02 mmol of DMAP, 4.10 mmol of 4-(dimethylamino)pyridine hydrochloride, 4.02 mmol of DCC, dry and ethanol-free $CHCl_3$ (60 ml), yield 60% (284 mg), silicagel column chromatography like **8c**, R_f 0.22), GC (t_{ret} 16.42); IR (film, cm^{-1}) $\tilde{\nu}$ 1735 (C=O), 1211 (C-O); Raman (cm^{-1}) $\tilde{\nu}$ 2281 and 2229 (C≡C), 1734 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.30 - 1.51 (m, 12 H), 1.67 (m, 2 H, CH_2CH_2O), 1.79 (tdd, J = 7.1, 7.1 and 5.6 Hz, 2 H, CH_2CH_2CO), 2.19 (m, 2 H, $CH_2C{\equiv}C$), 2.27 (m, 2 H, $CH_2C{\equiv}C$), 2.55 (t, J = 7.2 Hz, 2 H, CH_2CO), 4.15 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, ppm) δ 17.50 (t, C-4)*, 18.27 (t, C-7)*, 23.60, 25.76, 26.68, 27.08, 27.20, 27.71, 28.08, 28.15 (8 t, CH_2), 32.22 (t, C-2), 64.56 (t, C-15), 79.34 (s, C-5)**, 81.49 (s, C-6)**, 173.35 (s, C-1); MS (EI, %) *m/z* 236 (20.1) [$M^{\oplus}$], 218 (1.0) [$M^{\oplus}$ - H_2O], 79 (100.0); HRMS: calcd for $C_{15}H_{24}O_2$ (236.35), 236.17763, found 236.1774 (100.00); HRMS: calcd for $^{12}C_{14}{}^{13}CH_{24}O_2$, 237.18098, found 237.1808 (15.87).

(Z)-Selective Hydrogenation of ***8a-d***

General procedure: A suspension of **8a** (121 mg, 513 μmol) in ethyl acetate (22 ml) was hydrogenated at room temp., by using of 5% Pd-$CaCO_3$ (147 mg, 69.1 μmol) and freshly distilled quinoline (0.15 ml, 1.3 μmol). After 1 h the mixture was filtered with ether through silicagel. The residue was purified by silicagel column chromatography (Et_2O/*n*-pentane, 1:9) to provide (*Z*)-**9a** (108 mg, 88%) as colourless oil, GC (t_{ret} 16.01), temperature-program 150(5)-10-250(15); (*E*)-isomer, (t_{ret} 15.76), *Z*:*E* ratio 98.7:1.3, de 97.4%, R_f 0.38.

(*Z*)-8-Pentadecen-15-olide [(*Z*)-**9a**]. IR (film, cm^{-1}) $\tilde{\nu}$ 3002 cm^{-1} (C=C-H), 1735 (C=O), 1253 (C-O), 732 ((*Z*)-CH=CH-); ^1H NMR ($CDCl_3$, ppm) δ 1.29 - 1.48 (m, 12 H), 1.60 - 1.68 (m, 4 H), 1.99 - 2.08 (m, 4 H), 2.34 (m, 2 H, CH_2CO), 4.16 (m, 2 H, CH_2O), 5.37 (m, 2 H, therein 5.34, td, J = 6.3 and 10.8 Hz, 1 H, C*H* and 5.40, td, J = 6.5 and 10.8 Hz, 1 H, C*H*); ^{13}C NMR ($CDCl_3$, ppm) δ 24.99, 25.58, 25.75, 26.03, 27.35, 27.41, 27.74, 28.68, 28.70, 28.86 (10 t, CH_2), 34.54 (t, C-2),

#70 mg of starting material **7c** were isolated from the syringe and tubing.

64.29 (t, C-15), 129.96 (d, C-8)*, 130.06 (d, C-9)*, 174.05 (s, C-1); MS (EI, %) *m/z* 238 (31.2) [$M^{\oplus}$], 220 (6.0) [$M^{\oplus}$ - H_2O], 82 (100.0); Anal calcd for $C_{15}H_{24}O_2$ (238.37), C 75.58, H 10.99; found C 75.52, H 10.89.

