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Stereoselective Synthesis and Structural Variations of Ethyl Analogues of Galbanum Macrolides

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Abstract

Both enantiomers of 13-pentadecanolide and 15-heptadecanolide, higher analogues of galbanum macrolides, were prepared *via* ring enlargement of cyclodecanone and cyclododecanone, respectively. Conversion of the intermediate oxo lactones to methylenated ethyl galbanum macrolides by Wittig olefination shifted the olfactory properties dramatically.

Keywords: Hydroxy acids and derivatives; Wittig reactions; Macrolides; Flavours and fragrances.

Introduction

Galbanum is widely used in perfumery because of its typical, intense odour impression, referred to as green, spicy and reminiscent of green leaves. Kaiser and Lamparsky [1] isolated a series of homologous ω-methyl macrolides with a pleasant musk-like note which has minor influence on the entirely different characteristic galbanum odour impression of galbanum gum resin, the dried exudation of *Ferula galbaniflua* Boiss. et Buhse and *Ferula rubricaulis* Boiss. (fam. Umbelliferae). The most abundant of these trace constituents, (13*R*)-(-)-tetradecanolide (**1a**) and (15*R*)-(-)-hexadecanolide (**1b**) (Scheme 1), were also identified in the resin of *Pinus pinaster*, where they contribute to the woody-musky scent [2].

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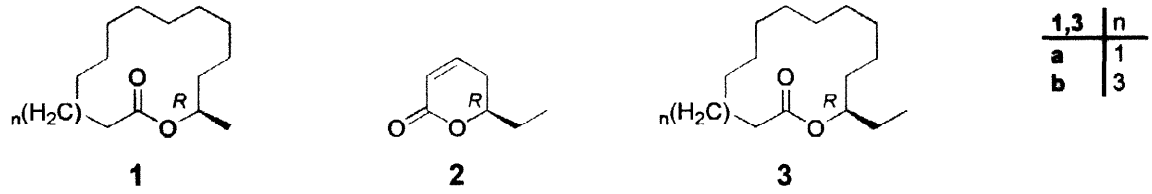


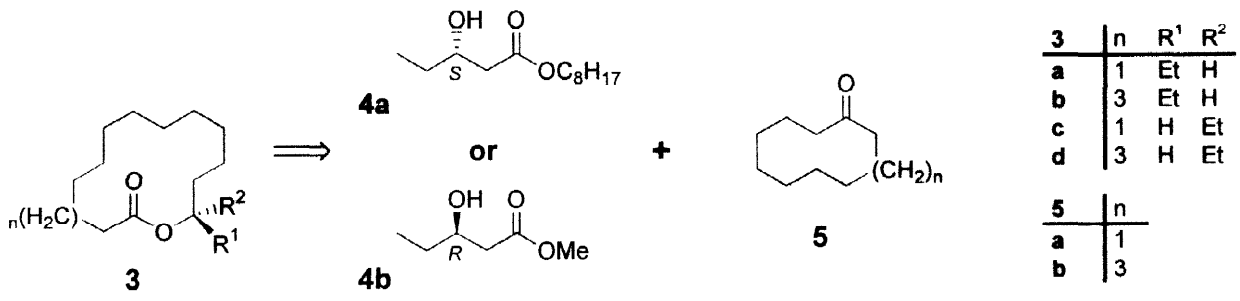
Scheme 1: Trace constituents of galbanum resin (**1**) and labdanum resin (**2**) and lead structures **3** of this work.

The ω-methyl group of **1a,b** is a common structural element of many naturally occurring macrolides due to a biogenesis according to an acetate pathway. The presence of an ethyl group attached to the alkoxy carbon atom is consistent with the incorporation of a propionate unit instead. The interesting ω-ethyl substituted δ-lactone **2** is found as a trace constituent of the woody-ambra Labdanum resin which smells leather-like [3]. Together with its higher homologues it has great impact on a well-balanced hay note.

In course of our investigations concerning the structure-odour relationships of macrocyclic musks [4-7], we became interested in lead structures **3**, because we wanted to examine how structural changes may influence the odour characteristics.

