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# Stereocontrolled Reactions Induced by a Thermolabile Group. Synthesis of Optically Active 1,3-Diols.

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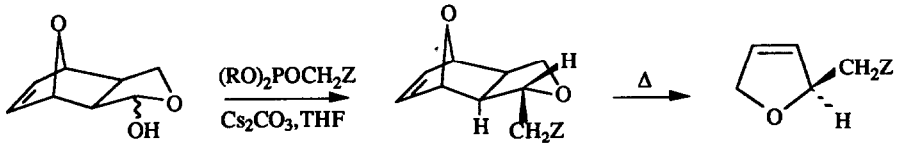
**Abstract** : Wittig Horner-Michael reactions of phosphonates with optically active lactol **1** lead preferentially to one diastereoisomer **2**. Force field calculations conducted on one pair of diastereoisomers **2c** and **2'c** predict that these isomers must exist in different conformations of similar energies. $^1$H NMR data are in good agreement with these predictions. The dihydrofurans obtained by retro Diels-Alder reactions of **2** are easily transformed into optically pure 1,3-diols, precursors of R-(+)-α-lipoic acid and (-)-(1R,3R,5S)- 1,3-dimethyl -2,9-dioxabicyclo [3.3.1]nonane.

During our investigations directed at the steric control of a variety of reactions by a thermolabile group, we have shown that tricyclic ethers **2**, precursors of optically active dihydrofurans **3** can be highly selectively obtained from chiral, non racemic lactol **1** by a tandem Wittig Horner-Michael reaction followed by a retro Diels-Alder cleavage [1].




**1** **2 (a-c)** **3 (a-c)**

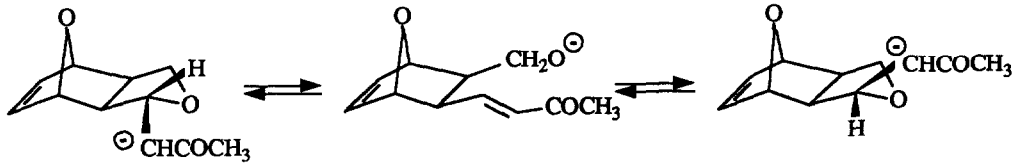
**a**, Z = $COOCH_3$ (de = 94%)
**b**, Z = CN (de › 98%)
**c**, Z = $COCH_3$ (de = 80%)

It has been postulated that the stereoselectivity of the intramolecular Michael reaction was probably due to the steric bulk of the thermolabile oxanorbornenyl group which favors the formation of the thermodynamically most stable ether **2** where the $CH_2Z$ substituent is in an exo position. We wish to report here the results of force field calculations supporting the influence of the oxanorbornenyl group on the stability of the stereoisomer **2** and the use of dihydrofurans **3** for the synthesis of optically pure 1,3-diols, interesting intermediates for the preparation of natural products [2].

## Force field calculations and n.m.r. data

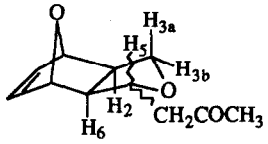
The Wittig Horner intramolecular Michael reaction giving rise to the isomeric ethers **2** and **2'** were carried on in refluxing THF in the presence of an excess of base. Under these conditions of prolonged heating under basic conditions, the diastereoisomers **2** and **2'** must undergo an equilibration leading ultimately to the predominant isomer **2**, thermodynamically more stable. In the case of **2c** and **2'c**, the diastereoisomeric ratio **2c/2c'** = 9/1 has been shown to be the thermodynamic ratio since pure isolated **2c** and **2'c** led in the same

conditions (24 hours in refluxing THF in the presence of $Cs_2CO_3$) to the same 9 to 1 ratio of stereoisomers through a base-catalyzed equilibrium :



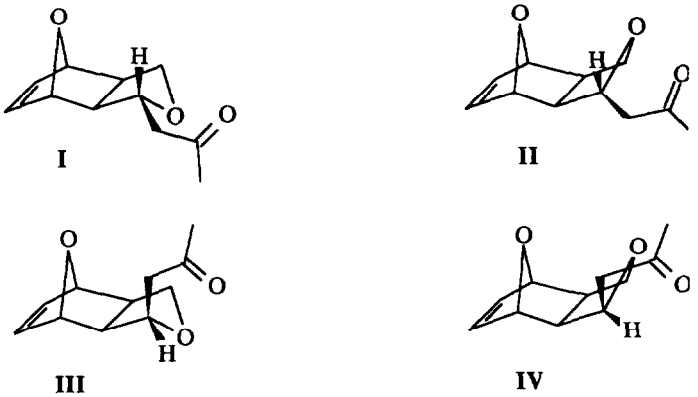
**2c** $^{\ominus}$ (90) **2'c** $^{\ominus}$ (10)

The relative stereochemistry of the two isomeric ketones **2c** and **2'c** has been determined by $^1H$ NMR : a strong nuclear Overhauser effect (7% enhancement) between the hydrogens $H_5$ and $H_6$ secured the stereochemical assignement **2'c** to the minor diastereoisomer since no effect was observed between the same two hydrogens of the major isomer **2c**.



