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Enantiopure Hydroxylactones from *L*-Ascorbic and *D*-Isoascorbic Acids. Part I.[1] Synthesis of (-)-Muricatacin

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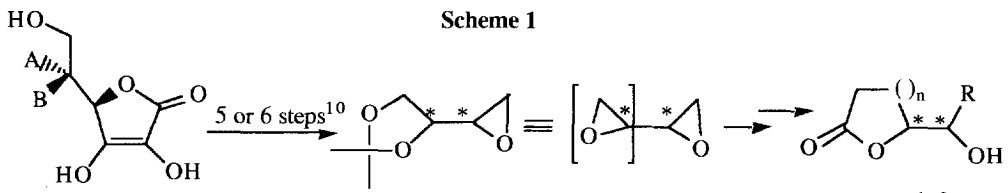
Abstract. From *D*-isoascorbic acid, *via* a formal bis-epoxide equivalent with a C-2 axis of symmetry, two possible syntheses of the (-)-Muricatacin are described.

Compounds with chiral hydroxylactone occupy important positions both as target bioactive molecules and useful synthetic equivalents in total syntheses. For example, natural 5-hydroxy-γ-lactones were identified as flavour constituents in wine,[2] sherry,[3] and tobacco smoke[4] and as a microbial metabolite in cultures of *Erwinia quernica*.[5] The isolation of 5-hydroxy-γ-decalactone (L-Factor) from cultures of *Streptomyces griseus*[6] which reveals autoregulatory properties and of 5-hydroxy-γ-heptadecalactone (Muricatacin) from seeds of *Annona muricata*,[7] an acetogenic derivative which shows some cytotoxicity on human tumour cell lines, has stimulated great interest and has been at the origin of synthetic strategies towards these products.[8,9]

Our general approach to enantiomerically pure hydroxy-γ-butyro and δ-valerolactones starts either from *L*-ascorbic or *D*-isoascorbic acids (Scheme 1). As previously described,[10] these commercial acids are converted in 40 % overall yield into each of the four possible stereoisomers of epoxybutanediol acetonide **2**. These epoxybutanediol acetonides are formal equivalents of bis-epoxide containing a free epoxide function, the other one being masked into the glycol ; successive regiospecific nucleophilic openings of both epoxide rings allow the introduction of the alkyl chain, on one hand and the formation of the lactone ring, on the other hand.

Scheme 1



D-isoascorbic acid A=OH, B=H

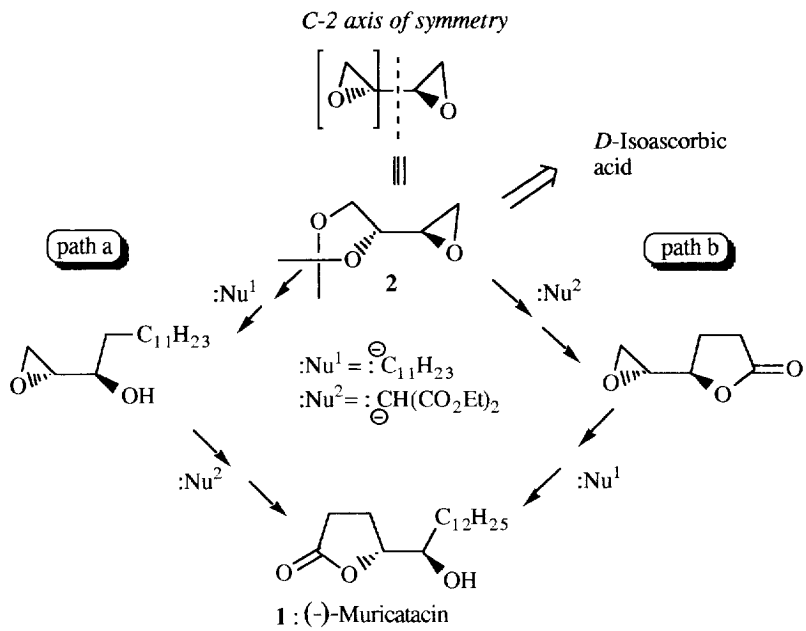
L-Ascorbic acid B=OH, A=H.

n = 1, 2

Following this strategy, we recently proposed a route to (-)-Muricatacin, [(4*R*,5*R*)-5-hydroxy-4-heptadecanolide **1**] and (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide,[1,9i] and the present report provides the details of that effort and describes a new route to (-)-Muricatacin.

In the specific case of the (-)-Muricatacin (Scheme 2) which has a *threo* relative configuration, this strategy requires a formal bis-epoxide with a C-2 axis of symmetry. We take advantage of this two fold axis to study two approaches (*path a* and *path b*) from the same epoxybutanediol acetonide, these two paths differ only by the order of introduction of nucleophiles.