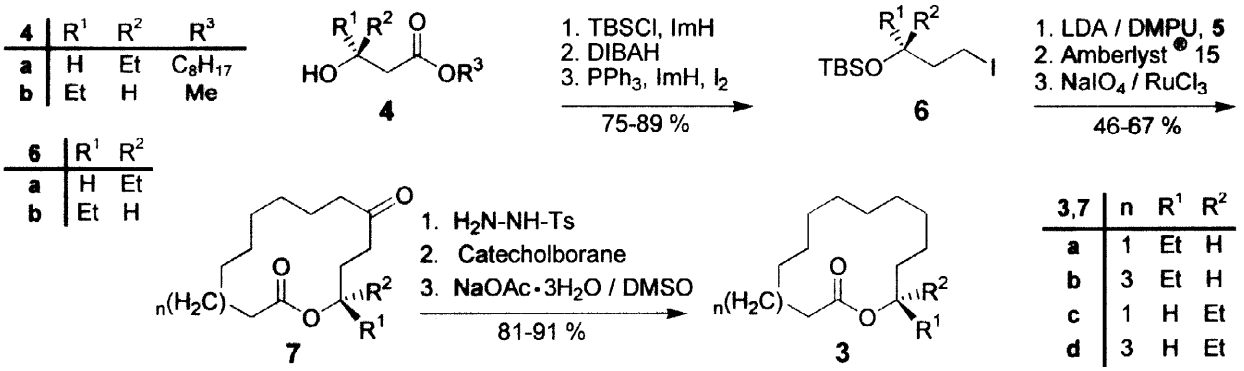
Results and Discussion

We focused on an enantioselective approach to both enantiomers of these ethyl galbanum macrolides **3**. The retrosynthetic analysis is based on our well-established ring-enlargement sequence and led to 3-hydroxypentanoates **4a** and **4b** with the opposite absolute configurations as chiral starting materials together with cycloalkanones **5** (Scheme 2).



Scheme 2: Retrosynthetic analysis of ethyl galbanum macrolides **3**.

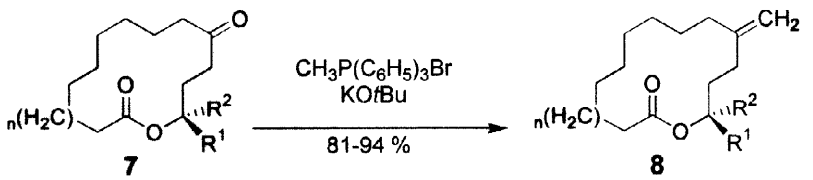
The commercially available copolymer of (*R*)-3-hydroxybutyrate and (*R*)-3-hydroxyvalerate (BIOPOL) is an attractive source for the chiral hydroxy ester **4b** [8]. We were interested in the preparation of both chiral hydroxy esters **4a** and **4b**. Therefore we chose the yeast reduction [9] of the corresponding keto esters, since the stereo-preference in the reduction step can easily be controlled either by variation of the size of the ester moiety [10] or by addition of allyl alcohol [11].



Scheme 3: Enantioselective synthesis of ethyl galbanum macrolides **3** by ring enlargement of cycloalkanones **5**.

Scheme 3 describes the enantioselective synthesis of both enantiomers of 13-pentadecanolide **3a,c** and 15-heptadecanolide **3b,d**, respectively. The conversion of yeast-reduction products **4** into chiral building blocks **6** was easily accomplished in our straightforward manner [5a,b] in 75 to 89% yield. Enolate alkylation of cycloalkanones **5** with chiral iodides **6** provided the corresponding alkylation products, which were further transformed to keto lactones **7** in overall yields up to 67%. This was achieved by direct cyclisation and subsequent oxidative cleavage of crude reaction products with ruthenium tetroxide, according to our recently improved general procedure [5d]. The last step in our reliable ring-enlargement sequence cleanly furnished target molecules **3** in 81-91% yield, amenable to straightforward olfactory evaluation.

By application of lactates and 3-hydroxybutyrates for the synthesis of both enantiomers of 13-tetradecanolides, we have previously shown, that the introduction of chiral information proceeds with complete retention of configuration [5b]. The determined enantiomeric excesses of 91.0 and 98.0 % for **3a** and **3c**, respectively, are in good agreement with this finding and with the expected selectivities for the yeast reduction step [10,11].



7,8	n	R^1	R^2
a	1	Et	H
b	3	Et	H
c	1	H	Et
d	3	H	Et

Scheme 4: Synthesis of exo-methylene macrolides **8** by Wittig reaction.

Our recent studies of the relationship between odour and structure of methylenated [6] or unsaturated macrolides [7] disclosed very encouraging results for further studies in this direction. Now, our efforts have focused on the investigation of chiral methylenated macrolides **8**. The intermediate keto lactones **7** proved to be ideal starting materials for the introduction of a semicyclic methylene substituent by Wittig reaction. The conversion of **7** was efficiently accomplished by treatment with methyltriphenylphosphonium bromide and KO*t*Bu in THF and gave **8** in 81 to 94% yield (Scheme 4).

Table 1.
Olfactory properties of the macrolides **3** and **8**.

Compound	Olfactory properties*
3a	weak musk odour with a smell of burning, musty, not fresh
3b	distinct musk odour: pleasant powdery and slightly fresh
3c	distinct woody, fresh and fruity, clearly musk
3d	weak, a touch of musk, slightly woody and fruity
8a	strong musk note, fresh and clearly woody with camphoraceous cedarwood-like aspects
8b	almost odourless
8c	weak musk odour with a musty-woody tonality
8d	odourless

