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2- AND 8- FUNCTIONALIZED 1,4,7,10-TETRAOXASPIRO[5.5]UNDECANES. I. SYNTHESIS OF (±)-E,E AND (±)-Z,E STRUCTURES.

Marielle Lemaire, Georges Jeminet*, Jean-Gabriel Gourcy and Gérard Dauphin

Université Blaise Pascal, U.R.A. 485 du CNRS, Laboratoire de Chimie Organique Biologique, 63177 Aubière cedex, France

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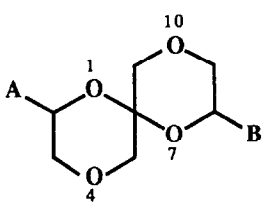
Abstract : The synthesis of (±)-E,E and (±)-Z,E 2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane is described. The selective modification of one sidechain is examined for the (±)-E,E isomer, and a tetraoxygenated analogue of a commonly encountered insect pheromone is prepared.

There is a large and growing list of biologically active compounds isolated from natural sources that contain a spiroacetal subunit in their skeleton. This has prompted active research on the synthesis of such molecular systems, mainly in the dioxaspiro domain[1]. Our contribution in this field has been directed towards calcimycin (or A.23187) analogues[2] and biomimetic models[3] to explore calcium transport by this specific ionophore. We recently proposed an enzymatic resolution of a synthetic precursor E,E-(±)-2,8-dibutyryloxy methyl -1,7-dioxaspiro[5.5]undecane[4].

In this work we investigated novel 1,4,7,10-tetraoxygenated spiroacetals (scheme 1) which can afford hydrophilic moieties for the design of new calcimycin models; analogues of pheromones can also be obtained easily, and an extension to supramolecular systems incorporating this unit should also be of interest. To our knowledge only some spirobi-1,4-dioxanes were synthesized previously by a multistep procedure from fructose[5].

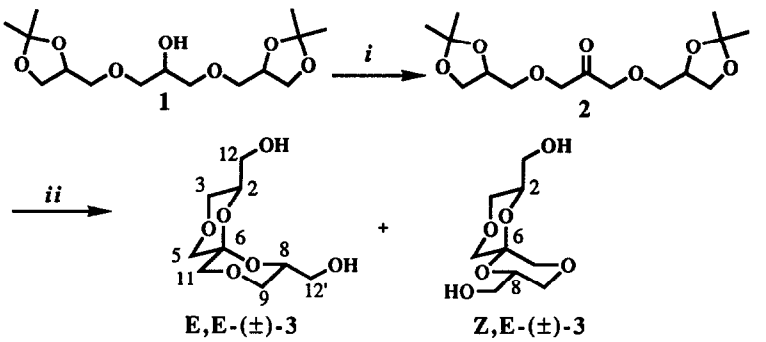


A = or ≠ B

Scheme 1

The various precursors which can serve as starting materials for the preparation of the target molecules bearing hydroxymethyl sidechains in the 2,8 positions include the semi-industrial compounds (±)-diisopropylidene triglycerol **1** in the series of glycerol oligomers[6]. A cyclodehydration reaction carried out on the corresponding ketone **2** preferentially yields (±)-E,E and Z,E isomers **3** by a well-documented approach in the 1,7-dioxaspiro series (Scheme 2)[1].

This paper describes the preparation of these compounds ; we also give a simple way to differentiate the chemical functions on the two sidechains using a lipase and finally a straightforward preparation of a pheromone analogue is described.



i : Nicotiniumdichromate (NDC); CH_2Cl_2. *ii* : 3% HCl; THF.

Scheme 2

RESULTS AND DISCUSSION

E,E(±) and Z,E(±) dihydroxymethyl spiroacetals (scheme 2)