Scheme 2

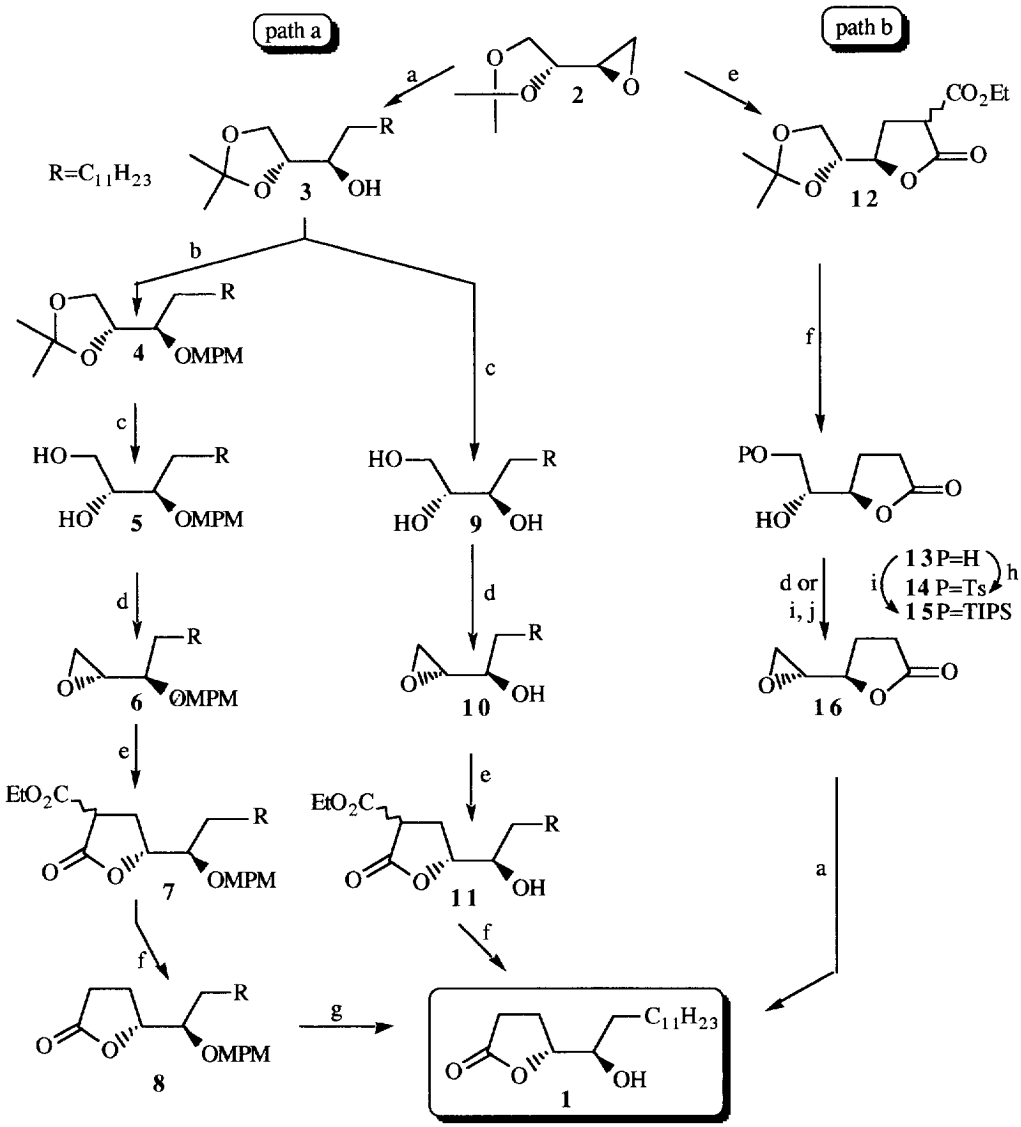


Path a : (Scheme 3)

The nucleophilic opening of (2*R*,3*R*)-3,4-epoxy-1,2-*O*-methylethylidenebutane-1,2-diol **2**, prepared from *D*-isoascorbic acid,[10] with undecylmagnesium bromide in the presence of Li_2CuCl_4 led to the alcohol **3** (80%) which was protected as a 4-methoxybenzylether **4** (NaH, DMF, imidazole, 4-methoxybenzylchloride, 93 %). Acidic hydrolysis (AcOH-H_2O) of **4** gave the diol **5** which was transformed into epoxide **6** either by action of NaH in DMF/THF followed by addition of tosylimidazole[11] (42 %) or in a higher yield (83 %) by Mitsunobu reaction[12] (PPh_3, DIAD, 125°C *in vacuo*).

Next step was the introduction of acetate functionality at the other epoxy site of the bis-epoxide equivalent. So, **6** was treated with ethylmalonate in presence of sodium ethoxide to afford a mixture of α-carbethoxy-γ-butyrolactones epimers **7** in 55 % yield. Smooth decarbethoxylation of this crude mixture by magnesium chloride hexahydrate in dimethylacetamide[13] followed by deprotection of the alcohol by dicyanodichloroquinone oxydation[14] of its paramethoxybenzyl protecting group led to the expected (-)-Muricatacin **1** in 71 % yield.

Scheme 3



a) $C_{11}H_{23}MgBr$, Li_2CuCl_4, THF, -35°C from **2** (80 %); and -78°C from **16** (58%). b) NaH, DMF, imidazole, 0°C then MPMCl, NBu_4I, 20°C, 93 %. c) $AcOH/H_2O$ 4/1, 20°C overnight : quantitative yield from **4** and **3** respectively. d) PPh_3, DIAD, 125°C *in vacuo* , 83 % from **5**, 70 % for **3** → **9** → **10**, 67 % from **13**. e) $CH_2(COOEt)_2$, EtOH-EtONa, 60°C, 6 hrs, 55 %, 80 % from **6**, **2** respectively. f) $MgCl_2.6H_2O$, $CH_3CON(CH_3)_2$, reflux 4 hrs, 90 % and 20 % overall yield from **12** and **10** respectively. g) DDQ, CH_2Cl_2/H_2O, 71 %. h) TsCl 1 eq, NEt_3 1.5 eq, CH_2Cl_2, -20° → 20°C, 26 %. i) TIPSCl 1.3 eq, pyridine, 0° → 20°C. 41 %. j) NaH, THF/DMSO 0° → 20°C, 2 hrs, **15** → **16**, 63 %.