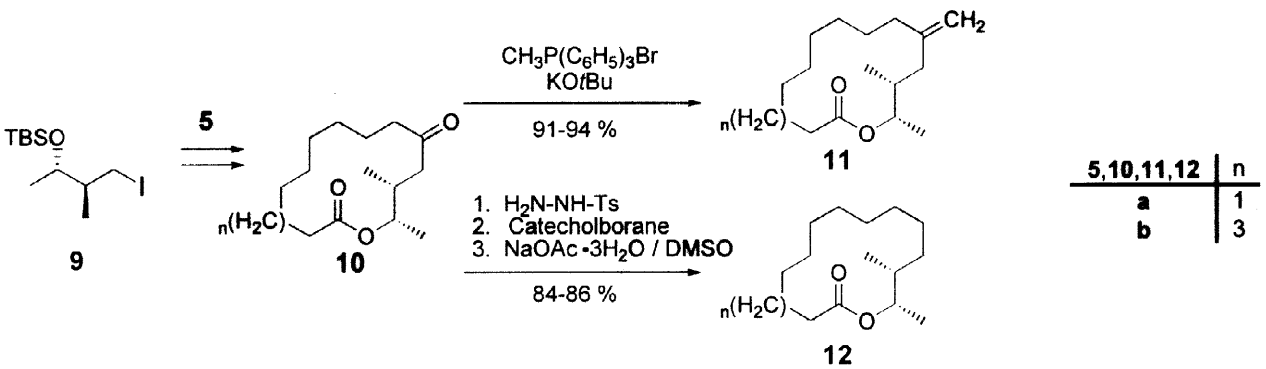
In contrast to the enantiomers of 13-tetradecanolide [5b], which possess a very similar woody combination odour with a faint musk-like character, the olfactory evaluation of enantiomeric ethyl macrolides **3a,c** showed striking differences in the odour characteristics. According to Table 1 the (*R*)-enantiomer **3a** has a weak and musty musk note, while its (*S*)-enantiomer **3c** differs significantly by a more pronounced woody note with a distinct fresh and fruity musk odour.

* Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.

The introduction of a methylene substituent into (*R*)-**3a** and (*S*)-**3c** has a dramatic effect on the olfactory properties and the most impressive fact is that now the enantiomer (*R*)-**8a** with opposite configuration smells more appealing.

In case of the higher homologues **8b,d** the methylene group caused a significant drop in the olfactory properties compared to the non methylenated macrolides **3b,d**. The methylene lactones **8b,d** are almost odourless, whereas both enantiomers **3b,d** smell similar to each other. Interestingly, the (*R*)-enantiomer **3b**, possesses a more distinct powdery musk note with a pleasant soft and slightly fresh odour impression which is quite superior to its enantiomer **3d**.

It seemed rather surprising to us and even unpredictable how the introduction of the methylene substituent shifts the olfactory properties, so we decided to further investigate structural isomers of **3c,d** and **8c,d** which have a structural variation in close distance to the lactone osmophore.



Scheme 5: Structural variations of macrolides **3c,d** and **8c,d**.

The structural isomers **11a,b** of methylenated macrolides **8c,d** are easily obtained from the corresponding keto lactones **10** as described above (Scheme 5). The synthesis of chiral intermediate **10a** and further transformation to **12a** is described in the preceding publication [12], while keto lactone **10b** was prepared by ring enlargement of **5b** employing chiral building block **9** [12] according to our general procedure without purification of intermediates. Reduction of crude **10b** yielded saturated lactone **12b** in 86% yield.

The structural variation of methylene lactones **8c,d** is accompanied by a dramatic change in odour quality and quantity. While **8c** possesses a weak musk odour with a musty-woody tonality and **8d** is even odourless, the olfactory evaluation of **11** disclosed more pleasant and also stronger musk notes. It is clearly fascinating how the introduction of the methylene substituent into **12b** transforms its weak and musty odour impression into the precious, erogenous and animalic one of **11b**.

Table 2.
Olfactory properties of macrolides **11**.

Compound	Olfactory properties*
11a	strong but odd musk note, strong and distinct woody odour with a sweet note, aniseed like
11b	natural erogenous, animalic, very elegant and noble musk note, resemblance to ambrettolide
12a	strong woody note with a relatively pronounced musk note
12b	very weak, musty

Conclusion

In summary we have shown that the stereoselective introduction of ethyl groups into macrolides *via* our ring-enlargement sequence leads to compounds with interesting odour sensations. This result is rather unexpected because in other cases the presence of ethyl or ethylidene groups cancels the musk note almost completely [6,13]. Further transformations of keto lactones **7** and **10** open the access to new fragrances [13].

Our results clearly indicate, that the introduction of functionality at positions far distant from the osmophore group tends to decrease (**8b,d**) or even reverse (**3a→8a**, **3c→8c**) the way of odour sensation in the olfactory process. A possible explanation for this interesting effect could be that the semicyclic methylene substituent alters the preference of the binding orientation of the macrocycle to the musk receptor or probably serves itself as polar binding site. Furthermore, structural variations in close distance to the lactone osmophore highly influence the odour sensation. This finding however is rather less surprising than the results described above.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1600 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra (reference: TMS int) were taken in $CDCl_3$ on Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. EI (70 eV) and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Gas chromatography (GC) was performed on a Satochrom gas chromatograph equipped with a 50 m PM β-cyclodextrin column (J&W),

* Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.

carrier gas H_2 (1.5 bar). Column chromatography was performed on Baker silicagel 30-60 μm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 spectropolarimeter in $CHCl_3$ using 1 dm cells. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach. Yeast reductions were performed according to the cited literature procedures using normal laboratory equipment. Yeast purchased from Deutsches Hefewerk Hamburg performed very well for the indicated transformations. Yields and optical rotations are in agreement with literature data. For details see ref. [13].