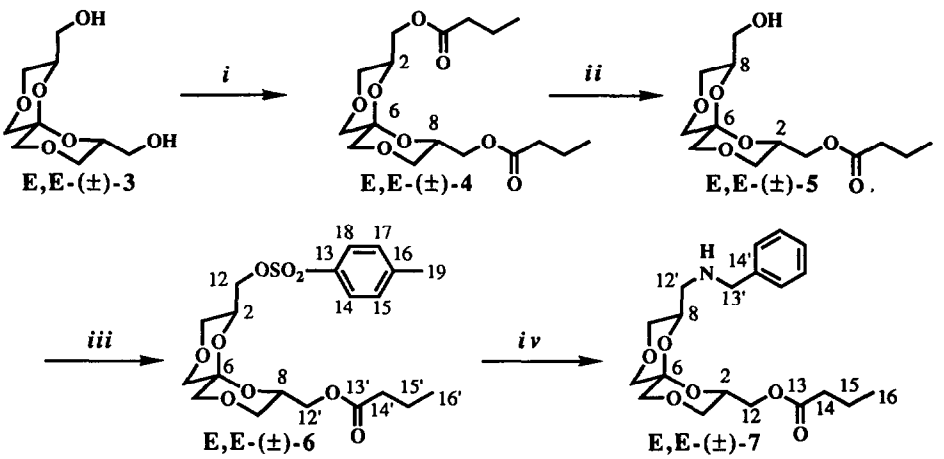
After several attempts with different oxidizing reagents, the preparation of ketone **2** was finally achieved from the commercial compound **1** by oxidation using nicotiniumdichromate (NDC) in CH_2Cl_2[7]. Although the yield for the reaction was high, it was not possible to avoid partial decomposition (30%) of **2** during the chromatographic purification on silicagel ; this explains the moderate yield finally obtained: 55% for the pure compound. Treatment of **2** in classical acid conditions led to the expected spiroacetals E,E and Z,E isomers as discussed in detail for the 1,7-dioxa series[8,9]. A third isomer was observed by ^{13}C-NMR in the crude reaction mixture, identified as 9-hydroxy-2-hydroxymethyl-1,4,7,11-tetraoxaspiro[5.6]dodecane, but this compound isomerized to the tetraoxaspiro[5.5]undecane system during purification on silicagel. Thus the isolated spiroacetals (yield: 73%) included only E,E and Z,E substituted bi-1,4-dioxanes.

The structures were confirmed by high field 1D and 2D NMR. As expected[10], the NMR analysis showed a C2 axis of symmetry for the E,E isomer giving conveniently simple spectra for ^{1}H and ^{13}C resonances, whereas all the resonances were present for the Z,E isomer. These isomers can exist in several conformations under our thermodynamically controlled cyclisations, as it was recently discussed for the similar compounds 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes[8b]. Analysis of coupling constants and chemical shifts for H_2 and H_8, led us to conclude that in both isomers **3** the two sidechains are equatorial, corresponding to the structures mentioned in scheme 2. ^{1}H spectra are described in the experimental section together with the $[M+H]^+$ and $[M+Na]^+$ values obtained using FAB-MS. ^{13}C values (in ppm, for the bicycle only) are given in table I for all the spiroacetals prepared. A complete NMR study of these compounds and relevant analogues will be published.

The two isomers were separated by crystallization. This enabled us to investigate the reactivity of the hydroxymethyl sidechains for the E,E system which is of particular interest given its helicoidal structure encountered in natural products.

E,E-(±)-N-benzylaminomethyl and butyryloxymethyl spiroacetals (scheme 3)

The problem of differentiating the two sidechains proved difficult to solve conveniently by a purely chemical approach. However this could be achieved by hydrolysing the corresponding dibutyrate **4** with a lipase acting for this purpose only as a cleaving reagent the reactivity of which is carefully monitored so as to obtain the monoester **5**. The butyrate substituent was chosen in the light of our previous results in this field[6]. Preparation of the benzylamine derivative **7** was accomplished via the tosylate **6** in high overall yield. Using the same general approach but with a chiral amine, we shall show in a forthcoming paper that the diastereoisomers obtained can be easily separated giving E,E enantiomeric spiroacetals.

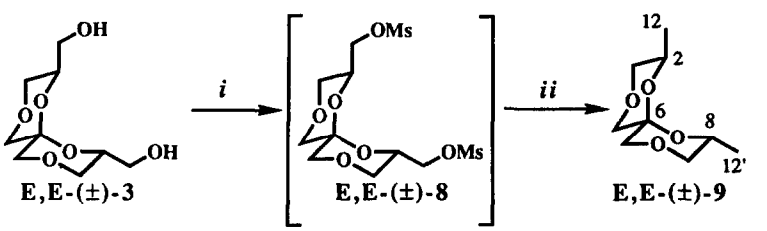


i : Butyric anhydride; pyridine. *ii* : MJL lipase; phosphate buffer; 0.08N NaOH.
iii : TsCl; pyridine. *iv* : Benzylamine; Δ; CH_3CN.

