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2- AND 8- FUNCTIONALIZED 1,4,7,10-TETRAOXASPIRO[5.5]UNDECANES. II. Synthesis of (+)-E,E and (±)-Z,E structures from chiral isopropylideneglycerols.

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Abstract: *Using a short synthetic protocol, the enantiomerically pure (+)-E,E title compound was made from (S,S)-diisopropylidenetriglycerol* ***4*** *in order to obtain a reference for correlations in this unexplored series. Analogously (S,R)-diisopropylidenetriglycerol* ***11*** *would afford the (±)-Z,E isomer which was also prepared. Conformations were deduced from* ^1H *NMR data .*

The synthesis of enantiomerically pure substituted or non-substituted spiroacetals has been the subject of considerable interest due to their presence in a wide range of natural products[1]. In this context, the interesting model compound, (-)-spirobi-1,4-dioxane, was prepared by Richardson et al.[2] from D-fructose.

We recently reported the preparation of new spirobidioxanes bearing functionalized sidechains at the 2,8 positions by a cyclodehydrative reaction carried out on a keto-diol precursor following a documented approach in the dioxaspiro series[3]. In this first attempt we decided to use racemic semi-industrial glycerol oligomers[4], specifically (±)-diisopropylidene triglycerol[5]. As expected, such a synthetic procedure normally gave a mixture of (±)-E,E and Z,E stereoisomers. These two sets of compounds were stable and easily separated. For converging reasons, the next chosen step was to study the selective preparation of each isomer from stereochemically defined precursors. This allowed us to confirm our assignments for stereoisomers and also to discuss our results in connection with the dioxaspiro series[6,7], especially concerning the NMR spectral data. Further, as we were simultaneously investigating the kinetic resolution of (±)-E,E systems by hydrolytic enzymes, it was necessary to have an enantiomerically pure reference for correlations in this unexplored series.

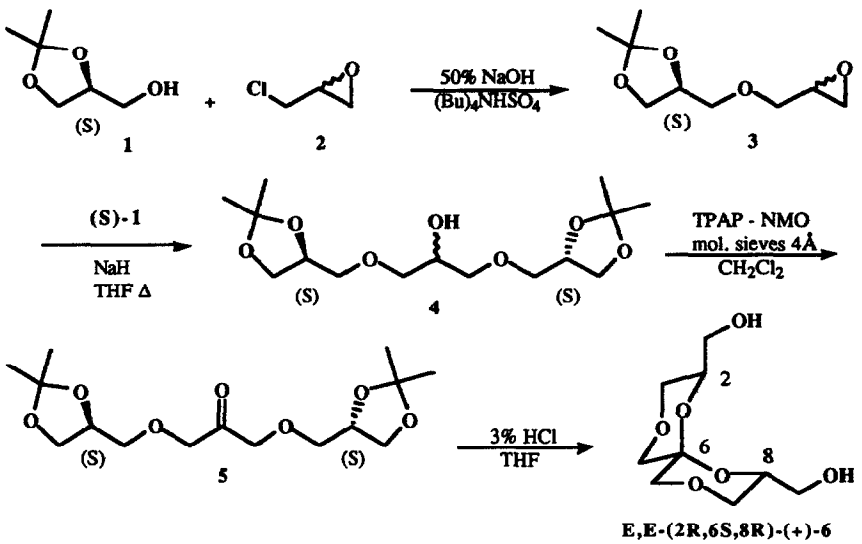
The present paper is dedicated to the preparation of the title compounds from D-α,β-isopropylidene glycerol **1** (scheme 1) and L-α,β-isopropylidene glycerol **9** (scheme 3) together with the mono and dibutyryl ester of the symmetrical spiroacetal (scheme 2) which will be used in a forthcoming paper where their enzymatic hydrolysis will be examined.

RESULTS AND DISCUSSION

(+)-E,E Dihydroxymethyl spiroacetal 6

Using an approach already applied in the pheromone dioxaspiroacetal field[6], the precursor **1** was chosen so as to build a biomimetic model structurally related to the ionophore calcimycin which is studied in our laboratory[3]. We thus obtained the compound (+)-**6** from the ketone **5** (scheme 1).