Yeast reductions

Preparation of chiral β-hydroxy esters

*Octyl (3S)-(+)-3-hydroxypentanoate (**4a**)* [10]. Scale 65.7 mmol, yield 65% (9.84 g), hR_f 23, (*n*-pentane:Et_2O, 5:1); $[\alpha]_D^{22}$ +22.5, $[\alpha]_{546}^{22}$ +26.6 (c = 4.0, $CHCl_3$) [ref. [16] $[\alpha]_D^{RT}$ +21.7 (c 5.9, $CHCl_3$)].

*Methyl (3R)-(-)-3-hydroxypentanoate (**4b**)* [11]. Scale 138 mmol, yield 63% (23.0 g), hR_f 31, (*n*-pentane:Et_2O, 1:1); $[\alpha]_D^{21}$ -36.4, $[\alpha]_{546}^{21}$ -43.0 (c = 3.9, $CHCl_3$).

Preparation of Chiral Building Blocks 6

General Procedure: See ref. [5a,b]

*(3S)-(+)-(tert-Butyldimethyl)-(1-iodopentyl-3-oxy)silane (**6a**).* Scale 39.1 mmol of octyl (3*S*)-(+)-3-hydroxypentanoate (**4a**) [10], yield 89% (11.4 g), hR_f 34 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 835 (s, ν_s Si-O-C), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.09 / 0.07 (2s, 6H, Si*Me*$_2$), 0.87 (t, *J* = 7.5 Hz, 3H, 5-H_3), 0.89 (s, 9H, C*Me*$_3$), 1.48 (ddd, *J* = 5.5, 7.5 and 13.7 Hz, 1H, 4-H_b), 1.49 (ddd, *J* = 5.9, 7.5 and 13.7 Hz, 1H, 4-H_a), 1.94 (dddd, *J* = 6.3, 7.7, 6.3 and 14.2 Hz, 1H, 2-H_b), 1.96 (dddd, *J* = 4.8, 7.5, 7.5 and 14.2 Hz, 1H, 2-H_a), 3.18 (ddd, *J* = 9.5, 7.7 and 7.5 Hz, 1H, 1-H_b), 3.24 (ddd, *J* = 9.5, 6.9 and 6.3 Hz, 1H, 1-H_a), 3.67 (dddd, *J* = 5.9, 5.7, 5.5 and 5.2 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.29 /-4.41 (2q, Si*Me*$_2$), 3.59 (t, C-1), 9.18 (q, C-5), 18.09 (s, *C*Me$_3$), 25.90 (q, C*Me*$_3$), 29.55 (t, C-4), 40.32 (t, C-2), 73.14 (d, C-3); MS (CI, %) m/z 329 (41) [$M^{\oplus}$ + H], 271 (5) [$M^{\oplus}$ - C_4H_9], 201 (14) [$M^{\oplus}$ - I], 197 (4) [$M^{\oplus}$ - $C_6H_{15}OSi$]; $[\alpha]_D^{22}$ +38.0, $[\alpha]_{546}^{22}$ +45.0 (c 2.1, $CHCl_3$).

*(3R)-(-)-(tert-Butyldimethyl)-(1-iodopentyl-3-oxy)silane (**6b**).* Scale 40.0 mmol of methyl (3*R*)-(-)-3-hydroxypentanoate (**4b**) [11], yield 75% (9.80 g), hR_f 34 (*n*-pentane); $[\alpha]_D^{22}$ -35.5, $[\alpha]_{546}^{22}$ -42.8 (c 4.0, $CHCl_3$).

Alkylations of Cycloalkanones 5 by Chiral Building Blocks 6 and 9, Subsequent Cyclisation and Oxidative Cleavage to Oxo Lactones 7 and 10b

General procedure: See ref. [5b,d]

(13R)-(+)-10-Oxo-13-pentadecanolide (7a). Scale 11.7 mmol of **6b**, yield 67% (2.00 g), hR_f 28 (*n*-pentane:Et_2O, 5:1), mp 39-40 °C; $[\alpha]_D^{22}$ +2.5, $[\alpha]_{546}^{22}$ +3.8 (c = 2.0, $CHCl_3$); Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.87, H 10.25.

(15R)-12-Oxo-15-heptadecanolide (7b). Scale 17.8 mmol of **6b**, yield 46% (2.33 g), hR_f 39 (*n*-pentane:Et_2O, 5:1).

