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Enantiopure Hydroxylactones from *L*-Ascorbic and *D*-Isoascorbic Acids. Part II.[1] Synthesis of (-)-(5*R*, 6*S*)-6-Acetoxy-5-Hexadecanolide and its Diastereomers

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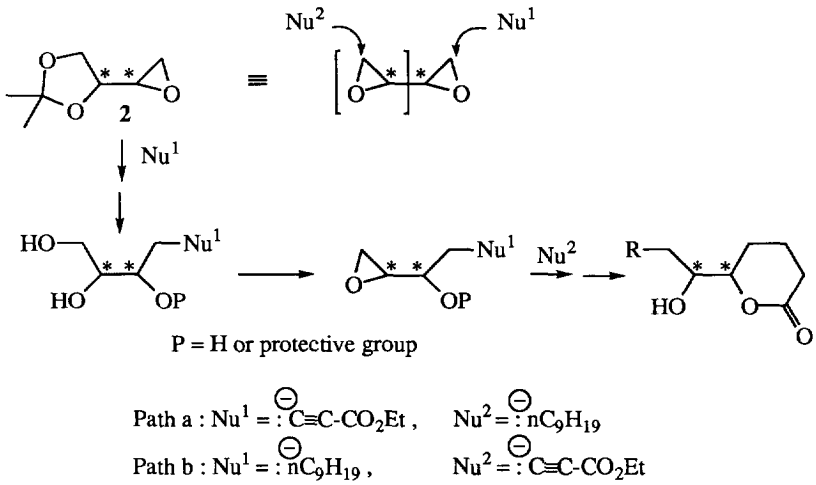
Abstract. Strategies to enantiopure 6-hydroxy-δ-valerolactones, through bis-epoxide formal equivalents issued from *L*-ascorbic and *D*-isoascorbic acids, are studied. The approaches notably involve Mitsunobu reaction on diols or triols and opening of the resulting epoxides.

The major oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*, a possible vector of filarial diseases, the (-)-(5*R*, 6*S*)-6-acetoxy-5-hexadecanolide **1**,[2] has been our target in a project aiming at developing general synthetic strategies towards chiral hydroxy-γ-butyro[1] and δ-valerolactones. These biologically active compounds are widely encountered especially among pheromones.[3] The absolute configuration of the active form being not always known, direct routes to all possible stereoisomers are useful and have been the topic of this study. A part of the results has already been reported in a preliminary form.[4]

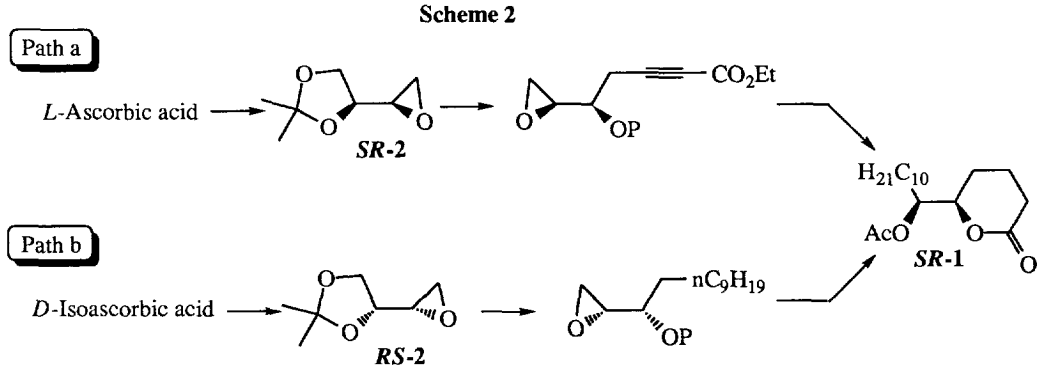
The four possible stereoisomers of enantiomerically pure epoxybutanediol acetonide **2** (Scheme 1) issued from *L*-ascorbic or *D*-isoascorbic acids (40 % overall yield)[5] are used as bis-epoxide formal equivalents containing a free epoxide function, the other one being masked into the glycol. Access to 6-hydroxy-δ-valerolactones requires the introduction of two nucleophiles : on one hand, ethyl lithiopropiolate leading to the formal introduction of $(CH_2)_2CO_2Et$ after hydrogenation ; and, on the other hand, an alkyl organometallic species. Our study involves two paths (a or b) which only differ by the order of introduction of the nucleophiles. Thus, we have examined the nucleophilic opening of 1,2-epoxy-3-ol, bearing a free or a protected hydroxyl group, obtained from the corresponding 1,2,3-triol protected or not in position 3.