(*Z*)-7-Pentadecen-15-olide [(*Z*)-**9b**]. Scale 723 µmol of **8b**, 97 µmol of 5% Pd-$CaCO_3$, 1.8 µmol of quinoline, ethyl acetate (30 ml), yield 95% (164 mg), GC (t_{ret} 15.99); (*E*)-isomer, (t_{ret} 15.71), *Z*:*E* ratio 99.1:0.9, de 98.2%, R_f 0.40; IR (film, cm^{-1}) $\tilde{\nu}$ 3000 cm^{-1} (C=C-H), 1735 (C=O), 1201 (C-O), 719 ((*Z*)-CH=CH-); ^1H NMR ($CDCl_3$, ppm) δ 1.24 - 1.42 (m, 12 H), 1.59 - 1.67 (m, 4 H), 1.98 - 2.09 (m, 4 H), 2.33 (m, 2 H, CH_2CO), 4.15 (m, 2 H, CH_2O), 5.36 (m, 2 H, therein 5.33, td, J = 6.8 and 10.9 Hz, 1 H, C*H* and 5.39, td, J = 6.8 and 10.9 Hz, 1 H, C*H*); ^{13}C NMR ($CDCl_3$, ppm) δ 25.11, 25.32, 26.14, 27.18, 27.29, 27.44, 28.06, 28.25, 28.33, 29.15 (10 t, CH_2), 34.29 (t, C-2), 63.95 (t, C-15), 129.83 (d, C-7)*, 130.08 (d, C-8)*, 173.87 (s, C-1); MS (EI, %) *m/z* 238 (19.0) [$M^{\oplus}$], 220 (6.0) [$M^{\oplus}$ - H_2O], 71 (100.0); HRMS: calcd for $C_{15}H_{26}O_2$ (238.37), 238.19328, found 238.1930 (100.00); HRMS: calcd for $^{12}C_{14}{}^{13}CH_{26}O_2$, 239.19664, found 239.1966 (16.05).

(*Z*)-6-Pentadecen-15-olide [(*Z*)-**9c**]. Scale 457 µmol of **8c**, 61.5 µmol of 5% Pd-$CaCO_3$, 1.1 µmol of quinoline, ethyl acetate (20 ml), yield 99% (107 mg), GC (t_{ret} 16.07); (*E*)-isomer, (t_{ret} 15.90), *Z*:*E* ratio 97.6:2.4, de 95.2%, R_f 0.34; IR (film, cm^{-1}) $\tilde{\nu}$ 2999 cm^{-1} (C=C-H), 1732 (C=O), 1231 (C-O), 718 ((*Z*)-CH=CH); ^1H NMR ($CDCl_3$, ppm) δ 1.24 - 1.42 (m, 12 H), 1.62 - 1.68 (m, 4 H), 2.02 - 2.09 (m, 4 H), 2.32 (t, J = 7.5 Hz, 2 H, CH_2CO), 4.13 (m, 2 H, CH_2O), 5.35 (m, 2 H, therein 5.33, td, J = 6.1 and 10.1 Hz, 1 H, C*H* and 5.37, td, J = 6.2 and 10.1 Hz, 1 H, C*H*); ^{13}C NMR ($CDCl_3$, ppm) δ 23.91 (t, C-13), 25.73 (t, C-3), 26.93 (t, C-8), 27.00 (t, CH_2), 27.22 (t, C-5), 27.50 (t, CH_2), 27.91 (t, C-14), 28.02, 28.49 (2 t, CH_2), 29.32 (t, C-4), 35.42 (t, C-2), 62.98 (t, C-15), 129.59 (d, C-6), 130.21 (d, C-7), 173.71 (s, C-1); MS (EI, %) *m/z* 238 (46.0) [$M^{\oplus}$], 220 (6.9) [$M^{\oplus}$ - H_2O], 81 (96.1), 67 (100.0); Anal calcd for $C_{15}H_{24}O_2$ (238.37), C 75.58, H 10.99; found C 75.61, H 10.96.

(*Z*)-5-Pentadecen-15-olide [(*Z*)-**9d**]. Scale 0.38 mmol of **8d**, 51.2 µmol of 5% Pd-$CaCO_3$, 0.93 µmol of quinoline, ethyl acetate (20 ml), yield 88% (80 mg), GC (t_{ret} 15.94); (*E*)-isomer, (t_{ret} 15.79), *Z*:*E* ratio 98.6:1.4, de 97.2%, R_f 0.41; IR (film, cm^{-1}) $\tilde{\nu}$ 3002 cm^{-1} (C=C-H), 1735 (C=O), 1238 (C-O), 716 ((*Z*)-CH=CH); ^1H NMR ($CDCl_3$, ppm) δ 1.25 - 1.47 (m, 12 H), 1.60 - 1.76 (m, 4 H), 2.01 - 2.14 (m, 4 H), 2.35 (m, 2 H, CH_2CO), 4.16 (m, 2 H, CH_2O), 5.36 (m, 2 H, C*H*); ^{13}C NMR ($CDCl_3$, ppm) δ 25.37, 25.50, 26.08, 26.48, 26.68, 26.76, 26.87, 27.26, 27.79, 27.87 (10 t, CH_2), 34.14 (t, C-2), 64.37 (t, C-15), 128.81 (d, C-5)*, 131.09 (d, C-6)*, 173.88 (s, C-1); MS (EI, %) *m/z* 238 (73.0) [$M^{\oplus}$], 220 (12.8) [$M^{\oplus}$ - H_2O], 96 (100.0); HRMS: calcd for $C_{15}H_{26}O_2$ (238.37), 238.19328, found 238.1932 (100.00); HRMS: calcd for $^{12}C_{14}{}^{13}CH_{26}O_2$, 239.19664, found 239.1964 (17.54).

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