Scheme 1



The epoxide (2RS,2'S)-**3** (yield: 90%) ($[\alpha]_J^{25}$ +15 (c = 0.024, $CHCl_3$)) was prepared using phase transfer conditions. Treatment of (S)-**1** by NaH in THF followed by addition of epoxide **3** led to the alcohol (2RS,2'S,2"S)-**4** (yield: 40%) ($[\alpha]_J^{25}$ +11 (c = 0.021, $CHCl_3$)). We applied Ley's oxidation method[8] to obtain the optically pure ketone (2'S,2"S)-**5** ($[\alpha]_J^{25}$ +17 (c = 0.032, $CHCl_3$)), and this method improved the yield (71%) compared with our previous result (55%) using NDC[3]. The deprotection-cyclization was done in 3% HCl/THF. The E,E-(2R,6S,8R) spiroacetal **6** was isolated (yield: 76%) with an optical rotation $[\alpha]_J^{25}$ +5 (c = 0.021, CH_3OH). The use of NMR shift reagent Eu(hfc)$_3$ with (±)-**6**[3] did not give satisfactorily resolved spectra to permit the differentiation of enantiomers. However it was possible to determine the enantiomeric purity of (+)-**6** on its derivatives **7** and **8**.

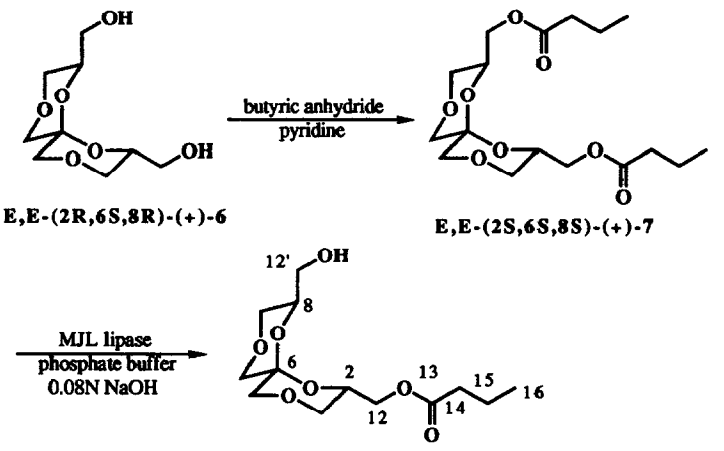
The E,E structure with two stabilizing anomeric effects was confirmed by high field 1D and 2D NMR analysis. All the chemical shifts of this spiroacetal were identical to the racemic compound[3]. The C2 axis of symmetry in the structure conveniently gave simplified spectra for ^1H and ^{13}C resonances.

(+)-E,E-dibutyryloxymethyl 7 and hydroxymethylbutyryloxymethyl spiroacetal 8

Split resonances on the butyrate sidechains for E,E-(±)-**7**[3] were observed by ^1H NMR using Eu(hfc)$_3$ corresponding to the two enantiomers. Thus, for E,E-(+)-**7** (scheme 2) it was possible to determine its e.e. which was found superior to 98% with an optical rotation $[\alpha]_J^{25}$ +7° (c = 0.023, $CHCl_3$). In previous work[3], we had shown that lipases could be conveniently used for the selective hydrolyse of one of the sidechains, and we applied this method (scheme 2) to obtain the monobutyrate (+)-**8** which gave an e.e. ≥ 98% and $[\alpha]_J^{25}$ +7 (c = 0.026, $CHCl_3$).

From these results it is possible to conclude that spiroacetal E,E-(+)-**6** and ketone (+)-**5** were obtained with an e.e. ≥ 98%.