Scheme 3

Pheromone analogue (scheme 4)

The spiroacetal moiety is widely encountered in insect pheromones. The compounds isolated generally contain unbranched arrangements ; among these E,E-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane is produced by many insects[1]. The preparation of a tetraoxygenated analogue is straightforward from **3** via the dimesylate **8**, which was not isolated, giving a nicely crystalline compound (yield : 77 % from **3**), while the corresponding pheromone is a highly volatile liquid.



i : MsCl; NEt_3; CH_2Cl_2. *ii* : LAH; Δ; THF.

Scheme 4

This example shows that the preparation of tetraoxygenated analogues of some well-known spiro[5.5] insect pheromones can be readily envisaged as racemates or as pure enantiomers.

Table 1. δ ^{13}C (p.p.m.)

C-number	Z,E-3 (a)	E,E-3 (a)	E,E-4 (b)	E,E-5 (b)	E,E-6 (b)	E,E-7 (b)	E,E-9 (b)
C-2	73.4	70.1	66.4	66.4	66.0	66.3	64.0
C-3	68.1	68.8	67.4	67.7	67.1	*68.5	71.6
C-5	71.3	69.6	68.4	68.4	68.4	68.7	68.5
C-6	92.6	93.0	91.9	91.9	91.9	91.8	91.7
C-8	70.4	70.1	66.4	68.9	66.5	67.6	64.0
C-9	68.9	68.8	67.4	67.2	67.4	*67.6	71.6
C-11	68.4	69.6	68.4	68.7	68.3	68.7	68.5
C-12	62.7	62.8	63.1	63.2	68.7	63.3	16.6
C-12'	62.7	62.8	63.1	62.3	63.1	49.6	16.6

(a): CD_3OD; (b). $CDCl_3$, * : interchangeable assignments

In conclusion, we have shown in several examples that 2- and 8-substituted 1,4,7,10-tetraoxygenated spiroacetals are stable systems which can be prepared in a few steps ; E,E and Z,E isomers were easily separated. We have proposed a chemo-enzymatic method to differentiate the sidechains. New polyether models can now be developed starting from these helicoidal subunits, which could be chiral if required as it will be shown.

EXPERIMENTAL

Infrared (IR) spectra were obtained using a Perkin-Elmer 881 spectrometer and bands 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 and at 60 MHz for ^1H and 15 MHz for ^{13}C on a JEOL FX60. All signals were expressed in ppm using tetramethylsilane as an internal standard (δ value). The following abbreviations are 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. 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 used. Anhydrous pyridine was obtained after distillation over KOH and anhydrous acetonitrile over P_2O_5.

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

A suspension of NDC (26.9 g, 58 mmol) in CH_2Cl_2 (100 ml) and pyridine (9.3 ml) was vigorously stirred and cooled to 0-5°C. Alcool (1) (3.8 g, 11.8 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 72 h. The reagent was filtered and was 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 / ethylacetate 60:40, to give the ketone (2) in 55% (2.066 g) yield. Colourless oil. IR (neat) : 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 and Z,E-(±)-2,8-dihydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (3).