Furthermore, similar coupling constants $J_{H2H3b} \sim J_{H5H6} \sim 6 - 8$ Hz were observed in the $^1H$ NMR spectra of both stereoisomers, but a significant difference was found for the vicinal coupling constant $J_{H2H3a}$ : 7.2 Hz for **2c** and 2.3 Hz for **2'c**. This general observation could also been made for others pairs of isomers **2** and **2'**. In order to find if these values could be due to distinct conformations assumed by the stereoisomers, force field calculations were conducted with the MMX program [3]. Two low energy conformations were found for both diastereoisomers **2c** and **2'c**. These conformations are displayed in Fig. 1 and the calculated energies, dihedral angles between hydrogens and vicinal proton-proton coupling constants are reported in Table 1.

**Fig.1. Low energy conformations for 2c and 2'c determined by MMX**



I II III IV

**Table 1. Calculated energies, dihedral angles and vicinal coupling constants for conformations I - IV**

| *Structure* | | *Energy (kJ/mol)* | *Coupling constants (Hz) and dihedral angles (degrees)* | | | |
|---|---|---|---|---|---|---|
| | | | $J_{H2H6}$ | $J_{H2H3a}$ | $J_{H2H3b}$ | $J_{H5H6}$ |
| | I | 161.3 | 12.2 (0) | 7.2 (145) | 7.4 (21) | 9.6 (146) |
| **2c** | II | 168.4 | 12.2 (1) | 1.9 (97) | 9.0 (29) | 1.1 (99) |
| | III | 172.6 | 12.1 (4) | 7.4 (146) | 7.1 (24) | 9.5 (11) |
| **2'c** | IV | 163.0 | 12.2 (0) | 1.7 (95) | 8.7 (28) | 8.4 (30) |

The energy difference between the lowest energy conformations I (**2c**) and IV (**2'c**) is only 2kJ/mol, with the diastereoisomer **2c** being slightly preferred. This is consistent with the thermodynamic preference of **2c** already observed (see above) in the equilibration experiments. In the two conformers I and IV, the $CH_3$-CO-$CH_2$ substituent is in a pseudo equatorial position minimizing the 1,2 and 1,3 diaxial interactions. Inspection of the data of Table 1 shows that for I and IV, an excellent agreement exists between the experimental and the calculated values of the vicinal coupling constants, in particular for $J_{H2H3a}$. It can be deduced that each stereoisomer assumed a distinct conformation :

- For the major isomers **2**, the substituents $CH_2Z$ are in an exo position and the oxygen of the tetrahydrofuran ring is down (conformer I). These isomers are characterized by coupling constants $J_{H2H3a} \sim J_{H2H3b} \sim 7$ Hz.
- For the minor isomers **2'**, the chain $CH_2Z$ is in an endo position and the oxygen of the tetrahydrofuran ring is up. For these isomers the coupling constants are different : $J_{H2H3a} \sim 2$ Hz.and $J_{H2H3b} \sim 7$ Hz

In conclusion, the stereochemistry of the diastereoisomers **2** and **2'** can be assigned by a simple examination of their $^1H$ NMR spectra.

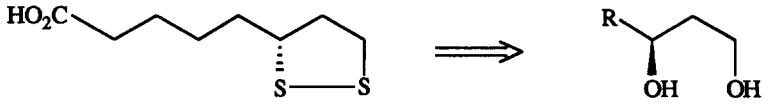
## Synthesis of optically active 1,3-diols

A number of natural compounds of interest contain a 1,3-diol substructure and various methods have been developed to build optically active 1,3-diols with good to excellent stereocontrol [4]. The cleavage of cyclic ethers can lead to polyfunctionnal acyclic compounds and in particular polyhydroxylated chains but this reaction had still not been extensively used. This might be due to the low level of selectivity displayed by a variety of reagents in non symmetrical cyclic systems. Very recently, however, a few reagents have been reported to ring open 2-substituted tetrahydrofuran derivatives in a regiocontrolled fashion : $BF_3$, $Et_3N^+$, $Br^-$ [5], $Me_2BBr$ [6] and $SiMe_3Cl$/NaI [7]. We have used the last two to cleave optically active cyclic ethers obtained by our method, giving an access to optically pure 1,3-diols. The synthetic utility of these diols is shown by the synthesis of a precursor of R-(+)-α-lipoic acid and of (1R,3R,5S)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane, an host specific substance for the ambrosia beetle.