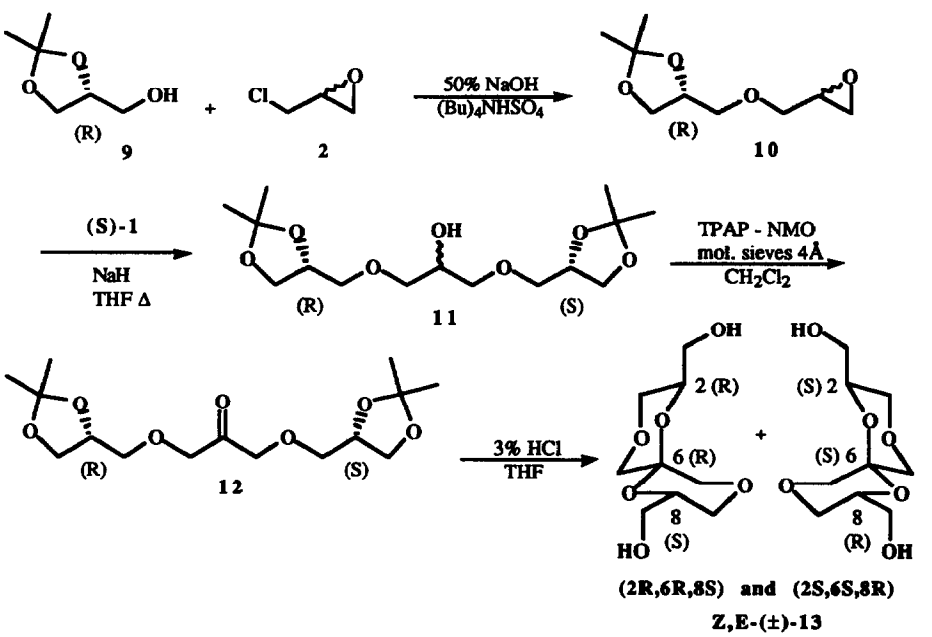
Scheme 2



(±)-Z,E dihydroxymethyl spiroacetal 13

The procedure described in scheme 1 was applied, but in the first step the precursor 1 was replaced by its antipode L-α,β-isopropylideneglycerol 9.

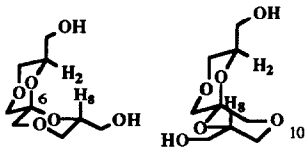
Scheme 3



For the epoxide (2RS,2'R)-**10**, the optical rotation was: $[\alpha]_J^{25}$ -13 . As expected, *meso* compounds were obtained for the alcohol **11** and the ketone **12** with $[\alpha]_J^{25}$ null. As already observed in the dioxa series[6], this afforded a mixture of enantiomers (2R,6R,6S) and (2S,6S,8R)-Z,E -**13**. These compounds presented only one stabilizing anomeric effect with the two sidechains equatorial. The conformer with an axial position for one of the sidechains with two stabilizing anomeric effects was not observed. This was deduced by ^{1}H NMR studies carried out on two sidechain types, and the differences in chemical shift for H2 and H8 (table 1) were the main evidence for that. For product Z,E-(±)-**13**, protons 2, 3e, 3a, 12A, 12B gave a second order spectrum not easy to simulate and no coupling constants were measured. This important part of the spectrum was slightly simplified for the dibutyrate derivative Z,E-(±)-**14** prepared as described in scheme 2.

In table 1 a comparison is made for the δ- and J-values of H2 and H8. For the E,E isomers, H2 and H8 are parallel to a C6-O bond (O1 and O7) with a δ of 4.15 ppm for **6** and 4.18 ppm for **7**. But for the E,Z isomers, H2 was shifted markedly upfield: - 0.25 and - 0.32 ppm respectively for **13** and **14** due to an 1,3-diaxial interaction with C11 methylene. H8 was deshielded (+ 0.18 and + 0.15 ppm respectively) with only a very slight change in the coupling constants, as this proton has the O1 atom in 1,3-diaxial relationship. Therefore H2 and H8 must be in axial position. These changes in the chemical shift of H2 and H8 must be due to the anisotropic effect caused by the oxygen atoms. The same conformation was proposed in the Z,E-dioxaspiroacetal series bearing two methyl groups in 2,8 positions: under thermodynamically controlled cyclization four conformations were theoretically possible, and two of them showed lowest evaluated energies (Me: a, e, 2 anomeric effects: 2.9 Kcal/mol; Me: e, e, 1 anomeric effect: 2.4 Kcal/mol). In the experimental results Me: e, e was the only conformer observed[9b]. The tetraoxa-spiroacetal series showed the same behavior.

Table 1



Product	Proton	δ	J_{2-3} or J_{8-9}	Δδ	ΔJ
E,E-**6**	H2 and H8	4.15	2.7, 10.5		
Z,E-**13**	H2	3.90	#	- 0.25[a]	#
	H8	4.33	3, 10.5	+ 0.18[b]	- 0.3, 0[c]
E,E-**7**	H2 and H8	4.18	3.5, 11.5		
Z,E-**14**	H2	3.86	3.5*, 4.5*	- 0.32[d]	- 1*, - 7*[e]
	H8	4.33	3, 11	+ 0.15[f]	- 0.5, - 0.5[g]