To a solution of THF (194 ml) and concentrated HCl (6 ml of 10N HCl), ketone **2** (16.3 g, 51.2 mmol) was added. The resulting mixture was stirred overnight at room temperature. To neutralize the hydrochloric acid, sodium hydroxide pellets (2.4 g) were added. After filtration of the salts, the filtrate was evaporated to dryness. The residue was chromatographed on silica gel with ethylacetate/methanol 95:5, and the diols (**3**) were obtained in 67% (7.55 g) yield. The separation of isomers E,E and Z,E was performed by crystallization from acetone. The isomer E,E was insoluble in this solvent while the isomer Z,E was very soluble. The symmetrical isomer E,E was obtained in 26% (2.98 g) yield. To isolate pure unsymmetrical isomer, a further chromatographic purification of the residue from crystallization was necessary. This isomer was obtained in 24% (2.75 g) yield. Data for E, E-(±)-**3** : m.p. = 127-128°C (acetone). White solid. IR (neat) : 1010-1150, 3400 cm^{-1}. MS (FAB$^+$) m/z : 243.0 $(M + Na)^+$, 221.0 $(M + H)^+$. Anal. Calcd for $C_9H_{16}O_6$ (220) : C 49.09, H 7.27. Found : C 48.80, H 7.34. ^{1}H-NMR (300 MHz, CD_3OD) δ : 4.15 (dtd, 2H, H2 and H8, each a, $J_{2,3e}$ 2.7 Hz, $J_{2,12A} = J_{2,12B}$ (apparent) 5 Hz, $J_{2,3a}$ 10.5 Hz), 3.91 (dd, 2H, H3 and H9, each e, $J_{3e,2} = J_{9e,8}$ 2.7 Hz, $J_{3e,3a} = J_{9e,9a}$ 11.5 Hz), 3.67 (d, 2H, H5 and H11, each e, $J_{5e,5a} = J_{11e,11a}$ 11.5 Hz), 3.66 (dd, AB system, 2H, H12A and H12'A, $J_{12A,2} = J_{12'A,8}$ (apparent) 5 Hz, $J_{12A,12B} = J_{12'A,12'B}$ 12.5 Hz), 3.62 (dd, AB system, 2H, H12B and H12'B, $J_{12B,2} = J_{12'B,8}$ (apparent) 5 Hz, $J_{12A,12B} = J_{12'A,12'B}$ (apparent) 12.5 Hz), 3.48 (pt, 2H, H3 and H9, each a, $J_{3a,2} = J_{9a,8}$ 10.5 Hz, $J_{3a,3e} = J_{9a,9e}$ 11.5 Hz), 3.36 (d, 2H, H5 and H11, each a, $J_{5e,5a} = J_{11e,11a}$ 11.5 Hz). ^{13}C-NMR (75.47 MHz, CD_3OD) δ : 93.0 (C6), 70.1 (C2-C8), 69.6 (C5-C11), 68.8 (C3-C9), 62.8 (C12-C12'). Data for Z,E-(±)-**3** m.p. = 97-99°C (acetone). White solid. IR (pur) : same as E,E. MS (FAB$^+$) m/z : 243.0 $(M + Na)^+$, 221.0 $(M + H)^+$. Anal. Calcd for $C_9H_{16}O_6$ (220) : C 49.09, H 7.27. Found : C 48.83, H 7.24. ^{1}H-NMR (CD_3OD) δ : 4.33 (dtd, 1H, H8, a, $J_{8,9e}$ 3 Hz, $J_{8,12'A} = J_{8,12'B}$ (apparent) 5 Hz, $J_{8,9a}$ 10.5 Hz), 4.11 (d, 1H, H11, e, $J_{11e,11a}$ 12 Hz), 3.91 (dd, 1H, H9, e, $J_{9e,8}$ 3 Hz, $J_{9e,9a}$ 11 Hz), 3.90 (m, AB system, 1H, H2, a), 3.89 (m, AB system, 1H, H12A), 3.87 (m, AB system, 1H, H3, e), 3.79 (m, AB system, 1H, H12B), 3.68 (m, AB system, 1H, H3, a), 3.61 (dd, ABX system, 1H, H12'A, $J_{12'A,8}$ (apparent) 5 Hz, $J_{12'A,12'B}$ (apparent) 12 Hz), 3.59 (dd, ABX system, 1H, H12'B, $J_{12'B,8}$ (apparent) 5 Hz, $J_{12'B,12'A}$ (apparent) 12 Hz), 3.59 (d, 1H, H5, e, $J_{5e,5a}$ 11.5 Hz), 3.47 (pt, 1H, H9, a, $J_{9a,8}$ 10.5 Hz, $J_{9a,9e}$ 11 Hz), 3.46 (d, 1H, H5, a, $J_{5a,5e}$ 11.5 Hz), 3.34 (d, 1H, H11, a, $J_{11a,11e}$ 12 Hz). ^{13}C-NMR (CD_3OD) δ : 92.6 (C6), 73.4 (C2), 71.3 (C5), 70.4 (C8), 68.9 (C9), 68.4 (C11), 68.1 (C3), 62.7 (C12 and C12').

