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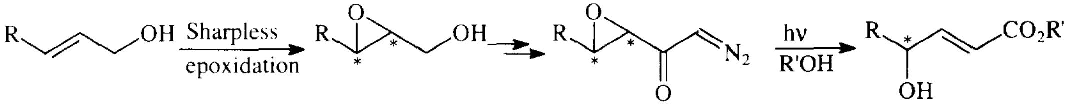
Synthesis of (4R,5R)-Muricatacin and its (4R,5S)-Analog by Sequential Use of the Photo-Induced Rearrangement of Epoxy Diazomethyl Ketones

Marcel P.M. van Aar, Lambertus Thijs and Binne Zwanenburg*

Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis,
University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Abstract: *The naturally occurring δ-hydroxy-γ-lactone (4R,5R)-muricatacin and its nonnatural (4R,5S)-analog are synthesized. The starting achiral allylic alcohols are converted into α,β-epoxy diazomethyl ketones followed by a stereospecific irradiation reaction of these compounds to give 4-hydroxy-2-alkene esters. Using this method in a sequential manner a successive introduction of stereogenic centers is realized, resulting in enantiopure 4,5-dihydroxy-2-alkene esters. These alcohols are converted into the δ-hydroxy-γ-lactone muricatacin.*

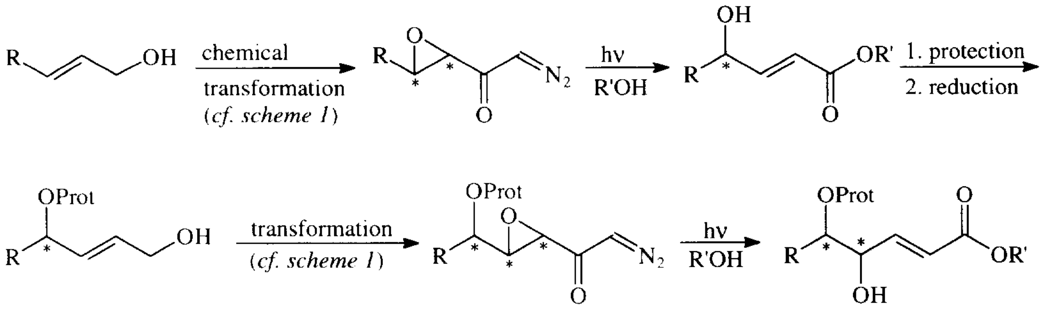
The photo-induced rearrangement of α,β-epoxy diazomethyl ketones in an alcoholic solvent is a convenient synthetic route to 4-hydroxy-2-alkene esters (scheme 1)[1]. The chiral integrity of the stereogenic center at the β-carbon atom of the epoxide function is retained in the product and therefore 4-hydroxy-2-alkene esters with defined stereochemistry at the C_4 carbon atom can be prepared[2]. This synthetic methodology was utilized for the total synthesis of a series of natural products, *viz.* aspicilin[3], colletallol[4], pyrenophorol[5], patulolid C[6,7] and isopatulolid C[7] and also for the macrocylic subunit of cytochalasin B[8]. Hydrogenation of the 4-hydroxy-2-alkene esters gives γ-hydroxy carboxylic esters, which readily give ring closure to yield enantiopure γ-lactones[9]. This method has successfully been applied in the synthesis of the naturally occurring γ-lactone rubrenolide[10].



Scheme 1

Recently the stereoselective synthesis of 4,5-dihydroxy-2-alkene esters was realized, starting with readily available enantiopure allylic alcohols that contain a protected secondary alcohol function at C_4 and using the photo-induced rearrangement of α,β-epoxy diazomethyl ketones[11].

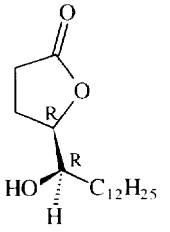
An attractive extension of the sequence of reactions depicted in scheme 1 would be if the starting allylic alcohol could be prepared from a 4-hydroxy-2-alkene ester which is synthesized by the same methodology from a simple achiral allylic alcohol. The proposed sequential use of the Sharpless epoxidation[12] is depicted in scheme 2.



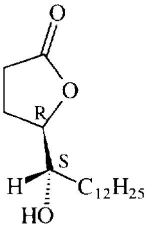
Scheme 2

This sequence of reactions has the attractive feature that the stereochemistry of the respective stereogenic centers in the ultimate product can be controlled at will simply by choosing the right chiral inductor in the sequential Sharpless epoxidations. 4,5-Dihydroxy-2-alkene esters can also be obtained by employing the Sharpless asymmetric dihydroxylation[13] using an osmium containing reagent. However, with this methodology the newly introduced alcohol functions at adjacent carbon atoms always have a *syn* relationship. Besides this, the asymmetric dihydroxylation of a *cis*-alkene does not proceed with high enantiomeric excess[14]. The proposed scheme 2 has the advantage of being completely flexible.

The strategy depicted in scheme 2 was applied in the total synthesis of the naturally occurring γ-lactone (4R,5R)-muricatacin **1**[15] and its unnatural (4R,5S) diastereomer **2**. In the last few years muricatacin **1** has been the subject of several synthetic studies[16]. However, none of these routes is a general synthetic method to enantiopure δ-hydroxy-γ-lactones. The so-called 'L-factors'[17,18], which also are δ-hydroxy-γ-lactones, demonstrate the importance of these types of compounds as targets for the evaluation of new synthetic methods.