Scheme 1



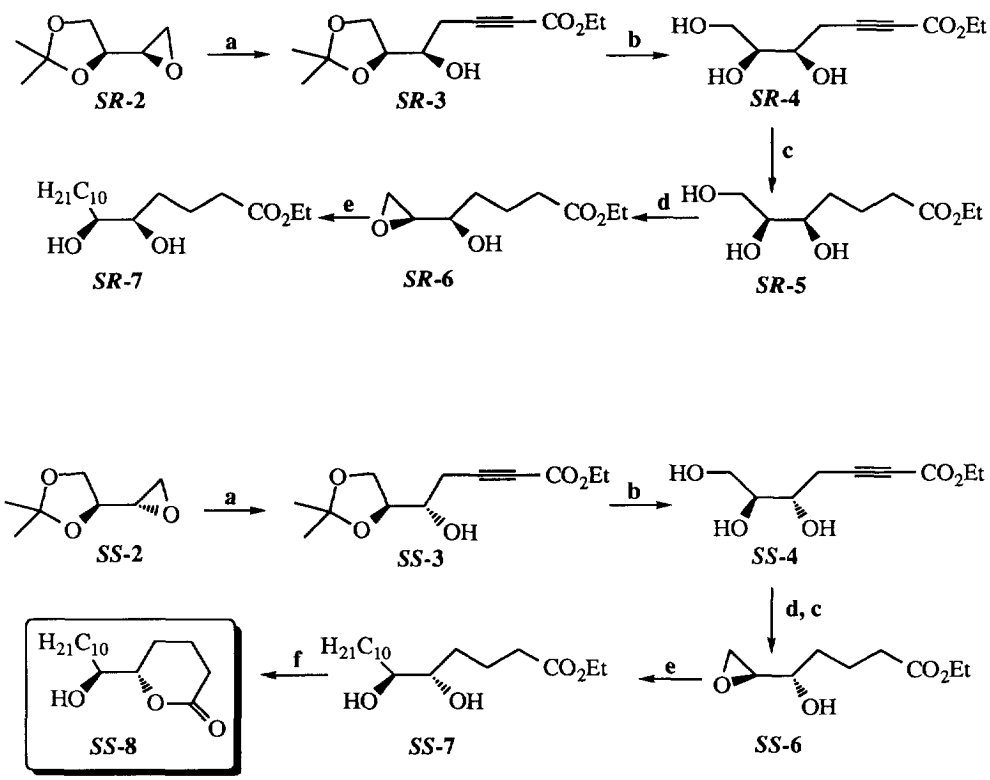
It is noteworthy that to reach the (-)-(5*R*, 6*S*)-6-acetoxy-5-hexadecanolide ***SR*-1** which has an *erythro* relative configuration (Scheme 2), it is necessary that path a start from the (2*S*, 3*R*)-3,4-epoxy-1,2-*O*-methylethylidene butane-1,2-diol ***SR*-2** derived from *L*-ascorbic acid while path b must start from its (2*R*, 3*S*) enantiomer ***RS*-2** coming from *D*-isoascorbic acid.

Scheme 2



Results concerning path a are summarized in Scheme 3.[6] The regiospecific nucleophilic opening of the epoxide ***SR*-2** by excess of ethyl lithiopropiolate in the presence of boron trifluoride etherate afforded the known homopropargylic alcohol[5] ***SR*-3** in 75 % yield. Mild hydrolysis of the acetonide moiety led to the unsaturated triol ***SR*-4** in 90 % yield which was entirely hydrogenated (PtO_2, H_2, 1 atm) to the triol ***SR*-5** in quantitative yield.[7] Epoxidation of the triol ester ***SR*-5** according to Mitsunobu conditions[8] (PPh_3, DIAD, 90°C to 130°C *in vacuo*) led to the epoxide ***SR*-6** in 36 % yield.[9] The regiospecific nucleophilic opening of the epoxide ***SR*-6** by nonyl magnesium bromide in the presence of Li_2CuCl_4[2d] was revealed to be problematical

Scheme 3.[6] **Path a**

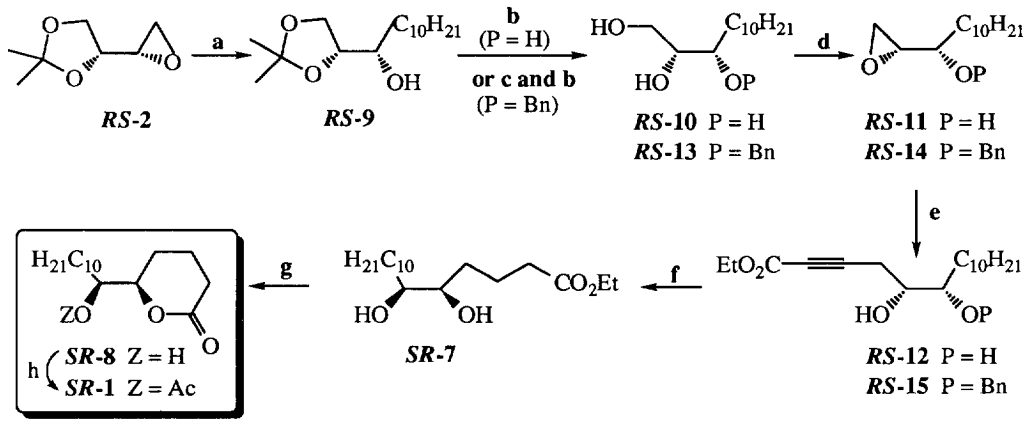


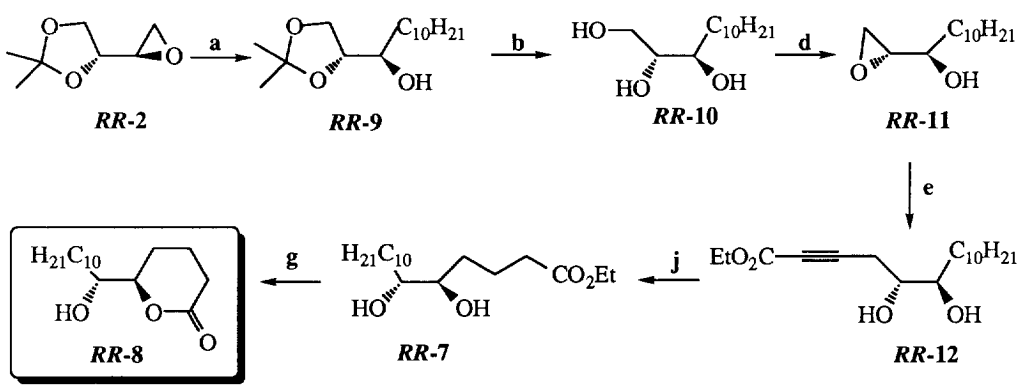
(a) Li-C≡C-CO_2Et, $BF_3.OEt_2$, THF, -100°C, 75 %.[5] (b) Amberlyst H-15 resin, EtOH abs, 50°C, 90 %.(c) H_2, PtO_2, EtOH abs, quantitative yield. (d) PPh_3, DIAD (diisopropyl azodicarboxylate), 90°C to 130°C *in vacuo*, 36 % and 75 % from ***SR*-5** and ***SS*-4**, respectively. (e) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, -50°C, 14 and 34 % from ***SR*-6** and ***SS*-6**, respectively. (f) (i) K_2CO_3, MeOH:H_2O 3:1 ; (ii) HCl 1N ; (iii) 150°C *in vacuo* (0.01 mm Hg), 52 %.

since only 14 % of diol ***SR*-7** was isolated. Opening of the epoxide by halides as well as 2,3-epoxide were detected as side products. The use of higher order mixed organocuprate[10] did not improve the yield.