DIAD : diisopropyl azadicarboxylate ; MPMCl : 4-methoxybenzylchloride.
TIPSCl : triisopropyl benzenesulfonyl chloride. DDQ : dicyanodichloroquinone.

An alternative way to (-)-Muricatacin from the acetonide alcohol **3** without protection of the hydroxyl group was tested. The 1,2-epoxy-3-alkanol **10** was obtained from the acyclic triol **9** in 70 % yield according to Mitsunobu conditions.[15] However its nucleophilic opening following by decarbethoxylation afforded the (-)-Muricatacin in 20 % from the epoxide **10** compared to 40 % in the protected way.

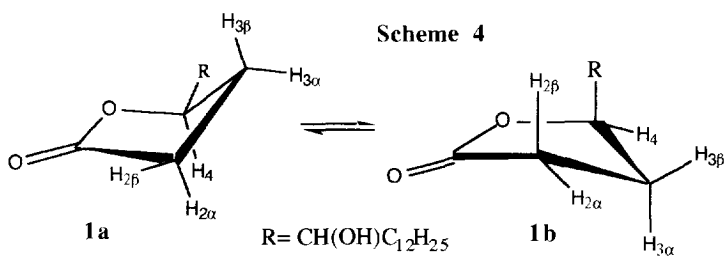
Path b : (Scheme 3)

Now, nucleophilic opening of the epoxide **2** with diethylmalonate in the presence of sodium ethoxide afforded a mixture of α-carbethoxy-γ-butyrolactone diastereomers **12a** and **12b** (70/30) in 80 % yield. Magnesium chloride hexahydrate in refluxing dimethylacetamide induced decarbethoxylation simultaneously with hydrolysis of the acetonide to afford **13** in 90 % yield. The selective activation of primary alcohol with tosylchloride (Et_3N, CH_2Cl_2) or triisopropylbenzenesulfonyl chloride in pyridine, was carried out with low yields ; **14** and **15** were obtained in 26 % and 41 % yield respectively and **15** was transformed (NaH, Me_2SO) in epoxylactone **16** in 63 % yield. Nevertheless, Mitsunobu reaction[12] (PPh_3, DIAD, 125°C *in vacuo*) achieved on the diol lactone **13** led directly to the epoxylactone **16** in 65 % yield.

Finally, the nucleophilic opening of the epoxylactone **16** by the undecylmagnesium bromide in presence of Li_2CuCl_4 led to (-)-Muricatacin **1** in 38 % yield together with 34 % of the starting material which could be easily recovered by flash column chromatography (58 % yield of **1** based on 66 % conversion of **16**).

The butyrolactones are known to exist in the envelope conformation and in solution an equilibrium of two conformers must be considered (scheme 4).[16] NMR study of **1** in $CDCl_3$ (see experimental section) shows that the (-)-Muricatacin takes up a predominant conformation with the 4-hydroxyalkyl chain in equatorial position. Thus, the expected values for $^3J_{3,4}$ (ax,ax) and $^3J_{3,4}$ (eq,eq) proton coupling should be 10 Hz and 2 Hz respectively.[16b] For the lactone **1** the experimental value (^3J 3β,4 = 8Hz, experimental error 0.5 Hz) may be interpreted as a slight contribution of **1b** which is evaluated as 25% by the equation: $2(1-\alpha) + 10\alpha = 8$ (α is the molar concentration of configuration **1a**).

Scheme 4



In summary, we have described two routes to (-)-Muricatacin from *D*-isoascorbic acid *via* an epoxy butanediol acetonide, a formal bis-epoxide equivalent with a C-2 axis of symmetry. One of them, *via* an epoxy-γ-butyrolactone (*path b*), involves only four steps without protection-deprotection sequences, and allows the introduction of the alkyl chain in an ultimate step of the synthesis.

A key feature of this method is that the enantiomer of the epoxybutanediol acetonide can also be obtained from *L*-ascorbic acid and therefore allows access to (+)-Muricatacin.

Furthermore, generalisation of this versatile procedure to other nucleophiles could also lead to a variety of enantiomerically pure 5-hydroxy-γ-butyrolactones such as :

- (4*S*, 5*S*)-5-hydroxy-4-decanolide (:Nu=C_4H_9), L-Factor.[6]
- (4*S*,5*S*)-5-hydroxy-4-pentadecanolide (:Nu=C_9H_{19}), an useful building block for the synthesis of disparlure.[17]
- (4*R*,5*R*)-5-hydroxy-7-phenyl-4-hexanolide (:Nu=C_6H_5), a microbial metabolite in culture of *Erwinia quercina*.[5]

EXPERIMENTAL SECTION

Prior to use, tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (AcOEt) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless indicated) on a Bruker AM 250. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. High Resolution Mass Spectra were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamps. All reactions were carried out under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 μm) or 60H (5-40 μm). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

(2*R*, 3*R*)-1,2-*O*-Methylethylidene-pentadecane-1,2,3-triol (3)