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

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 (**3**) (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 ethylacetate (50 ml) and was 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 was concentrated. The product (**4**) was chromatographed on silica gel with cyclohexane/ethylacetate 60:40, and obtained in 96% (3.95 g) yield. White wax. IR (KBr) : 1080-1130, 1740 cm^{-1}. MS (FAB^+) m/z : 361.5 $(M + H)^+$. Anal. Calcd for $C_{17}H_{28}O_8$ (360) : C 56.66, H 7.83. Found : C 56.86, H 7.97. ^{1}H-NMR ($CDCl_3$) δ : 4.18 (dtd, 2H, H2 and H8, each a, $J_{2,3e} = J_{8,9e}$ 3.5 Hz, $J_{8,12'A} = J_{8,12'B} = J_{2,12A} = J_{2,12B}$ 5 Hz, $J_{8,9a} = J_{2,3a}$ 11.5 Hz), 4.12 (dd, AB system, 2H, H12A and H12'A, $J_{12A,2} = J_{12'A,8}$ 5 Hz, $J_{12A,12B} = J_{12'A,12'B}$ 12 Hz), 4.08 (dd, AB system, 2H, H12B and H12'B, $J_{12B,2} = J_{12'B,8}$ 5 Hz, $J_{12A,12B} = J_{12'A,12'B}$ 12 Hz), 3.80 (dd, 2H, H3 and H9, each e, $J_{3e,2} = J_{9e,8}$ 3.5 Hz, $J_{3e,3a} = J_{9e,9a}$ 11.5 Hz), 3.60 (d, 2H, H5 and H11, each e, $J_{5e,5a} = J_{11e,11a}$ 11.5 Hz), 3.35 (pt, 2H, H3 and H9, each a, $J_{3a,2} = J_{9a,8}$ 11.5 Hz, $J_{3a,3e} = J_{9a,9e}$ 11.5 Hz), 3.23 (d, 2H, H5 and H11, each a, $J_{5a,5e} = J_{11a,11e}$ 11.5 Hz), 2.26 (t, 4H, H14 and H14', $J_{14,15} = J_{14',15'}$ 7.5 Hz), 1.61 (m, 4H, H15 and H15', $J_{14,15} = J_{14',15'} = J_{15,16} = J_{15',16'}$ 7.5 Hz), 0.91 (t, 6H, H16 and H16', $J_{16,15} = J_{16',15'}$ 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ : 173.2 (C13 and C13'), 91.9 (C6), 68.4 (C5 and C11), 67.4 (C3 and C9), 66.4 (C2 and C8), 63.1 (C12 and C12'), 35.9 (C14 and C14'), 18.3 (C15 and C15'), 13.6 (C16 and C16').

(±)-2-Butyryloxymethyl-8-hydroxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (5).