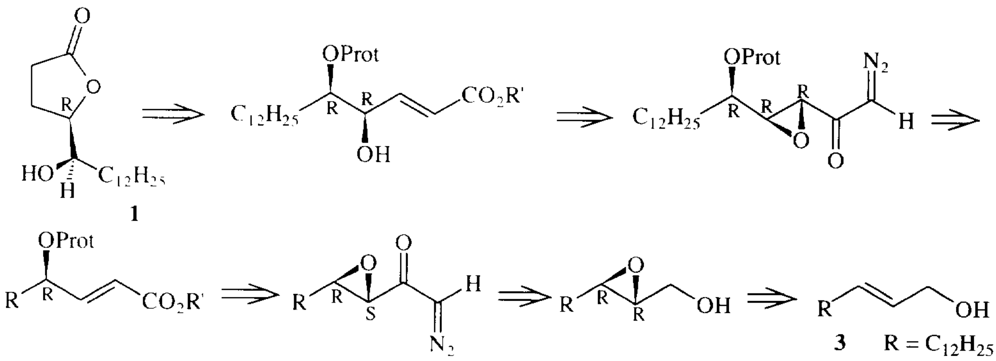


(4R,5R)-muricatacin **1**



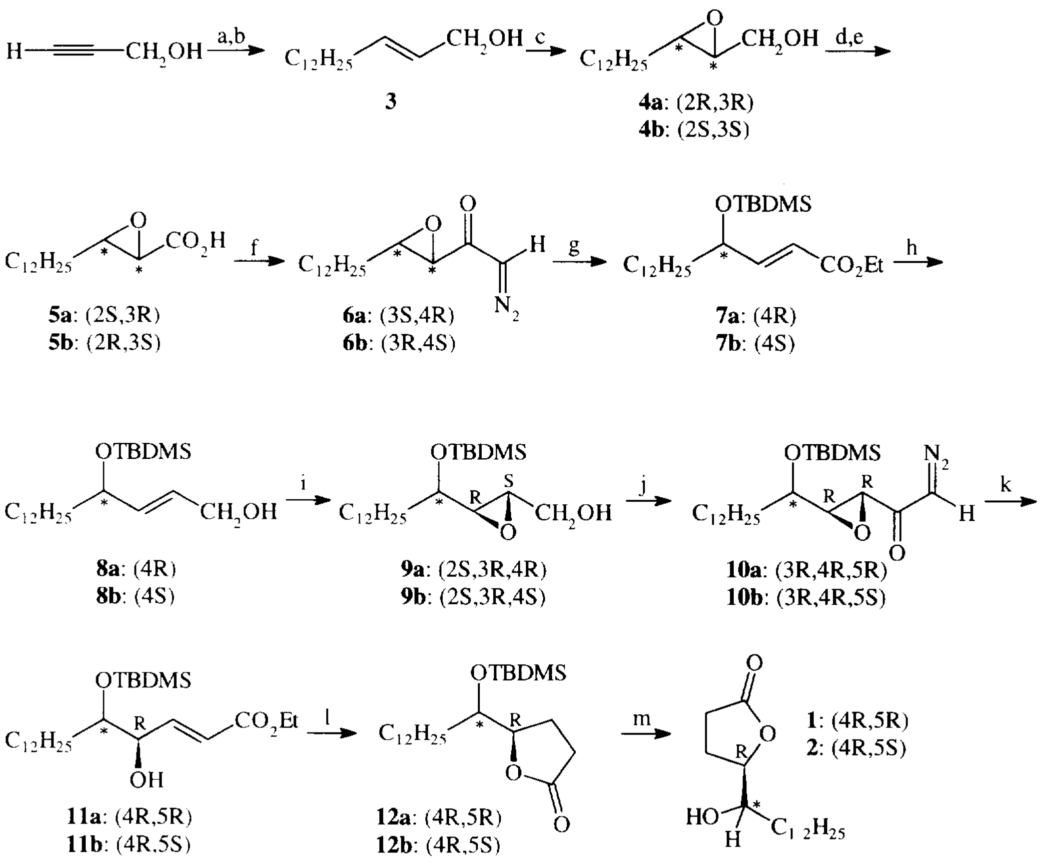
(4R,5S) diastereomer **2**

The retrosynthetic analysis of natural (4R,5R)-muricatacin, which makes use of the strategy shown in scheme 2, is presented in scheme 3. In principle, the lactone can be obtained from a 4,5-dihydroxy-2-alkenoate with the C_5 alcohol function selectively protected. The same retrosynthesis holds for the unnatural (4R,5S)-diastereomer, the only difference being the choice of the chiral inductor in the first Sharpless epoxidation.



Scheme 3

The actual synthesis is outlined in scheme 4. The required starting allylic alcohol **3** was readily obtained by a chain elongation of dodecyl bromide with the three-carbon unit of propargyl alcohol and subsequent reduction of the triple bond with LiAlH$_4$[9]. Asymmetric epoxidation of allylic alcohol **3** using D-DET as chiral inductor resulted in epoxy alcohol **4a** with the (2R,3R) configuration. This alcohol was converted into the corresponding carboxylic acid **5a** by a two-step procedure involving first the Swern oxidation[19] to the aldehyde and subsequently oxidation with sodium chlorite[20] to the acid. Diazomethyl ketone **6a** was prepared by a standard series of operations[9]. Irradiation of this diazo compound in ethanol gave the 4-hydroxy-2-alkene ester, which was silylated to derivative **7a**. The ester thus obtained was reduced with DIBAL-H to give the allylic alcohol **8a** for the second Sharpless epoxidation. It should be noted that this epoxidation was only successful when allylic alcohol **8a** was added to the reaction mixture prior to *tert*-butyl hydroperoxide. Reversed addition gave no epoxidation at all. With comparable allylic alcohols, all containing an alkoxy group at C$_4$, the same procedure was used in literature[21]. The oxidation of epoxy alcohol **9a** was carried out with ruthenium tetroxide[22] to give the corresponding carboxylic acid in one step. Under these oxidation conditions the silyl ether protecting function turned out to be stable. The oxidation used in the first part of the sequence, namely the Swern oxidation, gave poor results. The carboxylic acid was converted into epoxy diazomethyl ketone **10a** in the usual manner[9], which then was subjected to irradiation in ethanol as the solvent. The resulting alkene ester **11a** was then hydrogenated by using P-2 Nickel as the catalyst. The alkene ester was added to a solution of Ni(OAc)$_2$ in ethanol, followed by the addition of a NaBH$_4$/ethanol solution. It was possible to perform this reduction of alkene ester **11a** as obtained from the irradiation reaction, without additional purification and without a hydrogen atmosphere. During the reduction of the carbon double bond in **11a** partial lactonization to **12a** was observed. This lactonization was completed by treatment of the lactone/ester mixture with *p*-toluenesulfonic acid in benzene. Finally silyl ether **12a** was deprotected to give the desired (4R,5R)-muricatacin **1**, m.p. 72.5-73°C and $[\alpha]^{25}_{D}$ -23.3° (c = 0.5 in CHCl$_3$). These physical data as well as the spectral features (^{1}H-NMR, ^{13}C-NMR, IR, MS) were identical with those reported for the natural (4R,5R) product[16a,b,e,f,g].