(δ measured at 300MHz in CD_3OD for **6** and **13** and $CDCl_3$ for **7** and **14**) * apparent coupling constants
not measured
a- δH2 (Z,E-**13**) - δH2 (E,E-**6**)
b- δH8 (Z,E-**13**) - δH8 (E,E-**6**)
c- JH8 (Z,E-**13**) - JH8 (E,E-**6**)
d- δH2 (Z,E-**14**) - δH2 (E,E-**7**)
e- JH2 (Z,E-**14**) - J_{H2} (E,E-**7**)
f- δH8 (Z,E-**14**) - δH8 (E,E-**7**)
g- JH8 (Z,E-**14**) - JH8 (E,E-**7**)

CONCLUSION

In the present work we have shown that the chiral 2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5] undecanes are easily accessible from a (+) or (-) glycerol type synthon giving a new subunit with hydrophilic properties which could enter in the architecture of helicoidal structures. We are presently studying its incorporation in polyether macrocycles. Furthermore, it should be of interest for the study of its mode of action, to synthesize a conveniently designed biomimetic model of calcimycin (or A23187) constructed on a spirobi-1,4-dioxane system.

EXPERIMENTAL

Optical rotation values were measured on a Perkin-Elmer 141 polarimeter for the mercury J line ($\lambda = 578$ nm) at 25°C (c in g/mL). Infrared (IR) spectra were obtained using a Perkin-Elmer 881 spectrometer and the resonances are expressed in frequency units (ν cm^{-1}). NMR spectra were recorded at 300 MHz for ^1H and 75.47 MHz for ^{13}C on a Bruker MSL 300 spectrometer. All signals were expressed in ppm using tetramethylsilane as an internal standard (δ value). The following abbreviations were used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), pseudotriplet (pt), axial (a) and equatorial (e). Mass spectra were obtained from a ZAB-SEQ (FAB^+) spectrometer. Satisfactory analytical data were obtained for all new compounds (±0.3%) at the Service Central d'Analyse du CNRS, Solaize, France. Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium III ($Eu(hfc)_3$) was used as a shift reagent for enantiomeric excess determinations. Merck Silica gel 60 was used for column chromatography and commercial Kieselgel 60 F254 plates were used for thin layer chromatography (TLC). *Mucor javanicus* lipase was purchased from Fluka Biochemica (ref. 62304) and was used without any purification. All solvents were distilled before use. Anhydrous pyridine was obtained after distillation over KOH and anhydrous acetonitrile over P_2O_5.

(2RS,2'S)-1,2-Epoxy-3-(2',3'-O-isopropylideneglycerol)propane 3

A mixture of 50% aqueous NaOH (6.65 mL), epichlorhydrin (4.2 mL) **2** and tetrabutylammonium hydrogensulfate (0.141 g) was vigorously stirred at room temperature. D-α,β-isopropylideneglycerol (1.33 g, 10 mmol) ($[\alpha]_D^{20}$ +11.5° (c = 5, CH_3OH) **1** was added slowly while the temperature was maintained below 25°C. The resultant mixture was stirred at room temperature for 3.5 h and poured into water+ice (35 mL). The solution was extracted with ethyl acetate (3 x 20 mL)). The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation to dryness, the residue was chromatographed on silica gel with cyclohexane/ethyl acetate 60:40, to give the epoxide compound **3** (1.69 g) in 90 % yield. Colourless liquid. $[\alpha]_J^{25}$ +15 (c = 0.024, $CHCl_3$).

(2RS,2'S,2"S)-1-(2',3'-O-Isopropylideneglycerol)-3-(2",3"-O-isopropylideneglycerol)-2-propanol 4

D-α,β-isopropylideneglycerol (1.35 g, 10.2 mmol) **1** was added to a suspension of NaH (300 mg) in anhydrous THF (40 mL). The mixture was stirred and heated to 50°C under argon until the evolution of hydrogen ceased. Epoxide **3** (1.71 g, 9 mmol) was then added. The resultant mixture was refluxed and the reaction was followed by TLC. Water+ice were added, and the mixture was extracted with ethyl acetate. The

organic layer was washed with brine and dried over $MgSO_4$. After evaporation to dryness, the residue was chromatographed on silica gel with cyclohexane/ethyl acetate 30:70, to give the alcohol **4** (1.153 g) in 40 % yield. Colourless liquid. $[\alpha]_J^{25}$ +11 (c = 0.033, $CHCl_3$).