A solution of diester **4** (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. A solution of NaOH (0.08 N, 50 ml) was required to hydrolyse one ester function and was added over a period of 6 h. After filtration of the lipase, the filtrate was extracted with ethylacetate (3 x 30 ml). The combined extracts were dried with magnesium sulfate and were evaporated to dryness. The residue was chromatographed on silica gel with cyclohexane/ethylacetate 70:30 then 50:50 and the product (±)-**5** was isolated in 76% (886 mg) yield. White wax. IR (KBr) : 1010-1050, 1735, 3400 cm^{-1}. MS (FAB^+) m/z : 313.6 $(M + Na)^+$, 291.5 $(M + H)^+$. Anal. Calcd for $C_{13}H_{22}O_7$ (290) : C 53.79, H 7.58. Found : C 53.64, H 7.51. ^{1}H-NMR ($CDCl_3$) δ : 4.25 (dtd, 1H, H2, a, $J_{2,3e}$ 2.5 Hz, $J_{2,12A} = J_{2,12B}$ 5 Hz, $J_{2,3a}$ 11.5 Hz), 4.16 (dd, AB system, 1H, H12A, $J_{2,12A}$ 5 Hz, $J_{12A,12B}$ 12 Hz), 4.12 (m, 1H, H8, a, $J_{8,9e}$ 3.0 Hz, $J_{8,12'A}$ 4 Hz, $J_{8,12'B}$ 5.5 Hz, $J_{8,9a}$ 11.5 Hz), 4.08 (dd, AB system, 1H, H12B, $J_{2,12B}$ 5 Hz, $J_{12A,12B}$ 12 Hz), 3.86 (dd, 1H, H3, e, $J_{2,3e}$ 2.5 Hz, $J_{3e,3a}$ 11.5 Hz), 3.82 (dd, 1H, H9, e, $J_{9e,8}$ 3.0 Hz, $J_{9e,9a}$ 11.5 Hz), 3.72 (dd, AB system, 1H, H12'A, $J_{12'A,8}$ 4 Hz, $J_{12'A,12'B}$ 12 Hz), 3.65 (d, 2H, H5 and H11, each e, $J_{5e,5a} = J_{11e,11a}$ 11.5 Hz), 3.60 (dd, AB system, 1H, H12'B, $J_{12'B,8}$ 5.5 Hz, $J_{12'A,12'B}$ 12 Hz), 3.49 (pt, 1H, H9, a, $J_{9a,8}$ 11.5 Hz, $J_{9a,9e}$ 11.5 Hz), 3.41 (pt, 1H, H3, a, $J_{3a,2}$ 11.5 Hz, $J_{3a,3e}$ 11.5 Hz), 3.29 (d, 1H, H11, a, $J_{11a,11e}$ 11.5 Hz), 3.27 (d, 1H, H5, a, $J_{5a,5e}$ 11.5 Hz), 2.32 (t, 2H, H14, $J_{14,15}$ 7.5 Hz), 2.04 (m, 1H, OH), 1.66 (m, 2H, H15, $J_{14,15} = J_{16,15}$ 7.5 Hz), 0.96 (t, 3H, H16, $J_{16,15}$ 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ : 173.4 (C13), 91.9 (C6), 68.9 (C8), 68.7 (C11), 68.4 (C5), 67.7 (C3), 67.2 (C9), 66.4 (C2), 63.2 (C12), 62.3 (C12'), 36.0 (C14), 18.4 (C15), 13.7 (C16).

E,E-(±)-8-butyryloxymethyl-2-toxyloxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (6).

To a solution of alcohol **5** (0.886 g, 3 mmol) in pyridine (28 ml) cooled at 0°C under an argon atmosphere, *p*-toluenesulfonylchloride (1.4 g, 7 mmol) was added. The resulting mixture was stirred at room temperature for 10 h. Pyridine was then evaporated under reduced pressure and the residue diluted with $CHCl_3$. The solution was washed (twice) with 10% aqueous $CuSO_4$. The organic phase was dried over $MgSO_4$, filtered