muricatacin epimers	(4R,5R)	(4R,5S)		(4R,5R)	(4R,5S)
a. $C_{12}H_{25}Br$, $LiNH_2$, NH_3(l)	80%		g. hv, EtOH; TBDMSCl	55%	60%
b. $LiAlH_4$, Et_2O/THF = 7/8	93%		h. DIBAL-H	81%	90%
c. Ti(O*i*Pr)$_4$, TBHP, -20°C, mol. sieves	85% (D-DET) ee 91%	75% (L-DET) ee>99%	i. L-(+)-DET, Ti(O*i*Pr)$_4$, TBHP -20°C, mol. sieves; de>95%	92%	83%
			j. RuO_4; $ClCO_2$*i*Bu, Et_3N; CH_2N_2	52%	42%
d. DMSO, $(ClCO)_2$, -78°C, DIPEA	88%	85%	k. hv, EtOH	50%	70%
e. $NaClO_2$, NaH_2PO_4	90%	80%	l. $Ni(OAc)_2$, $NaBH_4$; pTsOH	50%	70%
f. $ClCO_2$*i*Bu, Et_3N; CH_2N_2	60%	50%	m. TBAF	75%	80%

Scheme 4

The same sequence of reactions was used to prepare the unnatural (4R,5S) diastereomer. The essential difference was the chiral inductor in the first Sharpless epoxidation, for which now L-DET was chosen. The unnatural diastereomer obtained in this manner has a m.p. of 71.5-72°C and an $[\alpha]^{25}_{D}$ of -13.6° (c = 0.4 in $CHCl_3$). The ^{1}H-NMR spectrum of this diastereomer differs in only one signal, namely that of the C_5 proton:

(4R,5R)-muricatacin has a multiplet at 3.58 ppm, the (4R,5S)-compound at 3.93 ppm. ^{13}C-NMR, IR and MS spectra show the same characteristics.

It is important to note that the initially introduced stereogenic center does not influence the asymmetric induction during the second Sharpless epoxidation. In neither the natural nor the unnatural diastereomer could any of the other epimer be detected in the ^{1}H-NMR spectrum.

The strategic sequential use of two Sharpless epoxidations in combination with epoxy diazo ketone chemistry constitutes a flexible synthesis of δ-hydroxy-γ-lactones as illustrated by the synthesis of (4R,5R)-muricatacin and its (4R,5S)-epimer. By choosing the appropriate chiral inductor in the respective epoxidation reactions the chirality of both stereogenic centers can be selected at wish. In principle, this methodology can be extended to the introduction of several contiguous chiral centers to produce, for instance, homochiral polyhydroxylated compounds. However, the disadvantage then will be that the method is a linear synthesis and therefore the ultimate yield is strongly affected by the number of steps.

EXPERIMENTAL SECTION

General remarks:

^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AC-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. ^{13}C-NMR spectra were recorded on a Bruker AM-400 (100 MHz, FT) spectrometer with $CHCl_3$ as internal standard. IR spectra were run on a Perkin-Elmer 298 spectrophotometer. Elemental analyses were standard carried out in triplicate on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For mass spectroscopy a double focusing VG 7070E was used. For the chemical ionization (CI) technique, methane was used as reacting gas. Melting points were measured on a Reichert Thermopan microscope and are uncorrected. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. GC was performed on a Hewlett-Packard 5890 or a Hewlett-Packard 5890 Series II instrument, equipped with a capillary HP cross-linked methyl silicone (25 m x 0.31 mm) column, connected to a HP 5890 calculating integrator. For chromatography the flash technique was used with silica gel 60H (Merck) as stationary phase and a pressure of about 1.5 bar. All solvents used were dried and distilled according to standard procedures. When diazomethane was used, proper safety precautions were taken.

Pentadec-2-yn-1-ol:

To a mechanically stirred solution of lithium (100 mg) in liquid ammonia (500 ml, under nitrogen at −35°C), were added a few crystals of $Fe(NO_3)_3.9H_2O$, followed by finely cut lithium (6.45 g, 0.90 mol) in small portions over 25 min. After the mixture turned gray, it was stirred for another 30 min. Distilled propargylic alcohol (25.30 g, 0.45 mol, dissolved in 26 ml of dry THF) was added over 20 min, followed by stirring for 90 min. Dodecyl bromide (72.25 g, 0.30 mol), dissolved in THF (73 ml), was added in 1 h. The mixture was stirred overnight to evaporate the ammonia. After adding water (400 ml) and ether (400 ml), and stirring for 30 min the layers were separated and the aqueous layer was extracted with ether (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, giving crude alkynol (72.03 g), which was distilled *in vacuo* (p 1.0 mm Hg, cooling with warm water). The fraction, boiling at 138-140°C was collected, which solidified at room temperature (49.0 g, 80%). M.p. 38-41°C. ^{1}H-NMR (100 MHz): δ 0.85 (t, 3H, CH_3, J 7 Hz), 1.20-1.50 (br s, 20H, $(CH_2)_{10}$), 1.85 (br s, 1H, OH), 2.15-2.25 (m, 2H, $CH_2C{\equiv}C$), 4.25 (br s, 2H, $C\underline{H_2}OH$) ppm. IR (CCl_4): ν 3610, 3400, 2920, 2850, 2290, 2220 cm^{-1}. MS (CI): *m/e* (%) 225 (1, M^++1), 193 (7,

-CH_2OH), 149 (7), 137 (8), 135 (25), 123 (23), 121 (39), 111 (50), 109 (57), 107 (31), 97 (32), 95 (100), 93 (64), 83 (54), 81 (94), 79 (53), 70 (61), 69 (60), 67 (85), 57 (63), 55 (81), 43 (86), 41 (88).