To a stirred solution of Li_2CuCl_4 (3.19 mmol, 0,1M in THF prepared from 1 mol. $CuCl_2$ and 2 mol. LiCl) at -35°C, undecylmagnesium bromide (31.9 mmol, 1M in THF prepared from magnesium turnings and 1-bromo undecane in refluxing THF for 30 min)[18] was added dropwise. After stirring for 30 min. at -35°C, epoxide **2** (1.044g, 7.25 mmol) in THF (42 mL) was added and the mixture was stirred 30 min. at -35°C. Hydrolysis with a saturated aqueous solution of ammonium acetate was followed by extraction with ether (4x75 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/AcOEt 90:10 Rf 0.16) afforded 1.66g (80 %) of **3** :

$[\alpha]_D$ +12.4 (c 1.11, CH_2Cl_2) ; ^1H NMR δ : 3.97 (2H, m, H-1), 3.70 (1H, m, H-2), 3.46 (1H, m, H-3), 1.41, 1.35 (6H, 2s, CMe_2), 1.1-1.45 (22H, m, $(CH_2)_{11}$), 0.85 (3H, t, CH_3, J=6.5Hz) ; ^{13}C NMR δ : 109.3 ($\underline{C}Me_2$), 79.2 (C-2), 72.3 (C-3), 66.2 (C-1), 33.7 (C-4), 31.9, 29.6, 29.3, 25.5, 22.7 (C-5-14), 26.7, 25.3 ($C\underline{Me}_2$), 14.1 (C-15). Anal. Calcd. for $C_{18}H_{36}O_3$: C, 71.95 ; H, 12.08. Found : C, 72.06 ; H, 11.99.

(2*R*, 3*R*)-1,2-*O*-Methylethylidene-3-*O*-*para*-methoxybenzyl-pentadecane-1,2,3 triol (4)

To a stirred suspension of NaH (148 mg, 6.16 mmol) in DMF (5.2 mL) at 0°C was added the alcohol **3** (463 mg, 1.54 mmol) in DMF (3.7 mL) and an imidazole crystal. After stirring 2 hrs at room temperature *para*-methoxybenzylchloride (733 μL, 5.4 mmol) was added dropwise. The mixture was stirred overnight then poured into water and extracted with ether (4x15 mL). The combined ether layers were washed with brine,

dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/AcOEt 90:10, Et_3N : 3 ‰ Rf 0.29) afforded 603 mg (93 %) of **4** :

$[\alpha]_D$ +29 (c 2.73, CH_2Cl_2) ; ^1H NMR δ : 7.28, 6.87 (4H, 2d, Ar-H, J=8Hz), 4.64, 4.54 (2H, 2d, CH_2-Ar, ^2J=11Hz), 4.19 (1H, ddd, H-2, $J_{1,2}$=7, $J_{1',2}$= $J_{2,3}$=6.5Hz), 3.97 (1H, dd, H-1, $J_{1,1'}$=8.2Hz, $J_{1,2}$=7Hz), 3.8 (3H, s, Ar-OCH_3), 3.66 (1H, dd, H-1', $J_{1,1'}$=8.2Hz, $J_{1',2}$=6.5Hz), 3.39 (1H, m, H-3), 1.44, 1.37 (6H, 2s, CMe_2), 1.55-1.05 (22H, m, $(CH_2)_{11}$), 0.88 (3H, t, CH_3, J=6.5Hz). ^{13}C NMR δ : 159.2, 131.0, 129.5, 113.7 (Ar), 109.2 ($\underline{C}Me_2$), 79.4 (C-2), 78.5 (C-3), 72.5 ($O\underline{CH_2}$), 66.0 (C-1), 55.2 (Ar-$O\underline{CH_3}$), 31.9, 30.7, 29.7, 29.3, 25.6, 22.7 (C-4-14), 26.6, 25.5 (CMe_2).

(2*R*, 3*R*)-3-*O*-*para*-Methoxybenzyl-pentadecane-1,2,3-triol (5)

The acetonide **4** (603 mg, 1.44 mmol) in CH_3COOH-H_2O 4-1 (10.3 mL) was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to give an oil which was purified by silicagel chromatography (CH_2Cl_2/MeOH 95:5, Et_3N 3‰ Rf 0.25) to give diol **5** (75 %) : m.p.=45°C,

$[\alpha]_D$ -21 (c 1.01, CH_2Cl_2) ; ^1H NMR δ : 7.28, 6.87 (4H, 2d, Ar-H, J=8Hz), 4.60, 4.39 (2H, 2d, CH_2-Ar , ^2J=11Hz), 3.8 (3H, s, Ar-OCH_3), 3.63 (3H, m, H-1-2), 3.46 (1H, m, H-3), 1.58 (2H, m, H-4), 1.4-1.2 (20H, m, $(CH_2)_{10}$), 0.88 (3H, t, CH_3, J=6.5Hz). ^{13}C NMR δ : 159.4, 130.4, 129.4, 140.0 (Ar), 79.3 (C-3), 73.0 (C-2), 71.9 ($O\underline{CH_2}$Ar), 64.1 (C-1), 55.2 (Ar-$O\underline{CH_3}$), 31.9 (C-4), 30.3, 29.8, 29.6, 29.3, 25.2, 22.6 (C-5-14), 14.0 (C-15).Anal. Calcd. for $C_{23}H_{40}O_4$: C, 72.59 ; H, 10.59. Found : C, 72.46 ; H, 10.58.