(13S)-(-)-10-Oxo-13-pentadecanolide (7c). Scale 11.7 mmol of **6a**, yield 57% (1.70 g), hR_f 28 (*n*-pentane:Et_2O, 5:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1716 (s, ν C=O, lactone), 1703 (s, ν C=O, ketone), 1260 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.90 (t, J = 7.5 Hz, 3H, 15-H_3), 1.18 - 1.41 (m, 8H, 4-H_2 - 7-H_2), 1.55 (m_C, 1H, 14-H_b), 1.60 - 1.70 (m, 4H, 8-H_2 and 3-H_2), 1.62 (m_C, 1H, 14-H_a), 1.78 (m_C, 1H, 12-H_b), 1.94 (m_C, 1H, 12-H_a), 2.27 - 2.32 (m, 2H, 2-H_b and 9-H_b), 2.36 - 2.43 (m, 2H, 2-H_a and 9-H_a), 2.47 (ddd, J = 18.1, 9.2 and 4.1 Hz, 1H, 11-H_b), 2.60 (ddd, J = 18.1, 9.1 and 6.7 Hz, 1H, 11-H_a), 4.90 (dddd, J = 6.9, 8.6, 6.0 and 2.7 Hz, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 9.70 (q, C-15), 23.82 / 24.71 (t, C-3 and C-8), 25.61 / 25.85 / 26.03 / 26.17 / 26.81 (t, C-4 - C-7 and C-14), 27.03 (t, C-12), 34.45 (t, C-2), 36.21 (t, C-11), 42.40 (t, C-9), 74.33 (d, C-13), 173.62 (s, C-1), 211.64 (s, C-10); MS (EI, %) m/z 254 (34) [$M^{\oplus}$], 236 (16) [$M^{\oplus}$ - H_2O], 225 (23) [$M^{\oplus}$ - C_2H_5], 141 (20) [$C_8H_{13}O_2^{\oplus}$]; $[\alpha]_D^{22}$ -4.4, $[\alpha]_{546}^{22}$ -5.5 (c 2.0, $CHCl_3$); Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.87, H 10.25.

(15S)-12-Oxo-15-heptadecanolide (7d). Scale 15.2 mmol of **6a**, yield 47% (2.00 g), hR_f 39 (*n*-pentane:Et_2O, 5:1).

(14R,15S)-(+)-14-Methyl-12-oxo-15-hexadecanolide (10b). Scale 12.2 mmol of **5b** and 12.2 mmol of **9**, yield 56% (1.92 g), hR_f 38 (*n*-pentane:Et_2O, 5:1).

Chemoselective Reductions of Oxo Lactones 7 and 10 to Lactones 3 and 12

General procedure: See ref. [5d]

(13R)-(-)-13-Pentadecanolide (3a). Scale 2.36 mmol of **7a**, yield 89% (505 mg), hR_f 28 (*n*-pentane:Et_2O, 50:1); $[\alpha]_D^{22}$ -13.3, $[\alpha]_{546}^{22}$ -15.4 (c 1.0, $CHCl_3$); GC (100°C, 2°C/min to 180°C: >91.0%ee; Anal calcd for $C_{15}H_{28}O_2$ (240.4), C 74.95, H 11.74; found C 74.91, H 11.68.

(15R)-(-)-15-Heptadecanolide (3b). Scale 4.09 mmol of **7b**, yield 90% (988 mg), hR_f 30 (*n*-pentane:Et_2O, 40:1); $[\alpha]_D^{22}$ -4.5, $[\alpha]_{546}^{22}$ -5.2 (c 3.7, $CHCl_3$); Anal calcd for $C_{17}H_{32}O_2$ (268.4), C 76.06, H 12.01; found C 76.09, H 12.02.

(13S)-(+)-13-Pentadecanolide (3c). Scale 2.67 mmol of **7c**, yield 81% (521 mg), hR_f 28 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν C=O, lactone), 1247 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, J = 7.5 Hz, 3H, 15-H_3), 1.17 - 1.43 (m, 16H, 4-H_2 - 11-H_2), 1.51 (m_C, 1H, 12-H_b), 1.53 (m_C, 1H, 14-H_b), 1.58 (m_C, 1H, 12-H_a), 1.59 (m_C, 1H, 3-H_b), 1.61 (m_C, 1H, 14-H_a), 1.73 (m_C, 1H, 3-H_a), 2.29 (ddd, J = 14.5, 8.3 and 3.5 Hz, 1H, 2-H_b), 2.43 (ddd, J = 14.5, 9.6 and 3.3 Hz, 1H, 2-H_a), 4.88 (m_C, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 9.89 (q, C-15), 24.89 (t, C-3), 27.12 (t, C-14), 26.39 / 25.92 / 25.86 / 25.80 / 25.43 / 23.89 / 23.71 / 21.68 (t, C-4 - C-11), 32.49 (t, C-12), 34.22 (t, C-2), 74.96 (d, C-13), 173.86 (s, C-1); MS (EI, %) m/z 240 (16) [$M^{\oplus}$], 222 (59) [$M^{\oplus}$ - H_2O], 211 (76) [$M^{\oplus}$ - C_2H_5], 182 (54) [$M^{\oplus}$ - $C_2H_2O_2$]; $[\alpha]_D^{24}$ +13.3, $[\alpha]_{546}^{24}$ +15.6 (c 3.9, $CHCl_3$); GC (100°C, 2°C/min to 180°C: >98.0%ee; Anal calcd for $C_{15}H_{28}O_2$ (240.4), C 74.95, H 11.74; found C 75.07, H 11.76.