*Synthesis of a primary, secondary 1,3-diol, precursor of R-(+)-α-lipoic acid*

R-(+)-α-lipoic acid **4** acts as a cofactor in the biochemical decarboxylation of α-ketoacids [8]. Since its discovery, lipoic acid has been found to be widely distributed in animal and plant tissue [9] and to display a high

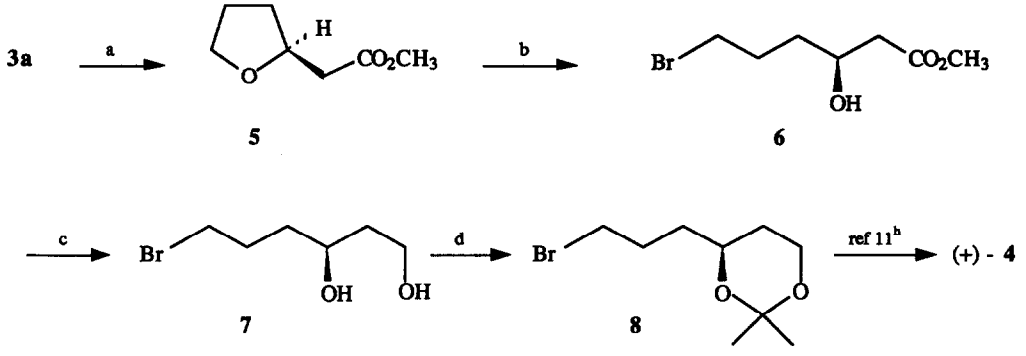
level of biological activity [10]. Subsequently a number of reports have recently appeared, describing the enantioselective synthesis of this acid [11], in most cases from an intermediate primary-secondary 1,3-diol :



**4**

We have found that the dihydrofuran **3a** was a good candidate for the synthesis of such 1,3-diols and we report here the obtention of S-(-)-6-bromo-1,3-hexanediol **7**, a precursor of **4** (Scheme 1).

Scheme 1



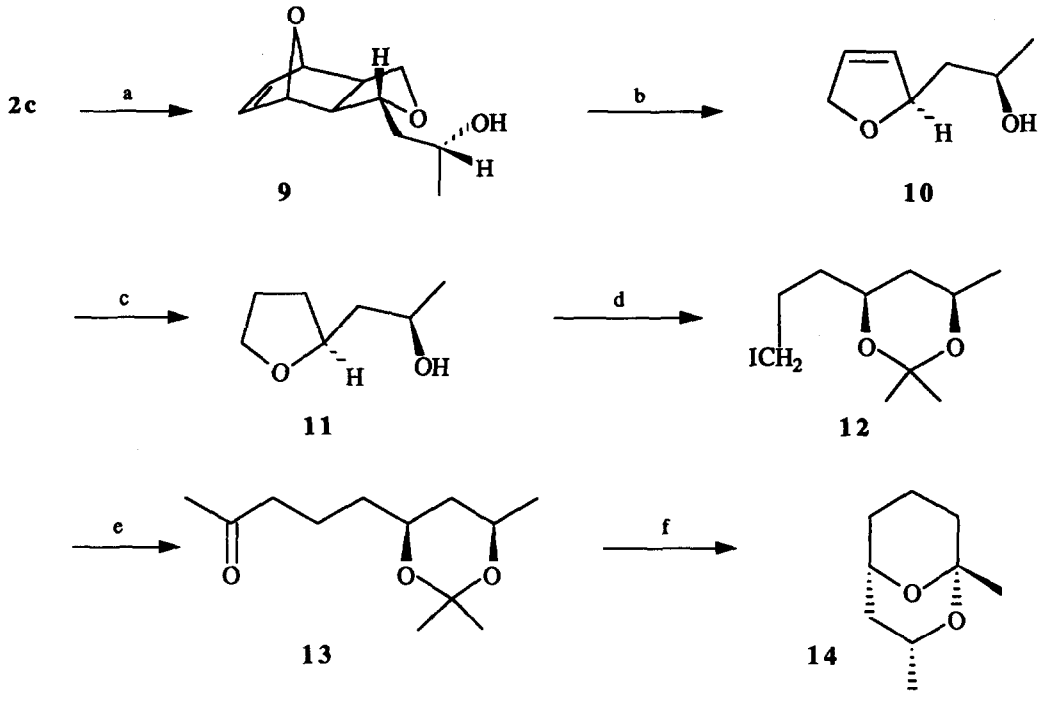
Reagents : a) $H_2$, Raney Ni, $CH_3OH$, 83% ; b) $Me_2BBr$, $CH_2Cl_2$, 0°C, 87% ; c) $LiBH_4$, THF, 0°C, 90% ; d) 2,2-dimethoxypropane, $CH_2Cl_2$, PPTS, 93%.