and concentrated to dryness. Purification of the residue using column chromatography on silica (cyclohexane/ethylacetate 60:40) afforded the title compound (6) (1.084 g, 80%) as a pale yellow wax. MS (EI) m/z (%) : 444.1 ($M^{+\cdot}$) (7.5), 155 ($CH_3C_6H_5SO_2^+$) (24.3), 91 ($C_7H_7^+$) (28.5), 86.9 ($C_4H_7O_2^+$) (15.8), 71.0 ($C_3H_3O_2^+$) (100). Anal. Calcd for $C_{20}H_{28}O_9S$ (444) : C 54.05, H 6.30, S 7.20. Found : C 53.87, H 6.39, S 7.07. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 7.79 (d, 2H, H14 and H18, $J_{14,15} = J_{18,17}$ 9 Hz), 7.36 (d, 2H, H15 and H17, $J_{15,14} = J_{17,18}$ 9 Hz), 4.21 (m, 1H, H2, a, $J_{2,3e}$ 2.5 Hz, $J_{2,3a}$ 11.5 Hz), 4.13 (m, 1H, H8, a, $J_{8,9e}$ 2.5 Hz, $J_{8,9a}$ 11.5 Hz), 4.11 (dd, AB system, 1H, H12'), 4.09 (dd, AB system, 1H, H12), 4.02 (dd, AB system, 1H, H12'), 4.00 (dd, AB system, 1H, H12), 3.83 (dd, 1H, H3, e, $J_{3e,2}$ 2.5 Hz, $J_{3e,3a}$ 11.5 Hz), 3.79 (dd, 1H, H9, e, $J_{9e,8}$ 2.5 Hz, $J_{9e,9a}$ 11.5 Hz), 3.59 (d, 1H, H5, e, $J_{5e,5a}$ 11.5 Hz), 3.54 (d, 1H, H11, e, $J_{11e,11a}$ 11.5 Hz), 3.36 (pt, 1H, H9, a, $J_{9a,8} = J_{9a,9e}$ 11.5 Hz), 3.34 (pt, 1H, H3, a, $J_{3a,2} = J_{3a,3e}$ 11.5 Hz), 3.22 (d, 1H, H11, a, $J_{11a,11e}$ 11.5 Hz), 3.21 (d, 1H, H5, a, $J_{5a,5e}$ 11.5 Hz), 2.45 (s, 3H, H19), 2.31 (t, 2H, H14', $J_{14',15'}$ 7.5 Hz), 1.64 (m, 2H, H15', $J_{15',14'} = J_{15',16'}$ 7.5 Hz), 0.94 (t, 3H, H16', $J_{16',15'}$ 7.5 Hz). ^{13}C-NMR (75.47 MHz, $CDCl_3$) δ : 173.3 (C13'), 145.1 (C13), 132.7 (C16), 130.0 (C15 and C17), 128.0 (C14 and C18), 91.9 (C6), 68.7 (C12), 68.4 (C5), 68.3 (C11), 67.4 (C9), 67.1 (C3), 66.5 (C8), 66.0 (C2), 63.1 (C12'), 36.0 (C14'), 21.7 (C19), 18.4 (C15'), 13.7 (C16').

E,E-(±)-8-N-benzylaminomethyl-2-butyryloxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (7).

The tosylate (6) (0.58 g, 1.3 mmol) and the benzylamine (0.56 g, 5.2 mmol) were dissolved in anhydrous acetonitrile (20 ml). The resulting mixture was refluxed under an argon atmosphere for 72 h. Evaporation under vacuum afforded a residue which yielded after purification by flash chromatography (ethylacetate/ cyclohexane 80:20) the amine 7 (0.325 g, 66 %) as a pale yellow lac. IR (neat) : 1050-1210, 1740, 3350 cm^{-1}. MS (FAB^+) m/z : 380.1 $(M + H)^+$, 290.1 $(M-C_4H_9O_2)^+$, 199.2 $(M-C_4H_9O_2-C_7H_7)^+$. Anal. Calcd for $C_{20}H_{29}NO_6$ (379) : C 63.31, H 7.70, N 3.69. Found : C 63.18, H 7.91, N 3.92. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 7.33-7.23 (large, 5H, H15'-H16'-H17'-H18' and H19'), 4.24 (m, 1H, H2, a, $J_{2,3e}$ 2.5 Hz, $J_{2,3a}$ 11.5 Hz, $J_{2,12A}$ (apparent) 11.5 Hz, $J_{2,12B}$ (apparent) 12 Hz), 4.20 (m, 1H, H8, a, $J_{8,9e}$ 3 Hz, $J_{8,12'}$ 7 Hz, $J_{8,9a}$ 11.5 Hz), 4.13 (dd, AB system, 1H, H12A, $J_{12A,2}$ (apparent) 11.5 Hz, $J_{12A,12B}$ (apparent) 27 Hz), 4.11 (dd, AB system, 1H, H12B, $J_{12B,2}$ (apparent) 12 Hz, $J_{12A,12B}$ (apparent) 27 Hz), 3.83 (dd, 1H, H3, e, $J_{3e,2}$ 2.5 Hz, $J_{3e,3a}$ 11.5 Hz), 3.81 (d, 2H, H13', $J_{13',NH}$ 3 Hz), 3.80 (dd, 1H, H9, e, $J_{9e,8}$ 3 Hz, $J_{9e,9a}$ 11.5 Hz), 3.62 (d, 1H, H11, e, $J_{11e,11a}$ 11.5 Hz), 3.60 (d, 1H, H5, e, $J_{5a,5e}$ 11.5 Hz), 3.42 (pt, 1H, H9, a, $J_{9a,8}$ 11.5 Hz, $J_{9a,9e}$ 11.5 Hz), 3.39 (pt, 1H, H3, a, $J_{3a,2}$ 11.5 Hz, $J_{3a,3e}$ 11.5 Hz), 3.26 (d, 1H, H11, a, $J_{11a,11e}$ 11.5 Hz), 3.24 (d, 1H, H5, a, $J_{5a,5e}$ 11.5 Hz), 2.67 (d, 2H, H12', $J_{12',8}$ 7 Hz, $J_{12',NH} < 1$ Hz), 2.31 (t, 2H, H14, $J_{14,15}$ 7.5 Hz), 2.13 (large, 1H, NH), 1.65 (m, 2H, H15, $J_{14,15}$ 7.5 Hz, $J_{15,16}$ 7.5 Hz), 0.94 (t, 3H, H16, $J_{16,15}$ 7.5 Hz). ^{13}C-NMR (75.47 MHz, $CDCl_3$) δ : 173.2 (C13), 139.9 (C14'), 128.4 (C15' and C19'), 128.2 (C16' and C18'), 127.1 (C17'), 91.8 (C6), 68.7 (C5 and C11), 68.5 (C3 or C9), 67.6 (C8, C9 or C3), 66.3 (C2), 63.3 (C12), 53.9 (C13'), 49.6 (C12'), 36.0 (C14), 18.3 (C15), 13.7 (C16).