(15S)-(+)-15-Heptadecanolide (3d). Scale 3.54 mmol of **7d**, yield 91% (865 mg), hR_f 30 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (s, ν C=O, lactone), 1173 (s, ν C-O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, J = 7.5 Hz, 3H, 17-H_3), 1.22 - 1.41 (m, 20H, 4-H_2 - 13-H_2), 1.45 - 1.63 (m, 4H, 14-H_2 and 16-H_2), 1.58 (m_C, 1H, 3-H_b), 1.78 (m_C, 1H, 3-H_a), 2.30 (ddd, J = 14.4, 6.8 and 6.2 Hz, 1H, 2-H_b), 2.34 (ddd, J = 14.4, 8.3 and 5.9 Hz, 1H, 2-H_a), 4.87 (m_C, 1H, 15-H); ^{13}C NMR ($CDCl_3$, ppm) δ 9.78 (q, C-17), 25.01 (t, C-3), 24.24 / 25.57 / 25.72 / 25.99 / 26.24 / 26.59 / 27.28 / 27.39 / 27.40 / 27.74 / 27.84 (t, C-4 - C-13, and C-16), 33.58 (t, C-14), 34.67 (t, C-2), 75.28 (d, C-15), 173.90 (s, C-1); MS (EI, %) m/z 268 (28) [$M^{\oplus}$], 250 (100) [$M^{\oplus}$ - H_2O], 239 (62) [$M^{\oplus}$ - C_2H_5], 210 (47) [$M^{\oplus}$ - $C_2H_2O_2$]; $[\alpha]_D^{22}$ +4.9, $[\alpha]_{546}^{22}$ +5.7 (c 3.5, $CHCl_3$); Anal calcd for $C_{17}H_{32}O_2$ (268.4), C 76.06, H 12.01; found C 75.94, H 12.14.

(14R,15S)-(+)-14-Methyl-15-hexadecanolide (12b). Scale 3.40 mmol of **10b**, yield 86% (785 mg), hR_f 34 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (s, ν C=O, lactone), 1178 (s, ν C-O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (d, J = 6.8 Hz, 3H, 14-Me), 1.19 (d, J = 6.3 Hz, 3H, 16-H_3), 1.21 - 1.50 (m, 16H, 5-H_2 - 12-H_2), 1.08 (m_C, 1H, 4-H_b), 1.22 (m_C, 1H, 13-H_b), 1.42 (m_C, 1H, 13-H_a), 1.53 (m_C, 1H, 4-H_a), 1.59 (m_C, 1H, 14-H), 1.60 (m_C, 1H, 3-H_b), 1.72 (m_C, 1H, 3-H_a), 2.26 (ddd, J = 14.3, 6.8 and 6.7 Hz, 1H, 2-H_b), 2.32 (ddd, J = 14.3, 7.8 and 6.5 Hz, 1H, 2-H_a), 4.66 (dq, J = 8.2 and 6.2 Hz, 1H, 15-H); minor diastereomer δ 4.95 (dq, J = 13.1 and 3.6 Hz, 1H, 15-H, 3.5%, 93 %de); ^{13}C NMR ($CDCl_3$, ppm) δ 15.53 (q, 14-Me), 18.17 (q, C-16), 24.72 (t, C-13), 24.85 (t, C-3), 25.53 / 25.93 / 26.20 / 26.26 / 26.38 / 27.04 / 27.48 / 27.55 (t, C-5 - C-12), 31.32 (t, C-4), 34.95 (t, C-2), 37.92 (d, C-14), 74.78 (d, C-15), 173.68 (s, C-1); MS (EI, %) m/z 268 (18) [$M^{\oplus}$], 250 (9) [$M^{\oplus}$ - H_2O], 239 (11) [$M^{\oplus}$ - C_2H_5], 224 (100) [$M^{\oplus}$ - C_2H_4O]; $[\alpha]_D^{22}$ +27.4, $[\alpha]_{546}^{22}$ +32.8 (c 3.0, $CHCl_3$); Anal calcd for $C_{17}H_{32}O_2$ (268.4), C 76.06, H 12.01; found C 76.03, H 12.14.

Wittig Reactions of Keto Lactones 7 and 10 to Macrolides 8 and 11

General procedure: A suspension of methyltriphenylphosphonium bromide (3.96 g, 11.1 mmol) and KO*t*Bu (1.16 g, 10.4 mmol) in anhydrous THF (40 mL) was heated at reflux for 30 min. The dark yellow mixture was allowed to cool to room temp before a solution of **7b** (1.15 g, 4.09 mmol) in dry THF (20 mL) was injected. The reaction mixture was heated for another1.5 h, then cooled to room temp and poured into Et_2O/H_2O (1:1, 150 mL), the organic layer was separated and the aqueous was extracted with Et_2O (3x 100 mL). The combined extracts were washed with brine (100 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica-gel column chromatography, hR_f 38 (*n*-pentane:Et_2O, 40:1), furnished **8b** (1.08 g, 94%) as colourless oil.

(13R)-(+)-10-Methylene-13-pentadecanolide (8a). Scale 2.67 mmol of **7a**, yield 90% (606 mg), hR_f 32 (*n*-pentane:Et_2O, 40:1); $[\alpha]_D^{22}$ +5.8, $[\alpha]_{546}^{22}$ +6.9 (c 2.5, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_2$ (252.4), C 76.14, H 11.18; found C 76.16, H 11.27.

(15R)-(-)-12-Methylene-15-heptadecanolide (8b). $[\alpha]_D^{24}$ -1.4, $[\alpha]_{546}^{24}$ -1.6 (c 3.4, $CHCl_3$); Anal calcd for $C_{18}H_{32}O_2$ (280.4), C 77.09, H 11.50; found C 77.15, H 11.45.