Hydrogenation of the dihydrofuran **3a** catalyzed by Raney Nickel gave rise with high yield to the optically pure tetrahydrofuran **5**. As described for the racemic compound [6b], dimethylboron bromide cleaved **5** with high regioselectivity, leading to the acyclic β-hydroxester **6**. The ring opening took also place without racemization since the enantiomeric excess of **6** was higher than 95% as shown by $^1H$ NMR in the presence of $Eu(hfc)_3$. The bromomethyl group, as well as the ester function, were reduced by LAH, so that the bromodiol **7** was best obtained by reduction of **6** with lithium borohydride. The diol **7**, quite unstable, showed a great tendency to recyclise and the hydroxy groups were protected rapidly to the acetonide **8**. This latter compound could be transformed to R-(+)-α-lipoic acid as already described for the chloro analog [12].

*Obtention of bis secondary 1,3-diols : synthesis of (-)(1R,3R,5S)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane* [13]

Endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **14** is an host specific substance for the ambrosia beetle which infests the bark of the Norway Spruce [14]. The absolute configuration of the natural product is not known with certainty so that several syntheses of one or the other enantiomer have been reported during these last few years [15]. The direct precursor of the bicyclo compound **14** is a syn-1,3 diol which can be obtained via the ring opening of a tetrahydrofuran as shown in the synthetic Scheme 2.

Scheme 2




Reagents : a) LAH, THF, -78°C, 85% ; b) 500°C, 82% ; c) $H_2$, Raney Ni, 81% ; d) $SiMe_3Cl/NaI$, $CH_3COCH_3$, 62% ; e) $Et_2NCH(CH_3)CN$, LDA, then $SiO_2$, 72% ; f) $SiO_2$ / $(CO_2H)_2$, 77%.

The reduction of the carbonyl group of the tricyclic compound **2c** by a variety of reagents gave two diastereoisomers **9** and **9'** (Table 2).

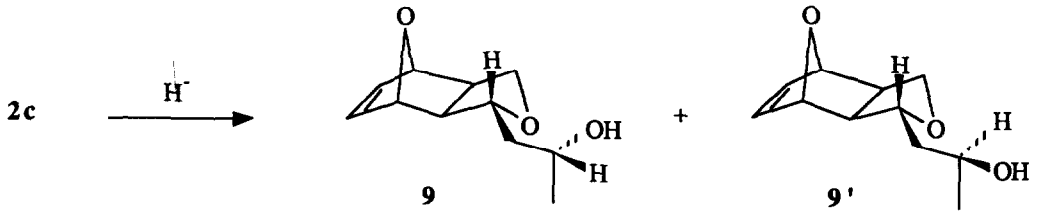


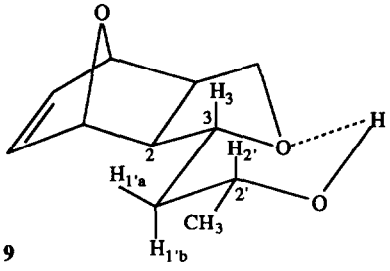
**Table 2. Diastereoselective reduction of the ketone 2c**

| Entry | Hydride | Solvent | Temp. (°C) | **9 : 9'** (a) (syn:anti) | Yield (%) (b) |
|---|---|---|---|---|---|
| 1 | $NaBH_4$ | MeOH | 0 | 70:30 | 89 |
| 2 | $LiAlH_4$ | $Et_2O$ | -78 | 83:17 | 98 |
| 3 | $LiAlH_4$ - LiI | $Et_2O$ | -78 | 79:21 | 90 |
| 4 | $LiAlH_4$ | THF | -78 | 91:9 | 98 |
| 5 | $LiAlH_4$ | $CH_2Cl_2$ | -78 | 50:50 | 98 |
| 6 | DIBAL | THF | -78 | 69:31 | 95 |
| 8 | L-Selectride | THF | -78 | 82:18 | 95 |

(a) **9:9'** ratios were determined by $^1H$ NMR analysis.
(b) Yields for isolated compounds (Mixture of diastereoisomers).

The best selectivity was obtained using simply $LiAlH_4$ in THF (entry 4). In contrast to the reduction of others β-alkoxy ketones [16], the addition of LiI as a chelating agent did not improve the selectivity. This may be due to the presence of the extra bridge oxygen which is also able to chelate the lithium cation.