E-*Pentadec-2-en-1-ol* (**3**):

Starting with pentadec-2-yn-1-ol (48.0 g, 0.214 mol), compound **3** was prepared according to literature procedures[9]. The crude product was purified by distillation *in vacuo* (p 0.7 mm Hg, cooling with warm water), the fraction boiling at 128-130°C was collected, which solidified at room temperature (43.5 g, 95%). M.p. 27-28°C. ^1H-NMR (100 MHz): δ 0.85 (t, 3H, CH_3, J 7 Hz), 1.20-1.45 (br s, 20H, $(CH_2)_{10}$), 1.65 (s, 1H, OH), 1.95-2.05 (m, 2H, $C\underline{H}_2CH{=}C$), 4.02-4.15 (m, 2H, $C\underline{H}_2OH$), 5.61-5.72 (m, 2H, $\underline{H}C{=}C\underline{H}$) ppm. IR ($CCl_4$): ν 3610, 3400, 2960, 2930, 2850, 1380, 970 cm^{-1}. MS (CI): *m/e* (%) 227 (1, M^++1), 226 (3, M^+), 225 (7, M^+-1), 209 (14, -H_2O), 208 (17), 153 (12), 139 (18), 137 (15), 125 (27), 123 (24), 111 (39), 109 (38), 97 (60), 95 (56), 83 (72), 81 (56), 69 (48), 67 (42), 57 (99), 55 (45), 49 (100), 43 (57), 41 (56).

(2R,3R)-2,3-epoxy-pentadecan-1-ol (**4a**):

Following literature procedures[12b], namely that for the preparation of 2,3-epoxy-octan-1-ol (using 5 mol% $Ti(OiPr)_4$ and 6 mol% D-(-)-DET), epoxy alcohol **4a** was synthesized in a total yield of 85% after recrystallization from ether. $[\alpha]^{25}_D$ + 23.6 (*c* 1.11), ee 91% (relatively low ee as compared with **4b** is due to temperature fluctuation during addition of reagents). M.p. 72.5-74°C. ^1H-NMR (100 MHz): δ 0.88 (t, 3H, CH_3, J 7 Hz), 1.26 (broad s, 20H, $(CH_2)_{10}$), 1.45-1.55 (br s, 2H, $C\underline{H}_2CHOCH$), 1.60 (s, 1H, OH), 2.96 (m, 2H, epox-H), 3.55-3.95 (m, 2H, $C\underline{H}_2OH$) ppm. ^{13}C-NMR (100 MHz): δ 14.0, 22.6, 25.8, 29.2 (2C), 29.4 (2C), 29.6 (3C), 31.4, 31.9, 55.2, 56.5, 64.7 ppm. IR (CCl_4): ν 3600-3300, 2920, 2850 cm^{-1}. MS (CI): *m/e* (%) 243 (62, M^++1), 225 (35, -H_2O), 207 (39), 165 (8), 151 (17), 135 (10), 125 (38), 123 (53), 121 (15), 111 (68), 109 (69), 97 (89), 95 (83), 83 (100), 81 (69), 71 (36), 69 (98), 67 (40), 57 (72), 55 (77), 43 (90). Calcd. for $C_{15}H_{30}O_2$ (242.403) C 74.33, H 12.47%, found C 74.34, H 12.72%.

(2S,3S)-2,3-epoxy-pentadecan-1-ol (**4b**):

Epoxy alcohol **4b** was prepared according to the literature procedure for compound **4a**, using L-(+)-DET as chiral inductor (75% yield). $[\alpha]^{25}_D$ −26.1 (*c* 1.05, $CHCl_3$). ee > 99%, according to 400 MHz NMR (using Eu(Fod)-shift reagent with the acetate of compound **4b**). ^1H-NMR, IR and MS: the same as for compound **4a**.

(2S,3R)-2,3-epoxy-pentadecanal:

To a stirred solution of freshly distilled oxalyl chloride (4.98 ml, 57 mmol) in dry dichloromethane (150 ml) at −78°C was added under nitrogen dimethyl sulfoxide (9.8 ml, 150 mmol dissolved in 60 ml of dry dichloromethane). The white suspension was stirred for 15 min, after which alcohol **4a** was added (12.0 g, 49.6 mmol as solution in dichloromethane/dimethyl sulfoxide 9:1 (200 ml)), giving a clear solution. This solution was added in 8 min (slower addition gave lower yields). Stirring for 90 min was followed by addition of diisopropylethylamine (36.0 ml, 275 mmol). The mixture was allowed to reach room temperature, after which it was washed with water. The organic layer was successively extracted with 1% HCl, 5% Na_2CO_3 and brine. After drying ($MgSO_4$) the mixture was concentrated *in vacuo*, yielding the crude aldehyde (12.2 g). ^1H-NMR (100 MHz): δ 0.88 (t, 3H, CH_3, J 7 Hz), 1.26 (br s, 20H, $(CH_2)_{10}$), 1.50-1.70 (m, 2H, $(CH_2)_{10}C\underline{H}_2CHO$), 3.09-3.28 (m, 2H, epox-H), 9.01 (d, 1H, C(O)H, J 6 Hz) ppm. IR (CCl_4): ν 2930, 2850, 1730 cm^{-1}. MS (CI): *m/e* (%) 241 (3, M^++1), 205 (2), 137 (3), 135 (3), 123 (7), 121 (4), 111 (13), 109 (13), 97 (25), 95 (21), 83 (32), 81 (19), 71 (100), 69 (36), 67 (14), 57 (38), 55 (29), 43 (32), 41 (31). For instability reasons, the product was immediately converted to the acid.

(2R,3S)-2,3-epoxy-pentadecanal:

The (2R,3S)-epoxy aldehyde was prepared in the same way as its (2S,3R)-enantiomer, giving 85% crude product. ^{1}H-NMR, IR and MS are the same as for the (2S,3R)-compound.

(2S,3R)-2,3-epoxy-pentadecanoic acid (**5a**):

Employing literature procedures[20] crude glycidic acid **5a** was synthesized in a total yield of 90%. The reaction mixture became cloudy after adding a $NaClO_2/NaH_2PO_4$-solution. After stirring overnight the mixture was concentrated to 350 ml (white suspension). Then work-up proceeded according to the literature[20]. ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3, J 7 Hz), 1.26 (br s, 20H, $(CH_2)_{10}$), 1.55-1.70 (m, 2H, $(CH_2)_{10}C\underline{H}_2CHO$), 3.12-3.33 (m, 2H, epox-H) ppm. IR (CCl_4): v 3550-2500, 2960, 2920, 2850, 1720 cm^{-1}. MS (CI): *m/e* (%) 257 (3, M^++1), 211 (51, $-CO_2H$), 193 (19, $-CO_2H$, $-H_2O$), 137 (16), 123 (26), 111 (40), 109 (45), 97 (69), 95 (68), 83(81), 81 (54), 69 (91), 67 (40), 57 (100), 55 (79), 43 (95), 41 (88). The crude product was immediately converted into diazo ketone **6a**.