(2*R*, 3*R*)-1,2-Epoxy-3-*O*-*para*-Methoxybenzyl-3-pentadecanol (6)

At 0°C, diisopropyl azodicarboxylate (DIAD, 338 µL, 1.71 mmol) was added dropwise to a stirred solution of diol **5** (496 mg, 1.3 mmol) and triphenylphosphine (443 mg, 1.69 mmol) in dry benzene (2 mL) (diol and triphenylphosphine were previously concentrated twice *in vacuo* from a toluene solution to avoid any trace of water). After stirring for 30 min at 0°C, the benzene was removed *in vacuo* and the residue was heated to 130°C (0.03 mm Hg) for 2 hrs. Flash chromatography of the residue (CH_2Cl_2, NEt_3 3‰, Rf 0.25) afforded 395 mg (83 %) of **6** :

$[\alpha]_D$ +20 (c 1.02, CH_2Cl_2) ; ^1H NMR δ : 7.28, 6.85 (4H, 2d, Ar-H, J=8Hz), 4.75, 4.5 (2H, 2d, CH_2-Ar, ^2J=11Hz), 2.99 (2H, m, H-2, H-3), 2.75 (1H, m, H-1), 2.47 (1H, m, H-1'), 1.2-1.5 (22H, m, $(CH_2)_{11}$), 0.86 (3H, t, CH_3, J=6.5Hz).^{13}C NMR δ : 159.0, 130.8, 129.3, 113.6 (Ar), 80.0 (C-3), 71.3 ($O\underline{CH_2}$Ar), 55.1 (Ar-$O\underline{CH_3}$, C-2), 43.1 (C-1), 32.3, 31.9, 29.6, 29.3, 25.5, 22.6 (C-5-14), 14.0 (C-15).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20 ; H, 10.56. Found : C, 76.11 ; H, 10.65.

(4*R*, 5*R*)-2-Carbethoxy-5-*O*-*para*-methoxybenzyl-4-heptadecanolide (7)

To a solution of EtONa [prepared from Na (24 mg, 1 mmol) in EtOH (750 µL)] was added diethylmalonate (172 µL, 1.1 mmol), followed by the epoxide **6** (205 mg, 0.56 mmol) in EtOH (650 µL). After refluxing for 6 hrs, the mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/AcOEt 80:20, NEt_3 3‰ Rf 0.2) afforded **7** (55 %).

^1H NMR δ : 7.24, 6.85 (4H, 2d, ArH, J=8Hz), 4.64, 4.5 (2H, 2d, CH_2-Ar, ^2J=11Hz), 4.5 (1H, m, H-4), 4.20 (2H, q, CH_2, J=7Hz), 3.80 (3H, s, Ar-OCH_3), 3.6 (1H, m, H-2), 3.48 (1H, m, H-5), 2.10 (2H, m, H-3), 1.46, 1.29 (27H, m, $(CH_2)_{12}$,CH_3), 0.84 (3H, t, CH_3, J=7Hz). ^{13}C NMR δ : 171.4 (C-1), 167.5

(COOEt), 159.2, 130.3, 129.6, 129.4, 113.8 (Ar), 81.5 (C-4), 80.2, 79.7 (C-5 dia), 72.8, 71.8 (OCH_2Ar dia), 66.1 (OCH_2CH_3), 55.2 (Ar-OCH_3), 46.8 (C-2), 31.9, 29.9, 29.6, 29.3, 28.6, 25.4, 25.1, 22.7 (C-6-16), 14.1 (CH_3).

(4*R*, 5*R*)-5-*O*-*para*-Methoxybenzyl-4-heptadecanolide (8)

To a solution of **7** (71 mg, 0.15 mmol) in N,N-dimethylacetamide (590 µL) was added $MgCl_2.6H_2O$ (152 mg, 0.75 mmol). The mixture was refluxed for 3 hrs with stirring. After cooling, the mixture was extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification.

^1H NMR (90 MHz) δ : 7.25, 6.90 (4H, 2d, ArH, J=8Hz), 4.5-4.3 (3H, m, OCH_2Ar, H-4), 3.8 (3H, s, Ar-OCH_3), 3.4 (1H, m, H-5), 2.7-2.3 (2H, m, H-2), 2.3-1.9 (2H, m, H-3), 1.7-1.0 (20H, m, $(CH_2)_{10}$), 0.9 (3H, t, CH_3, J=6.5Hz).

(2*R*, 3*R*)-Pentadecane-1,2,3-triol (9)

Acid hydrolysis of acetonide **3** by CH_3COOH-H_2O 4-1 was carried out under identical conditions as for **4** described above. Rf 0.09 (AcOEt/cyclohexane 7:3). The crude product was used in the next step without further purification.

^1H NMR (90 MHz) δ : 3.4-3.8 (4H, m, H-1-3), 1.32 (22H, m, $(CH_2)_{11}$), 0.90 (3H, t, CH_3, J=6.5Hz).

(2*R*, 3*R*)-1,2-Epoxy-3-pentadecaneol (10)

Mitsunobu reaction on **9** was carried out under identical conditions as for **5** described beforehand. Flash chromatography (cyclohexane/AcOEt 7:3, Rf 0.30) afforded **10** (70 % yield from **3**).

$[\alpha]_D$ +2 (c 1.32, CH_2Cl_2), $[\alpha]_{Hg\ 365}$ +9 (c 1.32, CH_2Cl_2). ^1H NMR δ : 3.41 (1H, m, H-3), 2.96 (1H, m, H-2), 2.80 (1H, dd, H-1, $^3J_{1,2}=^2J_{1,1'}=4.5Hz$), 2.69 (1H, dd, H-1', $^2J_{1,1'}=4.5Hz$, $^3J_{1',2}=3Hz$), 1.56 (2H, m, H-4-4'), 1.24 (20H, m, $(CH_2)_{10}$), 0.83 (3H, t, CH_3, J=6.5Hz). ^{13}C NMR δ : 71.3 (C-3), 55.0 (C-2), 44.8 (C-1), 34.0, 31.5, 29.2, 28.9, 24.9, 22.3 (C-4-14), 13.7 (CH_3).