E,E-(±)-2,8-Dimethyl-1,4,7,10-tetraoxaspiro[5.5]undecane (9).

To a solution of diol (3) (1.1 g, 5 mmol) in CH_2Cl_2 (20 ml), freshly distilled triethylamine (1.8 ml, 12 mmol) was added. The mixture was stirred and cooled to 0-5°C. Freshly distilled methanesulfonylchloride (1.39 g, 12 mmol) was then added dropwise. The reaction was stirred at room temperature for 2 h. The organic phase

was washed with brine (2 x 10 ml) and dried over $MgSO_4$. Evaporation of the solvent under vacuum yielded crude dimesylate (**8**) as a white wax (1.805 g, 96% yield). A fraction of this crude product (0.65 g, 1.7 mmol) was dissolved in anhydrous THF (20 ml). LAH (0.24 g, 6 mmol) was then added at 0°C. The resulting mixture was refluxed for 2 h. Excess of LAH was hydrolysed while cooling with an ice bath. After filtration of the solution, the cake was washed with THF (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and were evaporated under vacuum. The residue was chromatographed on silica gel with ethylacetate/cyclohexane 50:50 and the product (**9**) was obtained in 77% (0.246 g) yield as a white solid. m.p. = 77-79°C (ethylacetate/cyclohexane). IR ($CHCl_3$) : 1060-1100-1150, 1310-1380-1450 cm^{-1}. MS (FAB^+) m/z : 189.1 ($M+H^+$). Anal. Calcd for $C_9H_{16}O_4$ (188) : C 57.44, H 8.51. Found : C 57.59, H 8.49. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 4.09 (ddd, 2H, H2 and H8, each a, $J_{2,3e} = J_{8,9e}$ 2.6 Hz, $J_{2,12} = J_{8,12'}$ 6.7 Hz, $J_{2,3a} = J_{8,9a}$ 10.6 Hz), 3.71 (dd, 2H, H3 and H9, each e, $J_{3e,2} = J_{9e,8}$ 2.6 Hz, $J_{3e,3a} = J_{9e,9a}$ 11.5 Hz), 3.55 (d, 2H, H5 and H11, each e, $J_{5e,5a} = J_{11e,11a}$ 11.5 Hz), 3.19 (d, 2H, H5 and H11, each a, $J_{5a,5e} = J_{11a,11e}$ 11.5 Hz), 3.16 (pt, 2H, H3 and H9, each a, $J_{3a,2} = J_{9a,8}$ 10.6 Hz, $J_{3a,3e} = J_{9a,9e}$ 11.5 Hz), 1.10 (d, 6H, H12 and H12', $J_{12,2} = J_{12',8}$ 6.7 Hz). ^{13}C-NMR (75.47 MHz, $CDCl_3$) δ : 91.7 (C6), 71.6 (C3 and C9), 68.5 (C5 and C11), 64.0 (C2 and C8), 16.6 (C12 and C12').

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