(2R,3S)-2,3-epoxy-pentadecanoic acid (**5b**):

Compound **5b** was synthesized according to the procedure for compound **5a**. Yield: 80% of crude glycidic acid **5b**. ^{1}H-NMR, IR and MS are the same as for the (2S,3R)-enantiomer.

(3S,4R)-3,4-epoxy-1-diazo-hexadecan-2-one (**6a**):

Crude glycidic acid **5a** (7.4 g) was dissolved in dry ether (200 ml) under nitrogen at 0°C. *Iso*-butyl chloroformate (3.18 ml, 25 mmol) was added, followed by dried triethylamine (5.26 ml, 38 mmol). A white solid appeared, which was filtered off (under nitrogen) after 1 h of stirring. To the filtrate was added an ethereal 0.3 M diazomethane solution (250 ml). After stirring overnight, excess diazomethane was evaporated and the mixture was concentrated *in vacuo*, to give crude diazo ketone **6a** as a yellow solid (8.48 g). Chromatography (hexane/ethyl acetate 4:1) yielded pure epoxy diazo ketone as a solid (6.98 g). Total yield, calculated on epoxy alcohol **4a** (4 steps): 60%. M.p. 38.5-40°C. ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3, J 7 Hz), 1.26 (br s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 2H, $(CH_2)_{10}C\underline{H}_2CHO$), 2.90-3.02 (m, 1H, $C\underline{H}OCHC(O)$), 3.23 (d, 1H, $CHOC\underline{H}C(O)$, J 2 Hz), 5.47 (s, 1H, CHN_2) ppm. IR (CCl_4): v 3120, 2960, 2930, 2860, 2110, 1650 cm^{-1}. MS (CI): *m/e* (%) 281 (46, M^++1), 253 (7, $-N_2$), 211 (4, $-COCHN_2$), 193 (3, $-COCHN_2$, $-H_2O$), 123 (11), 121 (10), 111 (31), 109 (27), 97 (35), 95 (48), 83 (35), 81 (44), 71 (20), 69 (81), 67 (35), 57 (68), 55 (100), 43 (80), 41 (67). Calcd. for $C_{16}H_{28}N_2O_2$ (280.412) C 68.53, H 10.06, N 9.99%, found C 68.12, H 10.19, N 8.73%.

(3R,4S)-3,4-epoxy-1-diazo-hexadecan-2-one (**6b**):

Employing the procedure for compound **6a**, epoxy diazo ketone **6b** was prepared in a total yield of 50%, starting from epoxy alcohol **4b**. ^{1}H-NMR, IR and MS are the same as for diazo compound **6a**.

Ethyl E-*(R)-4-tert-butyldimethylsilyloxy-hexadec-2-enoate* (**7a**):

Diazo ketone **6a** (4.0 g, 14.3 mmol) was dissolved in nitrogen-flushed absolute ethanol (1 l) and irradiated at 300 nm under nitrogen. The progress of the reaction was monitored by IR (disappearance of the diazo peak).

After 2 h the reaction was completed. The solvent was evaporated *in vacuo*, yielding a yellowish/brown oil (3.4 g). After chromatography (hexane/ethyl acetate 6:1), pure *ethyl* E-*4-hydroxy-hexadec-2-enoate* was isolated as a solid. M.p. 28.5-29.5°C. ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.83 (t, 3H, $C\underline{H}_3(CH_2)_{10}$, J 6 Hz), 1.22 (br s, 20 H, $CH_3(C\underline{H}_2)_{10}$), 1.24 (t, 3H, $OCH_2C\underline{H}_3$, J 7 Hz), 1.45-1.60 (m, 2H, $(CH_2)_{10}C\underline{H}_2CHO$), 2.66 (d, 1H, OH, J 4.4 Hz), 4.23 (q, 2H, $OC\underline{H}_2CH_3$, J 7 Hz), 4.33 (m, 1H, $(CH_2)_{10}CH_2\underline{C}H(OH)$ 6.05 (dd, 1H, $CH{=}C\underline{H}C(O)$, J 15.6 Hz and 1.6 Hz), 6.99 (dd, 1H, $C\underline{H}{=}CH(O)$, J 15.6 Hz and 4.9 Hz) ppm. IR (CCl_4): ν 3610, 3520-3050, 2960, 2930, 2850, 1725, 1660 cm^{-1}. MS (CI): *m/e* (%) 299 (77, M^++1), 281 (38, $-H_2O$), 253 (50, -EtOH), 235 (12, -EtOH, $-H_2O$), 205 (19), 192 (6), 144 (15), 130 (18), 129 (40), 101 (100), 73 (27), 43 (8). The crude reaction mixture was dissolved in dimethylformamide (80 ml) under nitrogen. Imidazole was added (2.43 g, 35.8 mmol), followed by a solution of *tert*-butyldimethylsilyl chloride (TBDMSCl, 4.31 g, 28.6 mmol) in DMF (70 ml) and a few crystals of N,N-dimethylaminopyridin (DMAP). The mixture was stirred overnight. Water (100 ml) was added, followed by extraction with ether (3x). The combined organic layers were washed with brine and water. After drying ($MgSO_4$), the mixture was concentrated *in vacuo* to give the crude product (5.54 g). This was chromatographed (hexane/ethyl acetate 6:1), yielding protected unsaturated ester **7a** as an oil (3.04 g, 55%). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.00 and 0.02 (2s, 6H, $Si(CH_3)_2$), 0.85 (12 H: t, 3H, $C\underline{H}_3(CH_2)_{10}$, J 7 Hz and s, 9H, $(CH_3)_3CSi$), 1.22 (br s, 20H, $(CH_2)_{10}$), 1.25 (t, 3H, $OCH_2C\underline{H}_3$, J 7 Hz), 1.45-1.60 (m, 2H, $(C\underline{H}_2CHO)$, 4.15 (q, $OC\underline{H}_2CH_3$, J 7 Hz), 4.26 (m, 1H, $C\underline{H}OCH{=}C$), 5.93 (dd, 1H, $CH{=}C\underline{H}C(O)$, J 15 Hz and 1.6 Hz), 6.89 (dd, 1H, $C\underline{H}{=}CHC(O)$, J 15 Hz and 5 Hz) ppm. IR (CCl_4): ν 2960, 2930, 1860, 1725, 1385 cm^{-1}. MS (CI): *m/e* (%) 413 (14, M^++1), 367 (13, -EtOH), 355 (100, -tBu), 309 (9), 281 (9, $-OSiMe_2tBu$), 243 (20, $C_{12}H_{25}^+$+1), 149 (8), 103 (7), 81 (4), 75 (18), 73 (18), 57 (10), 43 (10), 41 (16). EI/HRMS: *m/e* calcd. 412.33727, found 412.33728 ± 0.00081 a.m.u.