Interestingly, the same reactions carried out from ***SS*-4** (*threo* relative configuration) took place in better yields (Scheme 3). Thus, epoxidation of the triol ***SS*-4** followed by triple bond reduction cleanly led to the epoxide ***SS*-6** in 75 % yield[9] and its opening by nonyl magnesium bromide in presence of Li_2CuCl_4 occurred in 34 % yield. (Starting material was partly recovered (20 %)). The basic hydrolysis of the ester function (K_2CO_3, MeOH-H_2O) followed by acidification (HCl 1N) and heating under reduced pressure[11] afforded the hydroxylactone ***SS*-8** in 50 % yield from ***SS*-7**.

Scheme 4.[6] **Path b**





(a) $C_9H_{19}MgBr$, Li_2CuCl_4, -35°C, 81 %. (b) AcOH:H_2O 4:1, 20°C, quantitative yield and 85 % for crude ***RS*-10** and ***RR*-10**, respectively and 83 % overall yield for ***RS*-13** from ***RS*-9**. (c) NaH, THF, imidazole, 50°C then BnBr, nBu$_4$NI, 20°C. (d) PPh_3, DIAD (diisopropylazodicarboxylate), 90°C to 130°C *in vacuo*, 25 to 35 % overall yield for ***RS*-9** → ***RS*-11**, 75 % for ***RS*-14** and ***RR*-11**. (e) Li-C≡C-CO_2Et, $BF_3.OEt_2$, THF, ≤ -70°C, 10 %, 22 % and 87 % for ***RS*-12**, ***RR*-12** and ***RS*-15** respectively. (f) H_2, Pd black, AcOH, quantitative yield for ***RS*-15** → ***SR*-7**. (g) (i) K_2CO_3, MeOH:H_2O 3:1 ; (ii) HCl 1N ; (iii) 150°C *in vacuo*, 52 % overall yield for ***RS*-15** → ***SR*-7** → ***SR*-8** and ***RR*-7** → ***RR*-8**. (h) Ac_2O, DMAP, CH_2Cl_2, 20°C, 90 %. (j) H_2, PtO_2, EtOH abs, quantitative yield.

Results concerning path b are summarized in scheme 4. The nucleophilic opening of the epoxide ***RS*-2** by nonyl magnesium bromide in the presence of Li_2CuCl_4[2d] gave the alcohol ***RS*-9** in 81 % yield. Subsequent acidic hydrolysis of the acetonide (AcOH:H_2O 4:1) followed by Mitsunobu reaction on the resulting triol afforded the 1,2-epoxy-alcohol ***RS*-11** in ≈ 30 % overall yield from ***RS*-9**.[9] Attempts of nucleophilic opening of this second epoxide moiety by ethyl lithiopropiolate (3 eq) in the presence of boron trifluoride etherate (3 eq) at -90°C for one hour and -70°C for 3 hours only afforded the stabilised 2,3-*threo*-epoxy-1-alkanol (72 % isolated yield) resulting from Payne rearrangement.[12] When the reaction was carried out in the presence of a larger excess of ethyl lithiopropiolate (5 eq) and boron trifluoride etherate (4 eq, prior to the introduction of the epoxide) at -70°C, the expected ***RS*-12** was isolated in 10 % yield.[13]

Starting from the *threo* epoxide ***RR*-2**, a similar behaviour was observed concerning the opening of the epoxy alcohol ***RR*-11** (scheme 4) obtained by nucleophilic opening of ***RR*-2** with nonyl magnesium bromide[2d] (87 % yield) then acetonide hydrolysis (90 % yield) and epoxidation[9] according to Mitsunobu conditions (75 % yield). However, a better yield (22 %) of the expected ***RR*-12** was obtained.[14] Triple bond reduction and lactonisation of ***RR*-12** in usual manner afforded the lactone ***RR*-8**.

Finally, due to a possible rearrangement of 1,2-epoxy alcohols, prior to or during their openings, and to obtain the pheromone ***SR*-1** in good yield, we turned to a temporary protection of the alcohol function at C-3 (Scheme 4). Thus, the alcohol function of ***RS*-9** was protected as a benzyl ether (NaH, THF, imidazole then BnBr, nBu$_4$NI) and subsequent hydrolysis of the acetonide afforded the diol ***RS*-13** in 83 % overall yield from ***RS*-9**. Optically pure epoxide ***RS*-14** was generated (PPh_3, DIAD) in 75 % yield. Its regiospecific nucleophilic opening by ethyl lithiopropiolate in the presence of boron trifluoride etherate at -80°C cleanly occurred affording the homopropargylic alcohol ***RS*-15** in good yield (87 %). Triple bond hydrogenation together with benzyl protective group hydrogenolysis was carried out in acetic acid by hydrogen (1 atm) in the presence of palladium black. The basic hydrolysis of the ester function (K_2CO_3, MeOH-H_2O) followed by acidification (HCl 1N) and heating under reduced pressure[11] afforded the hydroxylactone ***SR*-8** in 52 % overall yield from ***RS*-15**. Acetylation of the alcohol[2d] (Ac_2O, DMAP, CH_2Cl_2) gave the pheromone ***SR*-1** in 90 % yield.

In summary, the direct strategy through the unprotected 1,2-epoxy-3-ol shows itself to be a less promising method in the particular case of the synthesis of the major oviposition attractant pheromone of the mosquito *Culex pipiens fatigans* and its stereomers, since it involves opening of 1,2-epoxide either by a long chain alkyl magnesium weakly reactive (path a) or by ethyl lithiopropiolate which requires the presence of boron trifluoride etherate (path b), this latter one promotting the Payne rearrangement[12] and nucleophile introduction at C-2.