(13S)-(-)-10-Methylene-13-pentadecanolide (8c). Scale 2.36 mmol of **7c**, yield 81% (482 mg), hR_f 32 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 3069 (w, ν C-H exo methylene), 1732 (s, ν C=O, lactone), 1644 (m, ν C=CH_2), 1221 (s, ν C-CO-O, lactone), 889 (s, ν C-H exo-methylene); ^1H NMR ($CDCl_3$, ppm) δ 0.91 (t, *J* = 7.5 Hz, 3H, 15-H_3), 1.16 - 1.50 (m, 8H, 4-H_2 - 7-H_2), 1.35 (m_C, 1H, 8-H_b), 1.45 (m_C, 1H, 8-H_a), 1.58 (m_C, 1H, 3-H_b), 1.59 (m_C, 2H, 14-H_2), 1.65 (m_C, 1H, 12-H_a), 1.76 (m_C, 1H, 12-H_b), 1.77 (m_C, 1H, 3-H_a), 2.02 (m_C, 3H, 9-H_b and 11-H_2), 2.15 (m_C, 1H, 9-H_a), 2.32 (ddd, *J* = 14.7, 7.9 and 3.5 Hz, 1H, 2-H_b), 2.43 (ddd, *J* = 14.7, 10.1 and 3.3 Hz, 1H, 2-H_a), 4.68 (dddd, *J* = 2.0, 1.9, 1.8 and 0.5 Hz, 1H, C(10)=CH_b), 4.71 (dddd, *J* = 1.1, 1.1, 2.2 and 2.0 Hz, 1H, C(10)=CH_a), 4.95 (dddd, *J* = 2.7, 7.6, 7.6 and 5.8 Hz, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 10.01 (q, C-15), 25.03 (t, C-3), 24.24 (t, C-8), 24.56 / 25.36 / 25.91 / 26.39 (t, C-4 - C-7), 26.93 (t, C-14), 28.53 (t, C-11), 31.06 (t, C-12), 33.91 (t, C-2), 33.66 (t, C-9), 75.02 (d, C-13), 110.04 (t, C(10)=CH_2), 148.78 (s, C-10), 173.84 (s, C-1); MS (EI, %) m/z 252 (30) [$M^{\oplus}$], 237 (3) [$M^{\oplus}$ - CH_3], 223 (5) [$M^{\oplus}$ - C_2H_5], 181 (4) [$M^{\oplus}$ - C_5H_{11}]; $[\alpha]_D^{22}$ -6.5, $[\alpha]_{546}^{22}$ -7.7 (c 3.1, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_2$ (252.4), C 76.14, H 11.18; found C 76.19, H 11.08.

(15S)-(+)-12-Methylene-15-heptadecanolide (8d). Scale 3.54 mmol of **7d**, yield 92% (913 mg), hR_f 31 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 3074 (w, ν C-H exo-methylene), 1732 (s, ν C=O, lactone), 1644 (m, ν C=CH_2), 1250 (s, ν C-CO-O, lactone), 888 (s, ν C-H exo-methylene); ^1H NMR ($CDCl_3$, ppm) δ 0.90 (t, *J* = 7.5 Hz, 3H, 17-H_3), 1.24 - 1.46 (m, 14H, 4-H_2 - 10-H_2), 1.60 (m_C, 2H, 16-H_2), 1.61 (m_C, 1H, 3-H_b), 1.68 (m_C, 2H, 14-H_2), 1.73 (m_C, 1H,

3-H_a), 1.96 - 2.12 (m, 4H, 11-H_2 and 13-H_2), 2.30 (ddd, J = 14.3, 6.8 and 6.2 Hz, 1H, 2-H_b), 2.34 (ddd, J = 14.3, 8.3 and 6.0 Hz, 1H, 2-H_a), 4.69 (*br*, ddd, J = 1.9, 1.8 and 1.7 Hz, 1H, C(12)=CH_b), 4.73 (dddd, J = 1.0, 1.0, 1.0 and 1.8 Hz, 1H, C(12)=CH_a), 4.89 (dddd, J = 4.5, 7.2, 7.2 and 5.8 Hz, 1H, 15-H); ^{13}C NMR ($CDCl_3$, ppm) δ 9.75 (q, C-17), 24.95 (t, C-3), 25.63 / 26.15 / 26.22 / 26.41 / 26.56 / 27.24 / 27.26 / 27.67 (t, C-4 - C-10, C-16), 30.52 (t, C-11), 31.88 (t, C-14), 34.65 (t, C-2), 36.39 (t, C-13), 75.08 (d, C-15), 109.32 (t, C(12)=CH_2), 149.45 (s, C-12), 173.87 (s, C-1); MS (EI, %) m/z 280 (37) [$M^{\oplus}$], 265 (3) [$M^{\oplus}$ - CH_3], 251 (6) [$M^{\oplus}$ - C_2H_5], 237 (10) [$M^{\oplus}$ - C_3H_7]; $[\alpha]_D^{22}$ +1.3, $[\alpha]_{546}^{22}$ +1.5 (c 3.7, $CHCl_3$); Anal calcd for $C_{18}H_{32}O_2$ (280.4), C 77.09, H 11.50; found C 77.01, H 11.50.