Ethyl E-*(S)-4-tert-butyldimethylsilyloxy-hexadec-2-enoate* (**7b**):

Unsaturated ester **7b** was prepared following the procedure for compound **7a**, in a total yield of 60%. Spectra of **7b** are in full accord with those of its enantiomer **7a**.

(R)-4-tert-butyldimethylsilyloxy-hexadec-2-en-1-ol (**8a**):

Ester **7a** (1.9 g, 4.6 mmol) was dissolved in dry ether (75 ml) under nitrogen at 0°C. A DIBAL-H solution in hexane was added using a syringe (9.2 ml of a 1.0 M solution). After 1 h the ester was consumed (TLC) and $Na_2SO_4.10H_2O$ was added until no further reaction took place. Stirring for 1 h was followed by filtration over hyflo. The residue was washed with warm ether (2x). The combined filtrates were washed with water. After drying ($MgSO_4$) the solvent was evaporated *in vacuo*, yielding crude alcohol (1.8 g). Chromatography (hexane/ ethyl acetate 4:1) gave pure **8a** as an oil (1.38 g, 81%). ^{1}H-NMR (100 MHz): δ 0.03 and 0.05 (2s, 6H, $Si(CH_3)_2$), 0.90 (12H: t, 3H, $C\underline{H}_3(CH_2)_{10}$, J 7 Hz and s, 9H, $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 3H, $C\underline{H}_2CHOSi$ and OH), 4.14 (m, 3H, $CH_2C\underline{H}OCH{=}C$ and $C\underline{H}_2OH$), 5.73 (m, 2H, $C\underline{H}{=}C\underline{H}$) ppm. IR ($CCl_4$): ν 3610, 2960, 2920, 2850, 1390, 1375, 1360, 1250 cm^{-1}. MS (CI): *m/e* (%) 371 (6, M^++1), 353 (67, $-H_2O$), 313 (98, -tBu), 239 (29, $-OSiMe_2tBu$), 221 (55, $-OSiMe_2tBu$, $-H_2O$), 201 (83, $-C_{12}H_{25}$), 145 (17), 131 (29), 109 (38), 95 (56), 81 (48), 75 (100), 67 (35), 57 (58). EI/HRMS: *m/e* calcd. 370.3267, found 370.3261 ± 0.0011 a.m.u.

(S)-4-tert-butyldimethylsilyloxy-hexadec-2-en-1-ol (**8b**):

Unsaturated ester **8b** was synthesized following the same procedure as for compound **8a**. Yield: 90%. Spectra of **8b** were identical to those of **8a**.

(2S,3R,4R)-4-tert-butyldimethylsilyloxy-2,3-epoxy-hexadecan-1-ol (**9a**):

A suspension of finely powdered molecular sieves (4Å, 0.5 g) in dry dichloromethane (50 ml) under nitrogen was cooled to −20°C. L-(+)-DET (0.581 g, dissolved in 2 ml of dichloromethane, 1.2 equiv.) and $Ti(O\textit{i}Pr)_4$ (0.699 ml, 1.0 equiv.) were sequentially added. The mixture was stirred for 15 min and allylic alcohol **8a** (0.78 g, 2.11 mmol dissolved in 5 ml of dichloromethane,) was added. After stirring for 30 min a 4.0 M solution of *tert*-butyl hydroperoxide in 1,2-dichloroethane was added dropwise (1.17 ml, 2.0 equiv.). The mixture was kept at −20°C overnight. Work-up was performed as in ref.[12h] (*cf.* preparation of 2,3-epoxy-octan-1-ol), to give the crude product as an oil (1.06 g). Chromatography (hexane/ethyl acetate 4:1) gave pure epoxy alcohol **9a** as an oil (0.75 g, 92%). Diastereomeric excess > 95% (as was determined by capillary GC). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.05 and 0.09 (2s, 6H, $(CH_3)_2Si$), 0.86 (t, 3H, $C\underline{H}_3(CH_2)_{10}$, J 6 Hz), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 2H, $C\underline{H}_2CHOSi$), 1.80 (s, 1H, OH), 2.98 (m, 2H, epox-H), 3.26-3.75 (m, 3H, $C\underline{H}_2OH$), 3.80-4.02 (m, 1H, $CH_2C\underline{H}OSi$) ppm. IR (CCl_4): ν 3600, 2960, 2920, 2850, 1375 cm^{-1}. MS (CI): *m/e* (%) 378 (23, M^++1), 369 (39, $-H_2O$), 329 (100, -tBu), 311 (50, $-H_2O$, -tBu), 285 (47, -tBu, $-CH_2CH_2OH$), 255 (39, $-OSiMe_2tBu$), 237 (64, $-OSiMe_2tBu$, $-H_2O$), 219 (17), 131 (64), 117 (63), 95 (26), 81(23), 75 (91), 73 (39), 57 (26). EI/HRMS: *m/e* calcd. 386.3216, found 386.3215 ± 0.0011 a.m.u.