However, we have demonstrated that through 3-*O*-protected 1,2-epoxy-alkanol, the expected pheromone **1** could be obtained in good yield. Thus, starting either from *L*-ascorbic or *D*-isoascorbic acids, through bis-epoxide formal equivalents, access to enantiopure 6-hydroxy-δ-valerolactones of any absolute configuration is possible.

EXPERIMENTAL SECTION

General experimental techniques are the same as those in part I of this series.[1]

(2R, 3S)-1,2-O-Methylethylidenetridecane-1,2,3-triol ***RS*-9** *and its (2R,3R) diastereomer* ***RR*-9**

A solution of 1-bromononane (3.81 mL, 20 mmol) in THF (8.1 mL) was dropwise added to a stirred suspension of magnesium turnings (480 mg, 20 mmol) in refluxing THF (8.1 mL). The mixture was then stirred under reflux for 30 min.[15] After cooling to 20°C, an aliquot (12.2 mL) of this resulting 1M nonylmagnesium bromide solution was added to a -35°C cooled solution of lithium tetrachlorocuprate in THF (12.2 mL, 0.1 M prepared from cupric chloride (164 mg, 1.22 mmol) and lithium chloride (103.4 mg, 2.44 mmol) in THF (12.2 mL) at 20°C). After 20 min stirring at -35°C, the epoxide ***RS*-2** (or ***RR*-2**) (400 mg, 2.78 mmol) in THF (4 mL) was added and the mixture was stirred at -35°C for 45 min. The reaction was quenched at -35°C by the addition of saturated aqueous NH_4Cl (20 mL) and filtered through a celite pad which was rinsed with ether. After decantation and ether extraction (3x30 mL), the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane:AcOEt 7:3, Et_3N 0.002) afforded 608 mg (81 %) of ***RS*-9** (or ***RR*-9**) (Rf 0.44) as a colorless oil.

***RS*-9** : $[\alpha]_D$ +8.8 (c 1.03, CH_2Cl_2) ; ^1H NMR δ 0.85 (t, 3H, J=6.5, H-13), 1.15-1.60 (m, 18H, H-4-12), 1.35, 1.43 (2s, 6H, CMe_2), 3.76 (m, 1H, H-3), 3.82-4.08 (m, 3H, H-1,2) ; ^{13}C NMR δ 14.1 (C-13), 25.3, 26.5 (CMe_2), 22.7, 25.8, 29.3, 29.6, 31.9, 32.7 (C-4-12), 64.5 (C-1), 70.7, 78.7 (C-2,3), 108.9 (CMe_2) ; Anal. Calcd for $C_{16}H_{32}O_3$; C, 70.54 ; H, 11.84. Found : C, 70.65 ; H, 11.69.

***RR*-9** : $[\alpha]_D$ +14 (c 1.05, CH_2Cl_2) ; ^1H NMR δ 0.86 (t, 3H, J=6.5, H-13), 1.15-1.60 (m, 18H, H-4-12), 1.35, 1.42 (2s, 6H, CMe_2), 3.48 (m, 1H, H-3), 3.70 (m, 1H, H-2), 3.98 (m, 2H, H-1) ; ^{13}C NMR δ 14.1 (C-13), 22.7, 25.5, 29.3, 29.6, 31.9, 33.7 (C-4-12), 25.3, 26.7 (CMe_2), 66.2 (C-1), 72.3, 79.2 (C-2,3), 109.3 (CMe_2).

(2R, 3S)-Tridecane-1,2,3-triol ***RS*-10** *and its (2R, 3R) diastereomer* ***RR*-10**

The acetonide ***RS*-9** (or ***RR*-9**) (588 mg, 2.16 mmol) in a 4:1 acetic acid:H_2O mixture (26 mL) was stirred at 20°C for 24 h. Concentration *in vacuo* and co-evaporation with cyclohexane afforded the crude corresponding triols as white solids in quantitative yield. ***RS*-10** was used in the next step without further purification. T.l.c. control of ***RR*-10** (AcOEt:cyclohexane 8:2) revealed the presence of non polar impurities which were discarded by resuspending the crude in cyclohexane and filtered off the filtrate (3x20 mL). Thus, 424 mg (85 %) of the triol ***RR*-10** was isolated as a white solid (single spot in tlc).

***RS*-10** : ^1H NMR (90 MHz) δ 0.90 (t, 3H, H-13), 1.10-1.70 (m, 18H, H-4-12), 3.45-3.95 (m, 4H, H-1-3).

***RR*-10** : Mp 107°C ; $[\alpha]_D$ +9 (c 1.14, EtOH abs) ; ^1H NMR δ 0.90 (t, 3H, H-13), 1.20-1.45 (m, 14H, H-6-12), 1.45-1.65 (m, 4H, H-4-5), 3.57 (m, 1H, H-3), 3.65 (m, 1H, H-2), 3.72 (m, 1H, H-1), 3.78 (dd, J=11, J=3.5, H-1'); ^{13}C NMR (CD_3OD) 14.4 (C-13), 23.7, 27.0, 30.5, 30.8, 33.1, 34.3 (C-4-12), 64.6 (C-1), 72.7, 75.5 (C-2,3).

(2R, 3S)-1,2-Epoxy-3-tridecanol ***RS*-11** *and its (2R, 3R) diastereomer* ***RR*-11**

Both epoxides were obtained by Mitsunobu reaction (PPh_3 : 1.16 eq, DIAD (diisopropyl azodicarboxylate) : 1.18 eq, toluene, 0°C, 30 min then concentration *in vacuo* and heating to 130°C under P=0.01 mmHg) on the corresponding triols ***RS*-10** and ***RR*-10**.[9]

***RS*-11** was obtained in 25 to 35 % yield as white crystals.[9] Mp 30-32°C ; $[\alpha]_D$ +15 (c 2.1, $CHCl_3$) ; selected data : ^1H NMR δ 2.71 (dd, 1H, $J_{1,1'}$=5, $J_{1,2}$=4, H-1), 2.78 (dd, 1H, $J_{1',1}$=5, $J_{1',2}$=2.75, H-1'), 3.00 (ddd, 1H, $J_{2,3}$= $J_{2,1}$ =4, $J_{2,1'}$=2.75, H-2).