The major reduction product **9** was found by $^{13}C$ and $^1H$ NMR to possess a syn relationship between the newly created hydroxy group and the β-alkoxy group of the tetrahydrofuran ring. Monoprotected 1,3-diols exist preferentially in a cyclic conformation stabilized by hydrogen bonding [17]. As reported for such compounds we found that the two carbinols carbons resonate more upfield in the 1,3-anti diol **9'** ($\delta C_3$ = 64.5 ppm ; $\delta C_{2'}$ = 79.2 ppm) than in the 1,3-syn diol **9** ($\delta C_3$ = 66.7 ppm ; $\delta C_{2'}$ = 81.4 ppm), due to γ-gauche effects [18].




**9**

In $^1H$ NMR, the values of the coupling constants of the major stereoisomer **9** ($J_{H3H1'a} = J_{H2'H1'a} = 3$ Hz ; $J_{H3H1'b} = J_{H2'H1'b} = 9$ Hz) are in good agreement with axial positions of $H_3$ and $H_{2'}$, entailing a syn stereochemistry for the two C-O bonds.

Flash thermolysis at 500° of **9** gave the dihydrofuran **10** which was easily hydrogenated in the presence of Raney Ni into the tetrahydrofuran **11**. Completion of our synthesis now depended on the regioselective opening of the tetrahydrofuran ring at the least hindered carbon atom. We found that treatment of **11** with $Me_3SiCl/NaI$ in acetone, resulted in both the regioselective cleavage of the cyclic ether and the ketalization of the 1,3-diol formed, affording the iodo acetonide **12** in 62% yield. Alkylation of methyl N-diethyl aminoacetonitrile [19] by the iodide **12** followed by silicagel chromatography led to the ketone **13** of high enantiomeric purity (ee ≥ 95% as shown by $^1H$ NMR in the presence of $Eu(hfc)_3$). Finally the

deprotection of the hydroxy groups and the cyclization into (-) **14** ($[\alpha]_D^{20}$ = -35.7 ; c = 1, pentane) [20] was realized by an acid catalysis with $SiO_2$/oxalic acid [21].

## EXPERIMENTAL SECTION

**General** : IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Brucker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Flash thermolyses were effected with the apparatus previously used [1]. All reactions were carried out under an inert atmosphere of argon and were monitored by thin-layer chromatography (TLC). TLC was performed on Merck silicagel 60F-254 precoated on glass.

### (R)-2-Methoxycarbonyltetrahydrofuran 5

To a stirred suspension of 20 mg of Raney Ni in ethanol (5 mL) under an hydrogen atmosphere was added 300 mg (2.11 mmol) of dihydrofuran **3a** [1] in ethanol (2 mL). After 30 min. the required amount of hydrogen (47.3 mL, 2.11 mmol) has been taken up and the catalyst was removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by chromatography (eluant : ether/hexane : 80/20) to give 253 mg (83%) of tetrahydrofuran **5** $[\alpha]_D^{20}$ = +6.7 ($CHCl_3$, c 0.95). IR ($CCl_4$) : 1750, 1050 $cm^{-1}$. MS : m/e (relative intensity) : 144 ($M^+$, 0.2) ; 116 (26) ; 101 (11) ; 84 (17) ; 74 (13) ; 71 (100) ; 59 (18). $^1H$ NMR ($CDCl_3$, 200 MHz) δ : 1.50 (1H, m) ; 1.85 (2H, m) ; 2.05 (1H, m) ; 2.43 (1H, m) ; 2.54 (1H, m) ; 3.64 (3H, s) ; 3.63 - 3.88 (2H, m) ; 4.19 (1H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ : 24.8 ; 30.5 ; 39.6 ; 50.6 ; 67.1 ; 74.5 ; 170.7. Anal. calcd for $C_7H_{12}O_3$ : C, 58.32 ; H, 8.29. Found : C, 58.92 ; H, 8.38.

### (3S)-Methyl 6-bromo-3-hydroxy hexanoate 6

To a cold (0°C) stirred solution of compound **5** (202 mg, 1.4 mmol) in dry methylene chloride (10 mL) and triethylamine (0.03 mL) was added dropwise a solution of dimethylboron bromide (1,56M, 1.8 mL, 2.8 mmol) in methylene chloride. The solution was stirred for 2 h at 0°C. The reaction mixture was poured over a stirred saturated solution of sodium bicarbonate (10 mL) and extracted with methylenechloride (3 x 10 mL). The organic layer was washed with brine (2 x 15 mL), dried over magnesium sulfate, filtered and evaporated under reduce pressure. The residue was purified by column chromatography (eluent : ether/hexane : 80/20) to give 273 mg (87%) of bromide **6**. $[\alpha]_D^{20}$ = +10.3 ($CHCl_3$, c 1.2). IR (film) : 3450, 1740 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz) δ : 1.64 (2H, m) ; 1.87 - 2.18 (2H, m) ; 2.42 - 2.54 (2H, m) ; 2.84 (1H, s) ; 3.46 (2H, m) ; 3.72 (3H, s) ; 4.04 (1H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ : 28.6 ; 33.5 ; 34.6 ; 41.1 ; 51.6 ; 67.0 ; 172.9.