*(12R,13S)-(-)-12-Methyl-10-methylene-13-tetradecanolide (**11a**).* Scale 2.36 mmol of **10a** [12], yield 91% (542 mg), hR_f 22 (*n*-pentane:Et_2O, 60:1); IR (film, cm^{-1}) $\tilde{\nu}$ 3069 (w, ν C-H exo methylene), 1731 (s, ν C=O, lactone), 1642 (m, ν C=CH_2), 1226 (s, ν C-CO-O, lactone), 893 (s, ν C-H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 0.82 (d, J = 6.5 Hz, 3H, 12-Me), 1.22 (d, J = 6.3 Hz, 3H, 14-H_3), 1.10 - 1.62 (m, 6H, 5-H_2 - 7-H_2), 1.15 (m_C, 1H, 8-H_b), 1.25 (m_C, 1H, 4-H_b), 1.37 (m_C, 1H, 4-H_a), 1.57 (m_C, 1H, 3-H_b), 1.58 (m_C, 1H, 8-H_a), 1.68 (m_C, 1H, 12-H), 1.88 (m_C, 1H, 3-H_a), 2.00 (m_C, 1H, 9-H_b), 2.25 (m_C, 1H, 9-H_a), 1.58 (m_C, 1H, 11-H_b), 2.40 (m_C, 1H, 11-H_a), 2.32 (ddd, J = 14.5, 7.3 and 3.3 Hz, 1H, 2-H_b), 2.45 (ddd, J = 14.5, 11.2 and 3.3 Hz, 1H, 2-H_a), 4.69 (m_C, 1H, C(10)=H_b), 4.72 (dq, J = 9.7, and 6.3 Hz, 1H, 13-H), 4.73 (m_C, 1H, C(10)=H_a); ^{13}C NMR ($CDCl_3$, ppm) δ 15.04 (q, 12-Me), 18.89 (q, C-14), 23.45 (t, C-8), 25.11 (t, C-3), 25.40 (t, C-4), 24.05 / 24.75 / 26.52 (t, C-5 - C-7), 33.71 (t, C-2), 34.11 (t, C-9), 35.79 (d, C-12), 39.19 (t, C-11), 75.07 (d, C-13), 113.05 (t, C(10)=CH_2), 146.71 (s, C-10), 173.80 (s, C-1); MS (EI, %) m/z 252 (16) [$M^{\oplus}$], 237 (5) [$M^{\oplus}$ - CH_3], 223 (10) [$M^{\oplus}$ - C_2H_5]; $[\alpha]_D^{22}$ -5.0, $[\alpha]_{546}^{22}$ -6.5 (c 2.2, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_2$ (252.4), C 76.14, H 11.18; found C 76.09, H 11.10.

*(14R,15S)-(+)-14-Methyl-12-methylene-15-hexadecanolide (**11b**).* Scale 3.40 mmol of **10b**, yield 94% (896 mg), hR_f 38 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 3069 (w, ν C-H exo-methylene), 1732 (s, ν C=O, lactone), 1642 (m, ν C=CH_2), 1249 (s, ν C-CO-O, lactone), 892 (s, ν C-H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 0.85 (d, J = 6.7 Hz, 3H, 14-Me), 1.20 (d, J = 6.3 Hz, 3H, 16-H_3), 1.24 - 1.45 (m, 14H, 4-H_2 - 10-H_2), 1.57 (m_C, 1H, 3-H_b), 1.60 (m_C, 1H, 13-H_b), 1.66 (m_C, 1H, 3-H_a), 1.76 (m_C, 1H, 14-H), 1.92 (m_C, 1H, 11-H_b), 2.04 (m_C, 1H, 11-H_a), 2.27 (m_C, 2H, 2-H_2), 2.31 (m_C, 1H, 13-H_a), 4.67 (dq, J = 7.5 and 6.3 Hz, 1H, 15-H), 4.69 (dddd, J = 1.6, 1.6, 0.9 and 0.8 Hz, 1H, C(12)=CH_b), 4.78 (*br*, ddd, J = 2.4, 2.4 and 0.9 Hz, 1H, C(12)=CH_a); ^{13}C NMR ($CDCl_3$, ppm) δ 14.50 (q, 14-Me), 17.10 (q, C-16), 24.63 (t, C-3), 25.88 / 25.90 / 26.23 / 26.45 / 26.77 / 26.92 / 27.19 (t, C-4 - C-10), 34.82 (t, C-2), 34.88 (t, C-11), 35.70 (d, C-14), 39.20 (t, C-13), 74.62 (d, C-15), 112.17 (t, C(12)=CH_2), 147.42 (s, C-10),

173.65 (s, C-1); MS (EI, %) m/z 252 (16) [$M^{\oplus}$], 237 (5) [$M^{\oplus}$ - CH_3], 223 (10) [$M^{\oplus}$ - C_2H_5]; $[\alpha]_D^{22}$ +2.5, $[\alpha]_{546}^{22}$ +2.7 (c 4.0, $CHCl_3$); Anal calcd for $C_{18}H_{32}O_2$ (280.4), C 77.09, H 11.50; found C 76.97, H 11.45.

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