(2S,3R,4S)-4-tert-butyldimethylsilyloxy-2,3-epoxy-hexadecan-1-ol (**9b**):

Following the procedure for the synthesis of epoxy alcohol **9a**, compound **9b** was prepared in 83% yield as an oil. Diastereomeric excess > 95% (GC). ^{1}H-NMR (100 MHz): δ 0.04 (s, 6H, $(CH_3)_2Si$), 0.87 (12H: t, 3H, $C\underline{H}_3(CH_2)_{10}$, J 6 Hz; s, 9H, $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 2H, $C\underline{H}_2CHOSi$), 2.36 (broad s, 1H, OH), 2.91 (dd, 1H, $C\underline{H}OCHCH_2OH$, J 4.3 Hz and 2.3 Hz), 3.14 (qui, 1H, $CHOC\underline{H}CH_2OH$), 3.51-3.74 (m, 2H, $C\underline{H}_2OH$), 3.84-4.06 (m, 1H, $CH_2C\underline{H}OSi$) ppm. IR (CCl_4): ν 3600, 2960, 2920, 2850, 1375 cm^{-1}. MS (CI): *m/e* (%) 387 (2, M^++1), 369 (12, $-H_2O$), 329 (31, -tBu), 313 (27), 311 (46, -tBu, $-H_2O$), 285 (20, -tBu, $-CH_2CHOH$), 255 ($-OSiMe_2tBu$), 237 ($-OSiMe_2tBu$, $-H_2O$), 219 (10), 161 (20), 157 (22), 143 (15), 131 (65), 117 (100), 97 (21), 95 (30), 83 (27), 81 (29), 75 (98), 73 (68), 57 (41), 55 (27), 43 (48), 41 (47).

(3R,4R,5R)-5-tert-butyldimethylsilyloxy-3,4-epoxy-1-diazo-heptadecan-2-one (**10a**):

Epoxy alcohol **9a** (500 mg, 1.3 mmol) was dissolved in a mixture of acetonitrile (5 ml), tetrachloromethane (5 ml) and water (7.5 ml). Sodium *meta*periodate (0.9 g, 4.2 mmol) and a catalytic amount of $RuCl_3.xH_2O$ was added. The black mixture was stirred until the alcohol was consumed (TLC, 90 min). After adding dichloromethane (10 ml) the layers were separated and the aqueous layer was washed with dichloromethane (3x). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was taken up into dry ether (40 ml) under nitrogen at 0°C and *iso*-butyl chloroformate (162.5 μl, 1.3 mmol) was added, followed by triethylamine (262.2 μl, 1.9 mmol). The mixture was stirred at room temperature for 1 h, after which the solid was filtered off. To the filtrate was added a 0.3 M diazomethane solution in ether (15 ml) and the mixture was stirred for 1 h. Evaporation of excess diazomethane followed by concentration *in vacuo* gave a dark oil, which was chromatographed (hexane/ethyl acetate 4:1), to give pure epoxy diazo ketone **10a** as an oil (281 mg, 52%). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.05 and 0.07 (2s, 6H, $(CH_3)_2Si$), 0.85 (br s, 12H, $C\underline{H}_3(CH_2)_{10}$ and $(CH_3)_3CSi$), 1.25 (s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 2H, $C\underline{H}_2CHOSi$), 2.95 (m, 1H, $C\underline{H}OCHC(O)$), 3.15-3.65

(m, 2H, $CH_2C\underline{H}OSi$ and $CHOC\underline{H}C(O)$), 5.55 (s, 1H, CHN_2) ppm. IR (CCl_4): ν 3120, 2950, 2930, 2860, 2110, 1645, 1365 cm^{-1}.

(3R,4R,5S)-5-tert-butyldimethylsilyloxy-3,4-epoxy-1-diazo-heptadecan-2-one (**10b**):

Employing the procedure for the preparation of diazo compound **10a**, epoxy diazo ketone **10b** was synthesized in 42% yield from alcohol **9b**. ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.04 (s, 6H, $(CH_3)_2Si$), 0.87 (br s, 12H, $C\underline{H}_3(CH_2)_{10}$ and $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.45-1.60 (m, 2H, $C\underline{H}_2CHOSi$), 2.96 (m, 1H, $C\underline{H}OCHC(O)$), 3.46 (d, 1H, $CHOC\underline{H}C(O)$, J 2 Hz), 3.70-3.85 (m, 1H, $CH_2C\underline{H}OSi$), 5.48 (s, 1H, CHN_2) ppm. IR (CCl_4): ν 3120, 2950, 2920, 2850, 2110, 1640, 1360 cm^{-1}.

(R)-5-[(R)-1-tbutyldimethylsilyloxy-tridecyl]-dihydrofuran-2-one (**12a**):

Epoxy diazo ketone **10a** was converted into unsaturated ester **11a**, following the procedure for ethyl *E*-4-hydroxy-hexadec-2-enoate (*vide supra*). The crude alkene ester was then hydrogenated according to literature procedures[9]. No hydrogen atmosphere was needed for this reaction. IR-spectroscopy of the crude product (oil) indicated, that it was partly closed to the lactone. This reaction was completed by dissolving the mixture in a few ml of benzene, followed by the addition of a few crystals of *p*-toluenesulfonic acid. After 1 h of stirring, usual work-up gave the crude lactone. Chromatography (hexane/ethyl acetate 4:1) yielded pure lactone **12a** as an oil (27%, starting from diazo compound **10a** (3 steps)). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.07 (s, 6H, $(CH_3)_2Si$), 0.89 (br s, 12H, $C\underline{H}_3(CH_2)_{10}$ and $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.50-1.65 (m, 2H, $C\underline{H}_2CHOSi$), 2.02-2.20 (m, 2H, $C\underline{H}_2CH_2C(O)$), 2.35-2.55 (m, 2H, $CH_2C\underline{H}_2C(O)$), 3.45-3.60 (m, 1H, $CH_2C\underline{H}OSi$), 4.30-4.50 (m, 1H, CHOC(O)) ppm. IR (CCl_4): ν 2950, 2920, 2850, 1785, 1375 cm^{-1}. MS (CI): *m/e* (%) 399 (18, M^++1), 341 (100, -tBu), 323 (17), 313 (46, -lactone moiety), 267 (4, -$OSiMe_2tBu$), 249 (8), 185 (3), 171 (4), 159 (10), 145 (5), 129 (7), 115 (8), 97 (12), 83 (14), 75 (52), 73 (50), 69 (18), 57 (42), 55 (38), 43 (61).