***RR*-11** was obtained in 75 % yield as a white flocculent solid.[9] Mp 37°C ; $[\alpha]_D$ -3.2 (c 0.99, $CHCl_3$) ; selected data : ^1H NMR δ 2.70 (dd, 1H, $J_{1,1'}$=5, $J_{1,2}$=2.75, H-1), 2.80 (dd, 1H, $J_{1',1}$=5, $J_{1',2}$=4, H-1'), 2.96 (ddd, 1H, $J_{2,3}$=5, $J_{2,1'}$=4, $J_{2,1}$=2.75, H-2).

Ethyl (5R, 6S)-5,6-Dihydroxy-2-hexadecynoate ***RS*-12** *and its (5R, 6R) diastereomer* ***RR*-12**

To a solution of ethylpropiolate (366 µL, 3.62 mmol) in THF (4.2 mL) at -80°C was dropwise added *n*BuLi (1.17 M in hexanes, 3.09 mL, 3.62 mmol). The resulting orange solution was stirred at -80°C for 30 min and the epoxide ***RR*-11** (155 mg, 0.72 mmol) in THF (1.4 mL) and $BF_3.OEt_2$ (357 µL, 2.90 mmol) were successively added. For the ***RS*-12** isomer, boron trifluoride etherate was added prior to the introduction of the epoxide ***RS*-11** (same quantities). After stirring for 2 h at -70°C the reaction was quenched at -70°C by the addition of saturated aqueous NH_4Cl (10 mL) and diluted with ether (20 mL). After decantation and ether extraction (3x15 mL), the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (cyclohexane:AcOEt 6:4, Et_3N 0.002) respectively afforded :

- from ***RS*-11** : 23 mg (10 %) of ***RS*-12** (Rf 0.34) together with 34 mg (22 %) of transposed 2,3-epoxide ***SS*-17** (Rf 0.36) and 59 mg (26 %) of **18** (Rf 0.26) resulting from nucleophilic opening at C-2 of the 1,2-epoxide.[13]

- from ***RR*-11** : 50 mg (22 %) of ***RR*-12** (Rf 0.33) together with 97 mg (43 %) of a compound resulting from nucleophilic opening at C-2 of the 1,2-epoxide (Rf 0.26).

***RS*-12** : ^1H NMR δ 0.86 (t, 3H, J=6.5, H-16), 1.10-1.80 (m, 21H, H-7-15, OEt), 2.59 (m, 2H, H-4), 3.69-3.77 (2m, 2H, H-5,6), 4.20 (q, 2H, J=7, OEt).

***RR*-12** : $[\alpha]_D$ +12 (c 1.00, CH_2Cl_2) ; ^1H NMR δ 0.86 (t, 3H, J=6.5, H-16), 1.10-1.40 (m, 17H, H-9-15, OEt), 1.40-1.65 (m, 4H, H-7,8), 2.60 (d, 2H, $J_{4,5}$=6, H-4), 3.58 (ddd, 1H, $J_{6,7}$=$J_{6,7'}$=6, $J_{6,5}$=4, H-6), 3.69 (dt, 1H, $J_{5,4}$=$J_{5,4'}$=6, $J_{5,6}$=4, H-5), 4.20 (q, 2H, J=7, OEt) ; ^{13}C NMR δ 14.0, 14.1 (C-16,OEt), 22.7, 24.4, 25.5, 29.3, 29.6, 29.7, 31.9, 33.6 (C-4,7-15), 62.0 (OEt), 71.7, 73.0 (C-5,6), 75.0, 85.4 (C-2,3), 153.5 (C-1).

(2R, 3S)-3-O-Benzyltridecane-1,2,3-triol ***RS*-13**

To a suspension of sodium hydride (89.6 mg, 3.73 mmol) in dry THF (1.44 mL), at 0°C, was added the alcohol ***RS*-9** (442 mg, 1.62 mmol) in THF (3 mL). After addition of a crystal of imidazole, the temperature was raised to 20°C for 30 min and 50°C for an hour, and cooled again to 20°C prior to the introduction of benzylbromide (480 µL, 4.05 mmol) and *n*-tetrabutylammonium iodide (60 mg, 0.16 mmol). T.l.c. monitoring of the reaction after 12 h at 20°C (cyclohexane:AcOEt 9:1) revealed a ≈90 % conversion of ***RS*-9** (Rf 0.15) into benzyl alcohol (Rf 0.48) so that a further addition of NaH (1 eq) ImH (1 crystal) then heating for one hour at 50°C followed by addition of $PhCH_2Br$ (1 eq) at 20°C was performed in order to complete the reaction. After 6

h at 20°C, the reaction was quenched by the addition of methanol and concentrated *in vacuo*. Addition of ether (30 mL) and filtration through a celite pad was followed by addition of water (15 mL). After decantation and ether extraction (3x20 mL), the combined extracts were washed with brine, dried and concentrated *in vacuo*. Crude benzyl alcohol was isolated in quantitative yield. A sample was purified by flash chromatography (cyclohexane:AcOEt 9:1, Rf 0.48). $[\alpha]_D$ +5.4 (c 1.035, CH_2Cl_2) ; ^1H NMR δ 0.87 (t, 3H, J=6.5, H-13), 1.20-1.60 (m, 18H, H-4-12), 1.34-1.41 (2s, 6H, CMe_2), 3.53 (ddd, 1H, $J_{3,2}=J_{3,4}=5.5$, $J_{3,4'}=4$, H-3), 3.89 (dd, 1H, $J_{1,1'}=J_{1,2}=7$, H-1), 4.01 (dd, 1H, $J_{1',1}=J_{1',2}=7$, H-1'), 4.09 (ddd, 1H, $J_{2,1}=J_{2,1'}=7$, $J_{2,3}=5.5$, H-2) ; 4.57, 4.65 (AB, 2H, $J_{A,B}=11.5$, CH_2Ph), 7.32 (m, 5H, Ph) ; ^{13}C NMR δ 14.1 (C-13), 22.7, 25.0, 29.3, 29.6, 29.7, 31.3, 31.9 (C-4-12), 25.4, 26.6 (CMe_2), 66.2 (C-1), 72.3 (CH_2Ph), 78.0, 79.0 (C-2,3), 108.9 (CMe_2), 127.5, 127.7, 128.3, 138.7 (Ph).