### (3S)-6-Bromohexane-1,3 diol 7

To a cold (0°C) stirred solution of bromoester **6** (497 mg, 2.2 mmol) in dry tetrahydrofuran (10 mL) was added dropwise a solution of lithium borohydride (2M, 3.3 mL, 6.6 mmol) in tetrahydrofuran. The solution was stirred for half an hour at 0°C and then hydrolyzed with a saturated solution of ammonium chloride (10 mL). The two phases mixture was stirred for 30 min., and extracted with ether (3 x 15 mL). The organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated under vacuum.

The residue was purified by silicagel chromatography (ether) to afford 390 mg (90%) of bromodiol **7**. $[\alpha]_D^{20}$ = -4.8 ($CH_3OH$, c 0.6). $^1H$ NMR ($CDCl_3$, 200 MHz) δ : 1.65 (4H, m) ; 1.97 (2H, m) ; 3.12 (2H, s) ; 3.44 (2H, t, J = 7 Hz) ; 3.88 (3H, m).

**(3S)-6-Bromo-1,3-isopropylidendioxyhexane 8**

To a stirred solution of bromodiol **7** (246 mg, 1.25 mmol) in dry methylene chloride (10 mL) was added 2,2-dimethoxy propane (520 mg, 5 mmol) and pyridinium paratoluenesulfonate (PPTS, 10 mg). The solution was stirred for 4 hours, the solvent was evaporated under vacuum and the residue was chromatographed (silicagel, eluent : ether/hexane : 80/20) to give 276 mg (93%) or the protected diol **8**. $^1H$ NMR ($C_6D_6$, 250 MHz) δ : 1.37 (3H, s) ; 1.44 (3H, s) ; 1.5 - 1.7 (4H, m) ; 1.98 - 2.1 (2H, m) ; 3.42 (2H, m) ; 3.84 (1H, m) ; 3.97 (2H, m). MS : m/e (relative intensity) : 223 (31) ; 221 (29) ; 163 (17) ; 161 (16) ; 81 (100) ; 69 (15) ; 59 (43). Anal. calcd for $C_9H_{17}BrO_2$: C, 45,75 ; H, 7,26 ; Br, 33.43. Found : C, 45,39 ; H, 7,45 ; Br, 33.52.

**(1R,2S,3R,6S,7S,2'R)-3-(2'-hydroxypropyl)-4,10-dioxatricyclo[5.2.1.$O^{2,6}$]dec-8-ene 9**

A stirred suspension of lithium aluminium hydride (380 mg, 10 mmol) in dry tetrahydrofuran (50 mL) was cooled at -70°C (dry ice-acetone) under an argon atmosphere. To this suspension was added dropwise a solution of the ketone **2c** [1] (970 mg, 5 mmol) in dry tetrahydrofuran (10 mL). The reaction mixture was stirred for 1 hour at -70°C and then allowed to warm to room temperature. An aqueous solution of HCl (1N, 10 mL) was slowly added and the organic layer was separated. The aqueous layer was extracted with methylenechloride (3 x 20 mL) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent in vacuo and chromatography of the residue on silicagel (methylene chloride/methanol 95/5) gave 832 mg (85%) of pure **9** and 82 mg of an mixture of **9** and **9'** enriched in **9'**.

*Isomer* **9** : $[\alpha]_D^{20}$ = +1.9 ($CH_3OH$, c 1.1). IR (film) : 3440, 1050 $cm^{-1}$. CIMS ($NH_3$): m/e (relative intensity) : 214 ($MNH_4^+$, 75) ; 197 ($MH^+$, 100). $^1H$ NMR ($C_6D_6$, 250 MHz) δ : 1.15 (3H, d, J = 7 Hz) ; 1.40 (1H, dt, J = 14 Hz, J' = 3 Hz) ; 1.50 - 1.75 (2H, m) ; 1.98 (1H, dt, J = 7.5 hz, J' = 8 Hz) ; 3.24 (1H, dd, J = 8.5 Hz, J' = 7.5 Hz) ; 3.58 (1H, m) ; 3.68 (1H, m) ; 3.77 (1H, dd, J = 8.5 Hz, J' = 7.5 Hz) ; 3.96 (1H, m) ; 4.18 (1H, d, J = 1.5 Hz) ; 4.40 (1H, d, J = 1.5 Hz) ; 5.90 (1H, dd, J = 6 Hz, J' = 1.5 Hz) ; 5.84 (1H, dd, J = 6 Hz, J' = 1.5 Hz). $^{13}C$ NMR ($C_6D_6$, 50 MHz) δ : 22.9 ; 42.7 ; 47.6 ; 53.9 ; 66.7 ; 69.9 ; 79.9 ; 80.3 ; 81.4 ; 135.9 ; 136.1. Anal. calcd for $C_{11}H_{16}O_3$ : C, 67.32 ; H, 8.22. Found : C, 67.52 ; H, 8.38.