(R)-5-[(S)-1-tert-butyldimethylsilyloxy-tridecyl]-dihydrofuran-2-one (**12b**):

Lactone **12b** was prepared employing the procedure for compound **12a** in a total yield of 49% as an oil, starting from diazoketone **10b**. ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.06 and 0.07 (2s, 6H, $(CH_3)_2Si$), 0.87 (br s, 12H, $C\underline{H}_3(CH_2)_{10}$ and $(CH_3)_3CSi$), 1.25 (br s, 20H, $(CH_2)_{10}$), 1.40-1.55 (m, 2H, $C\underline{H}_2CHOSi$), 2.00-2.25 (m, 2H, $C\underline{H}_2CH_2C(O)$), 2.30-2.55 (m, 2H, $CH_2C(O)$), 3.80-3.95 (m, 1H, $CH_2C\underline{H}OSi$), 4.20-4.45 (m, 1H, CHOC(O)) ppm. IR (CCl_4): ν 2960, 2930, 2860, 1785 cm^{-1}. MS (CI): *m/e* (%) 399 (26, M^++1), 341 (100, -tBu), 323 (25), 313 (60, -lactone moiety), 259 (13), 249 (11), 169 (29, $C_{12}H_{25}^+$), 141 (11), 129 (9), 115 (12), 97(22), 86 (18), 84 (28), 75 (61), 73 (66), 69 (34), 57 (50), 55 (65), 49 (93), 43 (75), 41 (72).

(4R,5R)-muricatacin (**1**):

Silyl protected lactone **12a** (72 mg, 0.18 mmol) was dissolved in dry THF (15 ml) under nitrogen at 0°C. Tetrabutylammonium fluoride (TBAF, 360 μl of a 1.0 M solution in THF) was added and the reaction was followed by TLC. After 2 h it was complete and saturated NH_4Cl was added (15 ml). The layers were separated and the aqueous layer was washed with ether (3x). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (hexane/ethyl acetate 1:1) gave lactone **1**, (38 mg, 75%) which was further purified by recrystallization from petroleum ether 60-80. M.p. 72.5-73°C. $[\alpha]^{25}_D$ −23.3° (c 0.5, $CHCl_3$). Lit.[16a,b] −22.9° (c 1.1, $CHCl_3$), lit.[16c,f] −23.3° ($CHCl_3$), lit.[16g] −23.1° (c 2.36, $CHCl_3$). ^{1}H-NMR (400 MHz): δ

0.88 (t, 3H, CH_3, J 7.0 Hz), 1.26 (m, 20H, $(CH_2)_{10}$), 1.48-1.57 (m, 2H, $C\underline{H}_2CHOH$), 1.91 (d, 1H, OH, J 5.7 Hz), 2.06-2.16 (m, 1H, $C\underline{H}HCH_2C(O)$)), 2.21-2.29 (m, 1H, $CH\underline{H}CH_2C(O)$)), 2.49-2.65 (m, 2H, $CH_2C(O)$)), 3.58 (m, 1H, $CH_2C\underline{H}OH$), 4.42 (dt, 1H, CHOC(O), J 7.4 Hz and 4.6 Hz) ppm. ^{13}C-NMR (100 MHz): 14.1, 22.7, 24.1, 25.4, 28.7, 29.3, 29.5 (3C), 29.6 (3C), 31.9, 33.0, 73.7, 82.9, 177.1 ppm. IR (CCl_4): ν 3580, 2950, 2920, 2850, 1785 cm^{-1}. MS (CI): *m/e* (%) 285 (28, M$^+$+1), 267 (68, -H_2O), 239 (16, -H_2O, -CO), 199 (8, -lactone moiety), 125 (7), 111 (10), 97 (17), 87 (19, (lactone moiety)$^+$+1), 86 (100, (lactone moiety)$^+$), 85 (23, (lactone moiety)$^+$ -1), 83 (17), 69 (18), 57 (21), 55 (20), 43 (23). Calcd. for $C_{17}H_{32}O_3$ (284.441) C 71.79, H 11.34%, found C 71.10, H 11.08%.

(4R,5S)-muricatacin (**2**):

Lactone **12b** was deprotected following the procedure for compound **1**. Yield: 80%. $[\alpha]^{25}_D$ −13.6° (c 0.4, $CHCl_3$). M.p. 71.5-72°C, after recrystallization from petroleum ether 60-80. ^{1}H-NMR (400 MHz): δ 0.88 (t, 3H, CH_3, J 7.0 Hz), 1.26 (m, 20H, $(CH_2)_{10}$), 1.40-1.54 (m, 2H, $C\underline{H}_2CHOH$), 1.94 (broad s, 1H, OH), 2.13-2.18 m, 1H, $C\underline{H}HCH_2C(O)$)), 2.22-2.29 (m, 1H, $CH\underline{H}CH_2C(O)$)), 2.47-2.63 (m, 2H, $CH_2C(O)$)), 3.93 (m, 1H, $CH_2C\underline{H}OH$), 4.44 (dt, 1H, CHOC(O), J 7.4 Hz and 3.3 Hz) ppm. ^{13}C-NMR (100 MHz): 14.1, 21.1, 22.7, 25.6, 28.7, 29.3, 29.5 (3C), 29.6 (3C), 31.9 (2C), 71.4, 82.7, 177.4 ppm. IR (CCl_4): ν 3590, 3500-3300, 2920, 2850, 1770 cm^{-1}. MS (CI): *m/e* (%) 285 (11, M$^+$+1), 267 (31, -H_2O), 239 (9, -H_2O, -CO), 199 (7, -lactone moiety), 125 (6), 111 (8), 97 (14), 87 (16, (lactone moiety)$^+$+1), 86 (100, (lactone moiety)$^+$), 85 (20, (lactone moiety)$^+$-1), 83 (14), 69 (16). EI/HRMS: *m/e* calcd. 284.2351, found 284.23506 ± 0.00084. Calcd. for $C_{17}H_{32}O_3$ (284.441) C 71.79, H 11.34%, found C 70.96, H 10.94%.

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