The crude acetonide (≤ 1.62 mmol) in AcOH:H_2O 4:1 (12 mL) was stirred overnight at 20°C. Concentration *in vacuo* and flash chromatography (cyclohexane:AcOEt 1:1, Et_3N:0.002) of the residue afforded 434 mg (83 % overall yield from ***RS*-9**) of the diol ***RS*-13** (Rf 0.31) as a colorless oil. $[\alpha]_D$ +6.4 (c 1.07, CH_2Cl_2) ; ^1H NMR δ 0.87 (t, 3H, J=6.5, H-13), 1.10-1.75 (m, 18H, H-4-12), 3.57 (m, 1H, H-3), 3.72 (m, 3H, H-1,2), 4.54, 4.64 (AB, 2H, $J_{A,B}=11.5$, CH_2Ph), 7.32 (m, 5H, Ph) ; ^{13}C NMR δ 14.1 (C-13), 22.7, 25.4, 29.3, 29.6, 29.8, 30.5, 31.9 (C-4-12), 63.3 (C-1), 72.7 (CH_2Ph), 72.7, 81.3 (C-2,3), 127.8, 128.4, 138.2 (Ph) ; Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49 ; H, 10.63. Found : C, 74.54 ; H, 10.67.

(2R, 3S)-3-Benzyloxy-1,2-epoxy-tridecane ***RS*-14**

A solution of the diol ***RS*-13** (395 mg, 1.23 mmol) in toluene (7 mL) was concentrated twice *in vacuo* to avoid any trace of water. Then toluene (7 mL) and triphenylphosphine (598 mg, 2.28 mmol) were added and the resulting mixture was again concentrated *in vacuo*. After a further addition of toluene (7 mL), the mixture was cooled to 0°C and diisopropyl azodicarboxylate (460 µL, 2.34 mmol) was slowly added. After being stirred for 30 min at 0°C, the pale orange resulting mixture was concentrated *in vacuo* and heated under P=0.01 mm Hg to 130°C within 90 min including 10 min at 130°C. Flash chromatography of the crude (CH_2Cl_2, Et_3N : 0.002) afforded 280 mg (75 %) of pure epoxide ***RS*-14** (Rf 0.48). $[\alpha]_D$ -17 (c 1.16, CH_2Cl_2) ; ^1H NMR δ 0.87 (t, 3H, J=7, H-13),1.15-1.70 (m, 18H, H-4-12), 2.70 (dd, 1H, $J_{1,1'}=5$, $J_{1,2}=2.75$, H-1), 2.77 (dd,1H,$J_{1',1}=5$,$J_{1',2}=4$, H-1'), 2.92 (ddd, 1H, $J_{2,3}=6$, $J_{2,1'}=4$, $J_{2,1}=2.75$, H-2), 3.24 (ddd, 1H, $J_{3,2}=J_{3,4}=J_{3,4'}=6$, H-3), 4.49, 4.64 (AB, 2H, $J_{A,B}=11.5$, CH_2Ph), 7.31 (m, 5H, Ph) ; ^{13}C NMR δ 14.1 (C-13), 22.7, 25.2, 29.3, 29.6, 31.9, 32.9 (C-4-12), 45.6, 53.6 (C-1,2), 72.3 (CH_2Ph), 78.1 (C-3), 127.6, 127.7, 128.3,138.6 (Ph); Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90 ; H, 10.59. Found : C, 78.75 ; H, 10.44.

Ethyl (5R, 6S)-5-hydroxy-6-benzyloxy-2-hexadecynoate ***RS*-15**

To a solution of ethylpropiolate (130 µL, 1.28 mmol) in THF (1.8 mL) at -80°C was dropwise added *n*BuLi (1.3 M in hexanes, 985 µL, 1.28 mmol). The resulting orange solution was stirred at -80°C for 30 min and the epoxide ***RS*-14** (130 mg, 0.43 mmol) in THF (1.3 mL) and $BF_3.OEt_2$ (158 µL, 1.28 mmol) were successively added at -100°C. After 2 h at -100°C and 3 h at -80°C, the reaction was quenched at -80°C by the addition of saturated aqueous NH_4Cl (10 mL) and diluted with ether (20 mL). After decantation and ether extraction (3x10 mL), the combined organic layers were washed with brine and concentrated *in vacuo*. Flash chromatography of the residue (CH_2Cl_2:Et_2O 95:5) afforded 149 mg (87 %) of the homopropargylic alcohol

***RS*-15** as an oil. $[\alpha]_D$ +23 (c 1.21, CH_2Cl_2) ; ^1H NMR δ 0.86 (t, 3H, J=7, H-16), 1.15-1.70 (m, 21H, CO_2Et, H-7-15), 2.55, 2.63 (AB from ABX system, 2H, $J_{A,B}$=17.5, $J_{A,X}$=6, $J_{B,X}$=6.5, H-4), 3.48 (m, 1H, H-6), 3.92 (m, 1H, H-5), 4.20 (q, 2H, J=7, OEt), 4.54, 4.60 (AB, 2H, J_{AB}=11.5, CH_2Ph), 7.32 (m, 5H, Ph) ; ^{13}C NMR δ 14.0, 14.1 (C-16,OEt), 22.7, 22.9, 25.2, 29.3, 29.6, 29.8, 31.9 (C-4,7,8-15), 61.9 (OEt), 70.5, 80.8 (C-5,6), 72.4 (CH_2Ph), 74.8, 85.9 (C-2,3), 127.8, 127.9, 128.5, 138.2 (Ph), 153.5 (C-1) ; Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59 ; H, 9.51. Found : C, 74.55 ; H, 9.60.