(2'S,2"S)-1-(2',3'-O-Isopropylideneglycerol)-3-(2",3"-O-isopropylideneglycerol)propanone 5

To a suspension of 4Å molecular sieve (powder) in anhydrous CH_2Cl_2 (40 mL), N-methyl-morpholine-N-oxide (NMO) (1.4 g) and alcohol **4** (2.223 g, 6.9 mmol) were added, and the mixture was stirred vigorously for 1.5 h. TPAP (tetrapropylammoniumperrhutenate) (120 mg) was added, and the resulting mixture was stirred at room temperature for 3 h. The molecular sieve was filtered and washed several times with CH_2Cl_2. The combined filtrates were then concentrated. The residue was subjected to column chromatography on silica gel with cyclohexane/ethyl acetate 60:40, to give the ketone **5** in 71 % (1.57 g) yield. Colourless oil. $[\alpha]_J^{25}$ +17 (c = 0.032, $CHCl_3$). IR (pure) : 1030-1270, 1740 cm^{-1}. MS (EI) m/z (%) : 319.2 $(M + H)^+$ (3.9) ; 175.1 $(M-C_3H_7)^+$ (3.5) ; 145.1 ($C_7H_{13}O_3^+$) (11.5) ; 101.0 ($C_5H_9O_2^+$) (53.6) ; 57.1 ($C_3H_5O^+$) (52.4) ; 43.1 ($C_3H_7^+$) (100). Anal. Calcd for $C_{15}H_{26}O_7$ (318) : C 56.60, H 8.17. Found : C 56.47, H 8.03. ^{1}H-NMR (60 MHz, $CDCl_3$) δ : 4.27 (s large, 4H, H1 and H3), 3.50-4.30 (m, 6H, H2'-H2"-H3' and H3"), 3.50 (d, 4H, H1' and H1"), 1.30-1.35 (s, 12H, acetonide methyls). ^{13}C-NMR (15 MHz, $CDCl_3$) δ : 205.3 (C2), 109.5 (C quat. acetonides), 75.1 (C1 and C3), 74.6 (C2' and C2"), 72.6 (C1' and C1"), 66.4 (C3' and C3"), 25.3-26.7 (acetonide methyls).

E,E-(2R,6S,8R)-(+)-2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane 6

To a solution of THF (19.4 mL) and concentrated HCl (0.6 mL of 10N HCl), ketone **5** (0.31 g, 1 mmol) was added. The resulting mixture was stirred over night at room temperature. To neutralize the hydrochloric acid, sodium hydroxide pellets (0.24 g) were added. After filtration of the salt, the filtrate was evaporated to dryness. The residue was chromatographed on silica gel with ethyl acetate/methanol 95:5, and the diol **6** was obtained in 76% (0.163 g) yield. m.p. = 130-133°C (acetone). White solid. $[\alpha]_J^{25}$ +5 (c = 0.021, CH_3OH).

E,E-(2S,6S,8S)-(+)-2,8-Dibutyryloxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane 7

To a pyridine (10 mL) solution of butyric anhydride (6.20 g, 39.2 mmol) (+)-2,8-dihydroxymethyl-1,4-7,10-tetraoxaspiro[5.5]undecane **6** (2.50 g, 11.3 mmol) was added, and stirred at room temperature for 12 h. Pyridine was evaporated under vacuum, the residue was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $CuSO_4$ (2 x 25 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and concentrated. The product **7** was chromatographed on silica gel with cyclohexane/ethyl acetate 60:40, and obtained in 96 % (3.95 g) yield. White wax. $[\alpha]_J^{25}$ +7 (c = 0.023, $CHCl_3$) ; ee ≥ 98 % (by NMR).

E,E-(2S,6S,8R)-(+)-2-Butyryloxymethyl-8-hydroxymethyl-1,4,7,10-tetraoxaspiro[5.5] undecane 8

A solution of diester **7** (1.44 g, 4 mmol) in phosphate buffer (pH = 7, 0.02 M, 100 mL) was treated with *Mucor javanicus* lipase (100 mg (5 U/g)). The suspension was stirred at room temperature. The reaction was followed by the addition of NaOH (0.08 N, 50 mL for one ester function) over a period of 6 h. After filtration of the lipase, the filtrate was extracted with ethyl acetate (3 x 30 mL). The combined extracts were

dried with magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel with cyclohexane/ethyl acetate 70:30 then 50:50 product (+)-**8** was isolated in 76 % (886 mg) yield. White wax. $[\alpha]_J^{25}$ +7 (c = 0.026, $CHCl_3$) ; ee ≥ 98 % (by NMR).