(4*R*, 5*R*)-2-Carbethoxy-5-hydroxy-4-heptadecanolide (11)

Nucleophilic opening of the epoxide function by diethylmalonate on **10** was carried out under identical conditions as for **6** described beforehand. Rf 0.27 (cyclohexane/AcOEt 1/1).The crude product was used in the next step without further purification.

^1H NMR (90 MHz) δ : 4.4 (1H, m, H-4), 4.2 (2H, q, OEt), 3.3-3.8 (2H, m, H-2, H-5), 2.2-2.8 (2H, m, H-3), 1.2-1.8 (22H, m, $(CH_2)_{11}$), 0.9 (6H, t, CH_3, J=6.5Hz).

(4*R*, 5*R*)-2-Carbethoxy-5,6-dihydroxy-5,6-*O*-methylethylidene-4-hexanolide (12)

Nucleophilic opening of the epoxide function by diethylmalonate on **2** was carried out under identical conditions as for **6** described beforehand. From the epoxide **2** (720 mg, 5 mmol) a mixture of **12a** and **12b** diastereomers (80 % yield, 70/30) was obtained after flash chromatography (CH_2Cl_2/Et_2O 75/25, Rf 0.6).

IR (film) 1780, 1735 cm^{-1}. ^1H NMR δ : 4.55 (1H, ddd, H-4 maj, J=2, 4.1, 9.9Hz), 4.44 (1H, ddd, H-4 min, J=4.2, 6.6, 8.3Hz), 4.25 (2H, q, OCH_2CH_3 min, J=6.6Hz), 4.26 (2H, q, OCH_2CH_3 maj, J=6.6Hz), 4.2-4.1 (2H, m, H-5 maj, H-5 min), 3.83-4.0 (4H, m, H-6, H-6' maj and min), 3.73 (1H, dd, H-2 maj, J=8.3, 9.9Hz), 3.09 (1H, t, H-2 min, J=9.9Hz), 2.79 (1H, ddd, H-3), 2.35-2.60 (3H, m, H-3 maj,

H-3, H-3' min), 1.2-1.4 (9H, 4m, CH_3). ^{13}C NMR δ : 172.0 (C-1), 168.0 (COOEt), 111.0 (CMe_2), 78.0, 77.4 (C-4 dia),76.3 (C-5), 65.2, 65.0 (C-6 dia), 62.1 (OCH_2CH_3), 46.2, 46.0 (C-2 dia), 28.9, 27.5 (C-3 dia), 26.1, 25.7, 25.4, 25.2 (CMe_2 dia), 14.0 (CH_2-CH_3). MS *m/z* (relative intensity) : 243 (M^+-15 (100)), 213 (10), 155 (12), 109 (15), 137 (68), 101 (92). NH_3 chemical ionization 276 (M^++18), 259 (M^++1).

(4*R*, 5*R*)-5,6-Dihydroxy-4-hexanolide (13)

To a solution of **12** (776 mg, 3 mmol) in N,N-dimethylacetamide (12 mL) was added $MgCl_2.6H_2O$ (3.05 g, 15 mmol). The mixture was refluxed for 4 hrs with stirring. After cooling, the mixture was poured in brine and washed with ether (5x50 mL). After acidification of aqueous layers until pH=3 and liophilisation, the residue was extracted with chloroform in a Soxhlet. Removal of solvent at reduced pression afforded 430 mg of **13** (90%) . TLC : CH_2Cl_2/MeOH 8/1, Rf : 0.22.

$[\alpha]_D$ -43.3 (c 0.9, CH_2Cl_2). IR (film) : 3380, 1775 cm^{-1}. ^1H NMR δ : 4.57 (1H, m, H-4), 3.69 (3H, m, H-5-6), 2.52 (2H, m, H-2), 2.23 (2H, m, H-3). ^{13}C NMR δ : 178.0 (C-1), 80.7 (C-4), 73.5 (C-5), 63.3 (C-6), 28.4 (C-2), 23.9 (C-3).

(4*R*, 5*R*)-5-Hydroxy-6-*para*-toluenesulfonyloxy-4-hexanolide (14)

At -20°C to a solution of **13** (58 mg, 0.4 mmol) in CH_2Cl_2 (2mL) was added dropwise *para*-toluenesulfonyl chloride (75.3 mg, 0.4 mmol) in triethylamine (83 µL) and dichloromethane (800 µL). The mixture was stirred 3 hrs at -20°C, then overnight at room temperature and poured into water, extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue (CH_2Cl_2/AcOEt 8/2 ; Rf : 0.65 for the ditosyl and Rf : 0.21 for the monotosyl) afforded 10.6 mg of ditosyl product and 30.6 mg (26 %) of the monotosyl product **14**.

^1H NMR δ : 8.8, 7.35 (4H, 2d, Ar, J=8Hz), 4.54 (1H, dt, H-4, J=2.7, 7Hz), 4.09 (2H, m, H-6), 3.91 (1H, m, H-5), 2.2-2.8 (5H, m, H-2, H-3, OH), 2.43 (3H, s, OCH_3).