*Ethyl (5R, 6S)-5,6-dihydroxy-hexadecanoate **SR*-7 and its diastereomers (5R, 6R) **RR*-7 and (5S, 6S) **SS*-7**

The diol ***SR*-7** was obtained according to two ways :

. From ***RS*-15** : palladium black (18 mg, Aldrich) in acetic acid (10 mL) was completely hydrogenated prior to the addition of the benzylated alkyne ***RS*-15** (60 mg, 0.15 mmol) in acetic acid (5 mL). After the theorical volume of hydrogen (11 mL) had been absorbed, the catalyst was removed by filtration through a celite pad and rinsed with AcOH. Concentration *in vacuo* and azeotropic distillation with cyclohexane afforded the saturated ester-diol as a white solid in quantitative yield. It was used without further purification in the next step.

. From the ***SR*-6** epoxide : a solution of 1-bromononane (952 µL, 5 mmol) in THF (1.7 mL) was dropwise added to a stirred suspension of magnesium turnings (120 mg, 5 mmol) in refluxing THF (1.7 mL). The mixture was then stirred under reflux for 30 min.[15] After cooling to 20°C, an aliquot (1.08 mL, 1.24 mmol) of this resulting 1.15 M nonylmagnesium bromide solution was added to a -35°C cooled solution of lithium tetrachlorocuprate in THF (1.24 mL, 0.1M in THF prepared from LiCl and $CuCl_2$). After 20 min stirring at -35°C, the resulting organometallic mixture was added to a -80°C cooled solution of the epoxide ***SR*-6** (38.8 mg, 0.21 mmol) in THF (1.2 mL) so that the resulting temperature of the reaction was ≈ -50°C. After one hour stirring at -50°C, the reaction was quenched by the addition of saturated aqueous ammonium acetate (6 mL) and filtered through a celite pad which was rinsed with ether (20 mL). After decantation and ether extraction (3x15 mL), the organic layers were washed with brine and concentrated *in vacuo*. Flash chromatography of the residue (AcOEt:cyclohexane 6:4, Et_3N 0.002) afforded 9 mg (14 %) of the expected ***SR*-7** (Rf 0.39) as a white solid. 27 mg of a product resulting from opening of the epoxide by an halide (Rf 0.32) was also isolated.

***SR*-7** : Mp 91-93°C ; $[\alpha]_D$ +0.9 (c 0.7, CH_2Cl_2) ; ^1H NMR δ 0.85 (t, 3H, J=6.5, H-16), 1.15-1.90 (m, 25H, H-3,4,7-15, OEt), 2.34 (t, 2H, $J_{2,3}$=7, H-2), 3.58 (m, 2H, H-5,6), 4.11 (q, 2H, J=7, OEt) ; ^{13}C NMR δ 14.0, 14.2 (C-16,OEt), 21.2, 22.7, 26.0, 29.3, 29.6, 30.5, 31.5, 31.9, 34.1 (C-2-4,7-15), 60.4 (OEt), 74.1, 74.6 (C-5,6), 173.8 (C-1) ; Anal. Calcd for $C_{18}H_{36}O_4$: C, 68.31 ; H, 11.47. Found : C, 66.52 ; H, 11.14 in agreement with 2.7 % of H_2O.

The saturated diol ***RR*-7** was obtained from the homopropargylic diol ***RR*-12**. Platinum oxide (11 mg, Merck, PtO_2 80 %) in absolute EtOH (9 mL) was entirely hydrogenated prior to the addition of the alkyne ***RR*-12** (43 mg, 0.14 mmol) in EtOH abs (3 mL). After absorption of the theoretical volume of hydrogen (7 mL), the catalyst was removed by filtration through a celite pad and the organic layer was concentrated *in vacuo* to afford crude ***RR*-7** in quantitative yield. It was used without further purification in the next step. ^1H NMR δ 0.85 (t, 3H, J=7, H-16), 1.10-1.88 (m, 25H, H-3,4,7-15, OEt), 2.33 (t, 2H, $J_{2,3}$=7, H-2), 3.37 (m, 2H, H-5,6), 4.10 (q, 2H, J=7, OEt).

The diol ***SS*-7** was obtained by nucleophilic opening of the ***SS*-6** epoxide by nonylmagnesium bromide as described above for the opening of the ***SR*-6** epoxide and afforded the expected ***SS*-7** diol in 34 % yield (20 % of the starting material ***SS*-6** was recovered). The ^{1}H NMR spectrum of ***SS*-7** was identical to that of ***RR*-7**.

(5R, 6S)-6-Hydroxy-5-hexadecanolide ***SR*-8** *and its diastereomers (5R, 6R)* ***RR*-8** *and (5S, 6S)* ***SS*-8**

The same experimental protocol was followed for each compound. To the ester-diol ***SR*-7** (resp. ***RR*-7** or ***SS*-7**) (≤ 0.15 mmol) in MeOH:H_2O 3:1 (6 mL) at 20°C was added potassium carbonate (31 mg, 0.23 mmol). After 5 h at 20°C, the mixture was diluted with chloroform then acidified to pH 2 by addition of 1N HCl and the methanol was evaporated. Ether extraction (5x7 mL), drying ($MgSO_4$), filtration and concentration afforded the crude acid which was heated at 150°C *in vacuo* (0.01 mm Hg) for 20 min [11] (Büchi) to lactonize. Flash chromatography (AcOEt : cyclohexane 2:1, Et_3N : 0.002) afforded 21 mg (52 % overall yield from ***RS*-15**, resp. ***RR*-7** and ***SS*-7**) of the hydroxylactone ***SR*-8** (resp. ***RR*-8** and ***SS*-8**) each of them as crystals.