*Isomer* **9'**: $^1H$ NMR ($C_6D_6$, 250 MHz) δ : 1.13 (3H, d, J = 7 Hz) ; 1.40 - 1.70 (2H, m) ; 1.84 (1H, dd, J = 7 Hz, J' = 7 Hz) ; 2.00 (1H, m) ; 2.50 (1H, m) ; 3.32 (1H, dd, J = 8 hz, J' = 6 Hz) ; 3.60 - 3.90 (2H, m) ; 4.00 (1H, m) ; 4.17 (1H, d, J = 1Hz) ; 4.40 (1H, d, J = 1 Hz) ; 5.84 (1H, dd, J = 6 Hz, J' = 1 Hz) ; 5.88 (1H, dd, J = 6 Hz, J' = 1 Hz). $^{13}C$ NMR ($C_6D_6$, 50 MHz) δ : 23.7 ; 42.4 ; 48.1 ; 53.3 ; 64.5 ; 69.7 ; 79.2 ; 80.2 ; 81.4 ; 135.9 ; 136.1.

**(2R,2'R)-2-(2'-hydroxypropyl)-2,5-dihydrofuran 10**

790 mg (4 mmol) of tricyclic adduct **9** were evaporated through an horizontal mullite tube (500°C, $10^{-2}$ torr) and the product was collected in a trap cooled to liquid nitrogen temperature. After warming to room

temperature, the content of the trap was dissolved in ether and the resulting solution was dried over magnesium sulfate and after filtration, concentrated under reduced pressure. The residue was purified by chromatography (silicagel, methylene chloride/methanol, 93/7) to provide 423 mg (82%) of dihydrofuran **10**. $[\alpha]_D^{20}$ = -95 ($CH_3OH$, c 1.7). IR (film) : 3400, 1070 $cm^{-1}$. MS : m/e (relative intensity) : 128 ($M^+$, 2.2) ; 95 (10) ; 69 (100) ; 68 (14). $^1H$ NMR ($C_6D_6$, 200 MHz) δ : 1.18 (3H, d, J = 6 Hz) ; 1.52 (1H, dd, J = J' = 10 Hz) ; 1.70 (1H, dd, J = J' = 3 Hz) ; 3.48 (1H, m) ; 4.10 (1H, m) ; 4.68 (2H, m) ; 5.00 (1H, m) ; 5.78 (1H, m) ; 5.89 (1H, m). $^{13}C$ NMR ($C_6D_6$, 50 MHz) δ : 23.7 ; 44.9 ; 66.6 ; 74.9 ; 85.8 ; 126.2 ; 130.1. Anal. calcd for $C_7H_{12}O_2$ : C, 65.60 ; H, 9.44. Found : C, 65.83 ; H, 9.52.

**(2S,2'R)-2-(2'-hydroxypropyl)tetrahydrofuran 11**

Dihydrofuran **10** (300 mg, 2.34 mmol) was hydrogenated as described above for **3a** to give after silicagel chromatography (methylene chloride/ethanol, 98/2) 246 mg (81%) of compound **11**. $[\alpha]_D^{25}$ = -11.6 ($CH_3OH$, c 1.7). IR (film) : 3400, 1050 $cm^{-1}$. MS : m/e (relative intensity) : 130 ($M^+$, 0.2) ; 112 (11) ; 97 (22) ; 71 (100) ; 68 (24) ; 67 (18). $^1H$ NMR ($CDCl_3$, 200 MHz) δ : 1.17 (3H, d, J = 6 Hz) ; 1.42 - 1.60 (2H, m) ; 1.66 (1H, m) ; 1.88 (2H, m) ; 3.56 (1H, m) ; 3.78 (1H, m) ; 3.88 (1H, m) ; 4.00 (2H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ : 22.9 ; 24.6 ; 31.4 ; 43.5 ; 66.6 ; 67.2 ; 78.6. Anal. calcd for $C_7H_{14}O_2$ : C, 64.58 ; H, 10.84. Found : C, 64.75 ; H, 10.56.