(4*R*, 5*R*)-5-Hydroxy-6-triisopropylbenzensulfonyloxy-4-hexanolide (15)

At 0°C to a solution of **13** (58 mg, 0.4 mmol) in pyridine (900 µL) was added dropwise triisopropyl benzenesulfonyl chloride (160.7 mg, 0.53 mmol). The mixture was stirred 45 min at 0°C and overnight at room temperature. Then CH_2Cl_2 and an aqueous hydrochloride acid solution were added. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/AcOEt 1/1 ; Rf : 0.33) afforded 68 mg of **15** (41 %).

^1H NMR δ : 7.2 (2H, s, Ar), 4.55 (1H, m, H-4), 3.8-4.3 (4H, m, H-5,-6, OH), 2.0-3.1 (7H, H-2, 3, $CHMe_2$), 1.3 (18H, m, $CHMe_2$).

(4*R*, 5*R*)-5,6-Epoxy-4-hexanolide (16)

a) From **13** : Mitsunobu reaction on **13** was carried out under identical conditions as for **5** described beforehand. Flash chromatography (cyclohexane/AcOEt 2/8 ; Rf : 0.27) afforded **16** (65 % yield).

b) From **15** : At 0°C to a solution of **15** (250 mg, 0.6 mmol) in THF (6.5 mL) and dimethylsulfoxide (106 mL) was added NaH (17.4 mg, 0.73 mmol). After 2.5hrs stirring at room temperature, a saturated aqueous solution of NH_4OAc (2 mL) was added and the mixture was poured into a suspension of dichloromethane and brine. After extraction, the organic layers were dried ($MgSO_4$), filtered and concentrated

in vacuo to give an oil (65.7 mg) Flash chromatography of the oil (cyclohexane/AcOEt 2/8) afforded 49 mg of **16** (63 %).

^{1}H NMR δ : 4.53 (1H, m, H-4, $J_{4,5}$=3.4Hz, $J_{3,4}$=$J_{3',4}$=6.6Hz), 3.08 (1H, m, H-5, $J_{4,5}$=$J_{5,6}$=$J_{5,6'}$= 3.4Hz), 2.71 (2H, m, H-6), 2.4-2.7 (2H, m, H-2), 2.2-2.4 (2H, m, H-3). ^{13}C NMR δ : 176.5 (C-1), 77.2 (C-4), 53.1 (C-5), 43.8 (C-6), 27.7 (C-3), 24.9 (C-2).

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

a) From **8** : To a solution of **8** (25.3 mg, 0.063 mmol) in CH_2Cl_2 (640 µL) was added at room temperature, water (37 µL) and dicyanodichloroquinone (21.5 mg, 0.095 mmol). After 2 hrs stirring, the mixture was poured into an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. Organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography of the residue afforded 13 mg of (-)- Muricatacin **1** (71 %).

b) From **11** : Decarbethoxylation of crude product **11** (obtained from 181 mg of **10**) was carried out under identical conditions as for **7** described beforehand, and 41 mg of (-)-Muricatacin was obtained with 20 % yield from the epoxy alcohol **10** after flash chromatography (cyclohexane/AcOEt 7/3 ; Rf : 0.17).

c) From **16** : Nucleophilic opening of **16** (51 mg, 1.2 mmol) by undecyl magnesiumbromide in presence of Li_2CuCl_4 was carried out as for **3** described above but the mixture undecyl magnesiumbromide-Li_2CuCl_4 was poured at -78°C on the solution of the epoxylactone **16** in THF. After flash chromatography 34% of starting material **16** (20 mg) and 38% of (-)-Muricatacin **1** (49 mg) were obtained (58% yield of **1** based on 66% conversion of **16**).

1 : m.p. 71°C, lit. 72°C,[9a] 67-68°C,[9c] 73°C,[9h] 57-58°C,[8] $[\alpha]_D$ -22 (c 0.64, $CHCl_3$), -22 (c 0.67, MeOH), lit. -22.9 (c 1.1, $CHCl_3$),[9a] -23.3 ($CHCl_3$),[8] -22.9 (c 1.1, $CHCl_3$),[9b] -24.4 (c 1.70, MeOH),[9b] -23.5(c 1, $CHCl_3$),[9d] -18.8 (c 2.4, $CHCl_3$)[8]. IR (film) 3435, 1770 cm^{-1}.

^{1}H NMR (500 MHz) δ[19] : 4.39 (1H, part X highly coupled system ABCDXY, H-4, $J_{4,5}$=7.3Hz, $J_{4,3\beta}$=8Hz), 3.50 (1H, m, part Y, H-5, $J_{4,5}$=7.3Hz), 2.60 (1H, m, part AB, H-2α, $J_{2\alpha,3\beta}$=9.9Hz, $J_{3\alpha,2\alpha}$=4.8Hz, $J_{2\alpha,2\beta}$=-17.8Hz), 2.54 (1H, m, part AB, H-2β, $J_{2\beta,3\alpha}$=9.2Hz, $J_{2\beta,3\beta}$=9.2Hz, $J_{2\alpha,2\beta}$ =-17.8Hz), 2.22 (1H, m, part CD, H-3α ,$J_{3\alpha,4}$=4.6Hz, $J_{3\alpha,2\beta}$=9.2Hz, $J_{3\alpha,2\alpha}$=4.8Hz $J_{3\alpha,3\beta}$=-12.6Hz), 2.11 (1H, m, part CD, H-3β, $J_{3\beta,4}$=8Hz, $J_{3\beta,2\beta}$=9.2Hz, $J_{3\beta,2\alpha}$=9.9Hz, $J_{3\alpha,3\beta}$=-12.6Hz), 1.92 (1H, d, OH), 1.51 (2H, m, H-6-6'), 1.23-1.37 (20H, m, $(CH_2)_{10}$), 0.86 (t, 3H, CH_3, J=6.7Hz).