(2RS,2'R)-1,2-Epoxy-3-(2',3'-O-isopropylideneglycerol)propane 10

The same procedure applied to L-α,β-isopropylideneglycerol **9** yielded (2RS,2'R)-**10** in the same yield. $[\alpha]_J^{25}$ -13 (c = 0.073, $CHCl_3$).

(2RS,2'R,2"S)-1-(2',3'-O-Isopropylideneglycerol)-3-(2",3"-O-isopropylideneglycerol)-2-propanol 11

The same procedure applied to D-α,β-isopropylideneglycerol and (2RS,2'R)-**10** yielded (2RS,2'R,2"S)-**11** in the same yield. $[\alpha]_J^{25}$ 0° (c = 0.077, $CHCl_3$).

(2'R,2"S)-1-(2',3'-O-Isopropylideneglycerol)-3-(2",3"-O-isopropylideneglycerol)propanone 12

The same procedure applied to (2RS,2'R,2"S)-**11** yielded (2'R,2"S)-**12** in the same yield. $[\alpha]_J^{25}$ 0 (c = 0.037, $CHCl_3$).

Z,E-(2S,6S,8R) and (2R,6R,8S)-(±)-2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane 13

The same procedure applied to (2'R,2"S)-**12** yielded Z,E-(±)-**13** in the same yield. $[\alpha]_J^{25}$ 0° (c = 0.06, CH_3OH).

Z,E-(±)-2,8-Dibutyryloxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane 14

The same procedure applied to Z,E-(±)-**13** yielded Z,E-(±)-**14** in the same yield. IR (pure) : 1070-1125 cm^{-1}, 1740 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_8$ (360) : C 56.66, H 7.83 . Found : C 56.78, H 7.99. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 4.33 (dtd, 1H, H8, a, $J_{8,9e}$ 3 Hz, $J_{8,12'}$ 5 Hz, $J_{8,9a}$ 11 Hz), 4.27 (d, 2H, H12', $J_{12',8}$ 5 Hz), 3.92 (d, 2H, H12, $J_{12,2}$ 6.5 Hz), 3.86 (m, 1H, H2, a, $J_{2,3e}$ 3.5 Hz, $J_{2,12}$ 6.5 Hz, $J_{2,3a}$ 4.5 Hz), 3.75 (d, 1H, H11, e, $J_{11e,11a}$ 12 Hz), 3.70 (dd, 1H, H9, e, $J_{9e,8}$ 3 Hz, $J_{9e,9a}$ 11.5 Hz), 3.62 (m, AB system, 1H, H3, e, $J_{3e,2}$ 3.5 Hz, $J_{3e,3a}$ 12 Hz), 3.55 (m, AB system, 1H, H3, a, $J_{3a,2}$ 4.5 Hz, $J_{3a,3e}$ 12 Hz), 3.43 (d, 1H, H5, e, $J_{5e,5a}$ 11.7 Hz), 3.30 (d, 1H, H5, a, $J_{5a,5e}$ 11.7 Hz), 3.21 (pt, 1H, H9, a, $J_{9a,8}$ 11 Hz, $J_{9a,9e}$ 11.5 Hz), 3.09 (d,1H, H11, a, $J_{11a,11e}$ 12 Hz), 2.21 (t, 2H, H14', $J_{14',15'}$ 7.5 Hz), 2.20 (t, 2H, H14, $J_{14,15}$ 7.5 Hz), 1.53 (m, 2H, H15', $J_{15',14'} = J_{15',16'}$ 7.5 Hz), 1.51 (m, 2H, H15, $J_{15,14} = J_{15,16}$ 7.5 Hz), 0.83 (t, 6H, H16 and H16', $J_{16,15} = J_{16',15'}$ 7.5 Hz).^{13}C-NMR (75 MHz, $CDCl_3$) δ : 173.0 (C13), 172.7 (C13'), 91.0 (C6), 69.8 (C5), 69.1 (C2), 68.0 (C11), 67.2 (C9), 66.6 (C8), 66.5 (C3), 62.8 (C12'), 35.7 (C14), 35.5 (C14'), 18.1 (C15,15'), 13.3 (C16, C16').

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