**(2R,4S)-7-Iodo-2,4-isopropylidendioxyheptane 12**

To a stirred solution of sodium iodide dried at 110°C under vacuum (413 mg, 2.75 mmol) in dry acetone (5 mL) was added a solution of **11** (357 mg, 2.75 mmol) in acetone (0.5 mL) and then dropwise freshly distilled trimethylchlorosilane (0.36 mL, 2.75 mmol). The brown mixture was stirred for 4 hours at room temperature, filtrated and concentrated under vacuum. The residue was dissolved in ether (10 mL) and the solution was washed successively with saturated solutions of sodium carbonate and sodium thiosulfate. The organic layer was dried over magnesium sulfate,the solvent removed under reduced pressure and the residue was purified by chromatography on silicagel to give 520 mg (63%) of the iodocacetonide **12**. IR (film): 1380, 1260 $cm^{-1}$. $^1H$ NMR ($C_6D_6$, 200 MHz) δ : 1.06 (3H, d, J = 6 Hz) ; 1.10 (2H, m) ; 1.22 (3H, s) ; 1.22 - 1.45 (2H, m) ; 1.47 (3H, s) ; 1.50 - 1.88 (2H, m) ; 2.74 (2H, m) ; 3.35 (1H, m) ; 3.59 (1H, m). $^{13}C$ NMR ($C_6D_6$, 50 MHz) δ : 6.6 ; 19.9 ; 22.4 ; 29.7 ; 30.6 ; 37.4 ; 39.0 ; 65.1 ; 68.1 ; 98.4.

**(6S,8R)-6,8-Diisopropylidendioxynonan-2-one 13**

To a stirred solution of diisopropylamine (85 mg, 0.84 mmol) in dry THF (5 mL) was added a solution of butyllithium in hexane (1.5M, 0.56 mL) followed by 1 equiv. of hexamethylphosphoramide (150 mg, 0.84 mmol). After cooling at -70°C was added dropwise a solution of 2-diethylaminopropionitrile [19] (106 mg, 0.84 mmol) in THF (0.5 mL) followed by a solution of iodide **12** (250 mg, 0.84 mmol) in dry THF (0.5 mL). The reacting mixture was stirred for one hour at -70°C and allowed to warm up to room temperature. Water (5 mL) was added and the aqueous layer was extracted with ether (3 x 5 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The residue was hydrolyzed and purified by chromatography on silicagel (ether/hexane, 50/50) to give 139 mg (77%) of ketone **13**. $[\alpha]_D^{25}$ = -11.7 ($CH_3OH$, c 1.5). IR (film) : 1720, 1380, 1060 $cm^{-1}$. $^1H$ NMR ($C_6D_6$, 250 MHz) δ : 1.19 (3H, d, J = 6 Hz) ; 1.29 (3H, s) ; 1.52 (3H, s) ; 1.62 (3H, s) ; 1.12 - 1.8 (6H, m) ; 1.92 (2H, t, J = 7 Hz) ; 3.50 (1H, m) ; 3.63

(1H, m). $^{13}C$ NMR ($C_6D_6$, 50 MHz) δ : 19.7 ; 19.9 ; 22.4 ; 29.3 ; 30.6 ; 36.2 ; 39.0 ; 43.2 ; 65.1 ; 68.9 ; 98.3 ; 206.4. Anal. calcd for $C_{12}H_{22}O_3$ : C, 67.26 ; H, 10.35. Found: C, 67.51 ; H, 10.22.

**(1R,3R,5S)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane 14**

To a stirred suspension of silicagel (300 mg) in methylene chloride (0.5 mL) was added a 10% aqueous solution of oxalic acid (30 mg). After 5 min., 110 mg (0.51 mmol) of ketone **13** was added and the suspension was stirred for 3 hours. Solid sodium hydrogen carbonat (10 mg) was then added and the solid removed by filtration was washed with methylene chloride (2 x 1 mL). The solvent was evaporated under reduce pressure and the residue was purified by silicagel chromatography (Pentane/ether, 95/5) to give 61 mg (77%) of bicyclo compound **14**. $[\alpha]_D^{25}$ = -35.7 (Pentane, c 1.0) [20]. IR (film) : 2940, 1375, 1240, 1160, 1080 $cm^{-1}$. MS : m/e (relative intensity) : 156 ($M^+$, 6) ; 114 (25) ; 113 (11) ; 87 (31) ; 81 (14) ; 71 (15) ; 68 (12) ; 58 (16) ; 43 (100). $^1H$ NMR ($CDCl_3$, 200 MHz) δ : 1.16 (3H, d, J = 6 Hz) ; 1.23 (3H, s) ; 1.20 - 1.82 (6H, m) ; 1.95 - 2.19 (2H, m) ; 3.91 (1H, m) ; 4.23 (1H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ : 14.3 ; 20.8 ; 27.3 ; 29.7 ; 34.8 ; 36.9 ; 61.4 ; 66.8 ; 97.4.

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