^{13}C NMR (125MHz) δ : 177.1 (C-1), 92.9 (C-4), 73.6 (C-5), 33.0 (C-6), 31.9 (C-7), 29.6, 29.5, 29.3, (C-8-15), 28.7, (C-2), 23.1 (C-3), 22.6 (C-16), 14.1 (C-17).

Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.79 ; H, 11.34. Found : C, 71.78 ; H, 11.37.

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REFERENCES

1. Part II : see following paper in this issue.
2. Muller, C.J.; Kepner, R.T.; Webb, A.D. *Am. J. Enol. Viticult.* **1973**, *24*,5.
3. Muller, C.J.; Maggiora, L.; Kepner, R.E.; Webb, A.D. *J. Agric. Food. Chem.* **1969**, *17*, 1973.

4. Schumacher, J.N.; Green, C.R.; Best, F.W.; Newell, M.P. *J. Agric. Food. Chem.* **1977**, *25*, 310.
5. Wright, A.E.; Schäfer, M.; Miland, S.; Munnecke, D.E.; Sims, J.J. *Tetrahedron Lett.* **1989**, *30*, 5699.
6. Grafe, U.; Reinhardt, G.; Schade, W.; Krehes, D.; Eritt, I.; Fleck, W.F.; Heinrich, E.; Radics, L. *J. Antibiotics* **1982**, *38*, 609.
7. Rieser, M.J.; Kozlowski, U.F.; Wood, K.V.; McLaughin, J.L. *Tetrahedron Lett.* **1991**, *32*, 1137.
8. *L. Factor* : Kang, S.K.; Cho, H-S.; Sim, H-S.; Kim, B-K. *J. Carbohydr. Chem.* **1992**, *11*, 807 and references cited therein.
9. *Muricatacin* : a) Scholz, G.; Tochtermann, W. *Tetrahedron Lett.* **1991**, *32*, 5535. b) Figadère, B.; Harmange, J-C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539. c) Marshall, J.A.; Welmaker, G.S. *Synlett* **1992**, 537. d) Wang, Z.M.; Zhang, X.L.; Sharpless, K.B.; Sinha, S.C.; Sinha-Bazchi, A.; Keinan, E. *Tetrahedron Lett.*. **1992**, *33*, 6407. e) Tochtermann, W.; Scholz, G.; Bunte, G.; Wolf, C.; Peters, E.M.; Peters, K.; von Schnering, H.G. *Liebigs Ann. Chem.* **1992**, 1069. f) Yao, Z.J.; Zhang, Y.B.; Wu, Y.L.; Huaxue Xuebao *Acta Chimica Sinica* **1992**, *50*, 901. g) Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597. h) Makabe, H.; Tanaka, A.; Oritani, T. *Biosei. Biotech. Biochem.* **1993**, *57*, 807. i) Gravier-Pelletier, C.; Sanière, M.; Charvet, I.; Le Merrer, Y.; Depezay, J-C. *Tetrahedron Lett.* **1994**, *35*, 115.
10. Gravier-Pelletier, C.; Dumas, J.; Le Merrer, Y.; Depezay, J-C. *J. Carbohydr. Chem.* **1992**, *11*, 969.
11. Hicks, D.R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
12. a) Mitsunobu, O. *Synthesis* **1981**, 1. b) Abushanab, E.; Vemishetti, P.; Leiby, R.W.; Singh, H.K.; Mikkilineni, A.B.; Wu, D.C.J.; Saibaba, R.; Panzica, R.P. *J. Org. Chem.* **1988**, *53*, 2598. c) For a recent review : Hughes, D.L. *Organic Reactions* **1992**, *42*, 335-640.
13. Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 381.
14. Horiba, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitru, O. *Tetrahedron* **1986**, *42*, 3021.
15. Gravier-Pelletier, C.; Le Merrer, Y.; Depezay, J.C. *Synthetic Commun.* **1994**, *24*, 2843.
16. a) Dana, G.; Gharbi-Benarous, J.; Vaissermann, J.; Philoche-Levisalles, M.; Bois, C. *Tetrahedron* **1988**, *44*, 6357.
b) Gharbi-Benarous, J.; Dana, G.; Philoche-Levisalles, M.; Bois, C. *Magn. Reson. Chem.* **1988**, *26*, 457.
17. a) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842. b) Keinan, E.; Sinha, S.C.; Sinha-Bagchi, A.; Wang, Z.M.; Zhang, X.L.; Sharpless, K.B. *Tetrahedron Lett.* **1992**, *33*, 6411. c) Kang, S.K.; Kim, Y.S.; Lim, J.S.; Kim, S.G. *Tetrahedron Lett.* **1992**, *32*, 363 and references cited therein.
18. Wang, Z.H.; Qian, X.H.; Zhou, W.S. *Tetrahedron Lett.* **1990**, *46*, 1191.
19. The assignments have been made using 1D ^{1}H, ^{13}C and 2D heteronuclear (F2 decoupled) NMR spectra on a Bruker AMX 500 spectrometer at room temperature (500 MHz for ^{1}H and 125 MHz for ^{13}C). ^{1}H-^{1}H coupling constants were evaluated by simulation of the signals of H-2, H-3, H-4, H-5. The spectrum simulation was done on a Macintosh II computer using the software NMR II.

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