***SR*-8** : Mp 67-68°C (Büchi), (lit.[11] 67-68°C) ; $[\alpha]_D$ -12.6 (c 1.05, $CHCl_3$), (lit. -12.5 (c 0.54, $CHCl_3$)[11], -13.9 (c 0.4, $CHCl_3$)[16], -12.4 (c 5.0, $CHCl_3$)[17] ; ^{1}H NMR δ 0.86 (t, 3H, J=6.8, H-16), 1.15-1.65 (m, 18H, H-7-15), 1.65-2.05 (m, 4H, H-3,4), 2.46, 2.60 (2m, 2H, $J_{2,2'}$=18, H-2,2'), 3.80 (m, 1H, H-6), 4.24 (m, 1H, H-5) ; ^{13}C NMR δ 13.9 (C-16), 18.1, 21.0, 22.4, 25.6, 29.3, 31.7 (C-2-4,7-15), 72.2, 83.3 (C-5,6).

***RR*-8** : Mp 68-70°C ; (lit. 67-69°C,[18] 73-74°C [2c]) ; $[\alpha]_D$ -10.2 (c 0.87, $CHCl_3$), (lit. -12.2 (c 1.4, $CHCl_3$)[18], -11 (c 0.9, $CHCl_3$)[2c]) ; ^{1}H NMR δ 0.88 (t, 3H, J=6.9, H-16), 1.18-1.65 (m, 18H, H-7-15), 1.65-2.05 (m, 4H, H-3,4), 2.46, 2.64 (2m, 2H, $J_{2,2'}$=18, H-2,2'), 3.57 (m, 1H, H-6), 4.19 (m, 1H, H-5) ; ^{13}C NMR δ 14.1 (C-16), 18.4, 22.7, 24.2, 25.4, 29.3, 29.6, 31.9, 32.7 (C-2-4,7-15), 73.4, 83.2 (C-5,6), 171.3 (C-1) ; HRMS calcd for $C_{16}H_{30}O_3$ (M^+) 270.2195, found 270.2192.

***SS*-8** : Mp 68-70°C ; $[\alpha]_D$ +11.5 (c 1.0, $CHCl_3$) ; ^{1}H NMR spectrum was identical to that of ***RR*-8** ; ^{13}C NMR (500 MHz) δ 14.1 (C-16), 18.4, 22.7, 24.2, 25.4, 29.3, 29.5,29.6, 29.7, 31.9, 32.7 (C-2-4,7-15), 73.4, 83.2 (C-5,6), 171.3 (C-1) ; HRMS calcd for $C_{16}H_{30}O_3$ (M^+) 270.2195, found 270.2195.

(5R, 6S)-6-Acetoxy-5-hexadecanolide ***SR*-1**

To the ***SR*-8** hydroxylactone (20.6 mg, 0.08 mmol) in CH_2Cl_2 (500 µL), at 20°C, was added 4,4-dimethylamino pyridine (65.6 mg, 0.54 mmol) and acetic anhydride (50 µL, 0.53 mmol). After 1 hour at 20°C, the reaction was quenched with brine. Extraction with CH_2Cl_2 (3x10 mL), drying ($MgSO_4$), filtration, concentration *in vacuo* and flash chromatography (AcOEt : cyclohexane 1:1, Et_3N : 0.002) afforded 21 mg (88 %, Rf 0.47) of the pheromone ***SR*-1** as a colorless oil. $[\alpha]_D$ -38 (c 1.02, $CHCl_3$), (lit. -38.5 (c 0.51, $CHCl_3$)[11], -37.4 (c 1.55, $CHCl_3$)[17], -36.8 (c 1.0, $CHCl_3$)[2c], -38.1 (c 0.4, $CHCl_3$)[2d]) ; ^{1}H NMR δ 0.86 (t, 3H, J=6.8, H-16), 1.10-1.45 (m, 16H, H-8-15), 1.50-2.00 (2m, 6H, H-3,4,7), 2.06 (s, 3H, OAc), 2.43, 2.60 (2m, 2H, H-2,2'), 4.33 (m, 1H, H-5), 4.96 (m, 1H, H-6) ; ^{13}C NMR δ 14.1 (C-16), 18.3, 22.7, 23.5, 25.3, 29.3, 29.4, 29.5, 31.9 (C-2-4,7-15), 21.0 (OAc), 74.3, 80.5 (C-5,6), 170.4, 170.8 (C-1,OAc) ; Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19 ; H, 10.32. Found : C, 69.18 ; H, 10.31.

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1. Part I : see previous paper in this issue.

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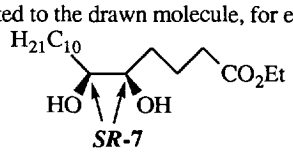
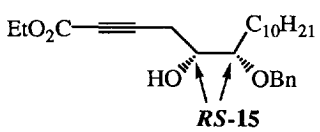
6. For all compounds, the absolute configuration of each carbon atom is always indicated from the left to the right related to the drawn molecule, for example :

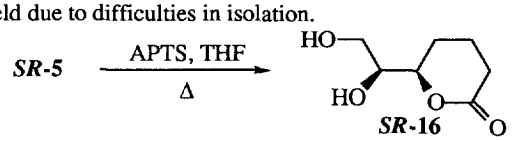


***SR*-7**



***RS*-15**

7. The lactone-diol ***SR*-16**, a possible precursor of the pheromone ***SR*-1**, can be obtained from the triol ***SR*-5** in only 40 % yield due to difficulties in isolation.



***SR*-16**

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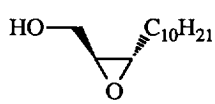
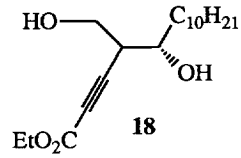
13. Apart from the expected ***RS*-12** isolated in 10 % yield, the *threo* 2,3-epoxy-1-alkanol ***SS*-17**, resulting from Payne rearrangement and **18**, resulting from nucleophilic introduction of the ethyl propiolate at C-2 catalysed by boron trifluoride etherate, were respectively isolated in 22 and 26 % yields.



***SS*-17**



18

14. In this case, no *erythro* 2,3-epoxy-1-alkanol was detected but the compound resulting from introduction of ethyl propiolate at C-2 was the major product (43 % isolated yield).

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