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Diastereoface Differentiation in Addition of Lithium Enolates to Chiral α,β-Epoxyaldehydes

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Abstract : The aldolisation reaction of lithium ester enolates with chiral α,β-epoxyaldehydes **2a-2f** has been investigated. The reaction proceeds with diastereofacial preference in favour of the *anti* isomer (*anti:syn* ~ 4:1) and can be greatly enhanced in the case of *cis* α,β-epoxyaldehydes **2a-2c** by a synergic effect of temperature and enolate excess (*anti:syn* 13:1). The Felkin-Ahn model can explain the results obtained on asymmetric induction.

INTRODUCTION

During the last two decades the synthesis of natural products or their analogues possessing interesting biological activities [1] (antibiotics, antivirals, antitumors...) has become an important topic in organic chemistry. A great part of this research has been directed towards the synthesis of optically active compounds having a 1,3 or 1,2,3 polyhydroxylated frame [2] which are useful synthons for the synthesis of natural products. Two strategies have been developed, the first taking into account the existing optically active natural products, especially carbohydrates, [3] the second orientated towards a *de novo* synthesis of the target molecules.[4]

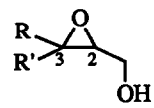
In the course of our studies towards the *de novo* synthesis of chiral polyhydroxylated compounds we required a strategy that permitted stereocontrolled construction of three contiguous asymmetric centres. Optically active α,β-epoxyaldehydes can be used as versatile intermediates for this synthesis.[5] On the other hand, aldol reactions of metal enolates with carbonyl compounds are among the most useful methods used to obtain products with the desired functionality and stereocontrol during C-C bond formation.[6] While numerous studies describe the 1,2 asymmetric induction during reaction of α- or β-alkoxy aldehydes [7] with carbon nucleophiles only few report on the diastereofacial selectivity of α,β-epoxyaldehydes.[8,9] We have recently reported some preliminary results [10] on the stereochemistry of the addition of lithium enolates to chiral α,β-epoxyaldehydes. The present paper describes this study in more detail.

RESULTS AND DISCUSSION

Chiral α,β-epoxyaldehydes **2a-2f** were obtained in high yield by oxidation of the corresponding epoxyalcohols **1a-1f**, readily available by a two or four step procedure from *cis*-2-butene-1,4-diol as starting material (scheme 1).

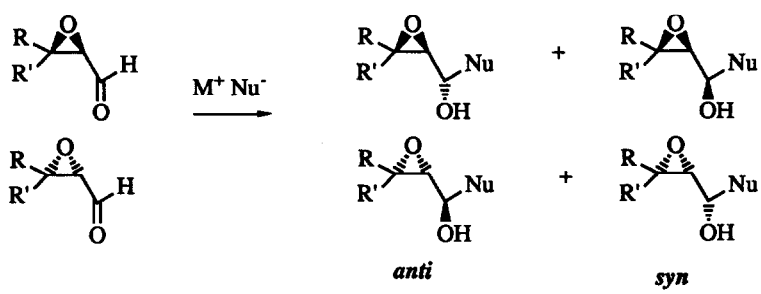
Cis-2-butene-1,4-diol was monoprotected according to recently reported methodology.[11] *Trans* allylic alcohols were obtained in an overall yield of 76-81% by i) oxidation-isomerisation to the *trans* α,β-ethylenic aldehydes following the Doering procedure [12] and ii) $NaBH_4$ reduction of the aldehyde. Finally Sharpless asymmetric epoxidation [13] of the allylic alcohols yielded the corresponding epoxy alcohols **1a-1f**. The optical purity of the compounds (table 1) was determined either by ^{1}H-NMR spectroscopy by using $Eu(hfc)_3$ as shift reagent or by comparison of the $[\alpha]_D^{25}$ values with those reported in the literature.

Table 1. Yields, optical purities and absolute configurations of the epoxyalcohols **1a-1f**



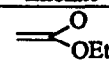
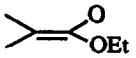
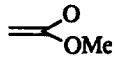
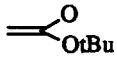
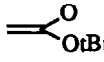
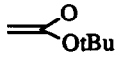
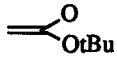
Compound	R	R'	yield(%) of epoxidation	$[\alpha]_D^{25}$ (ee%)	absolute configuration	
1a	H	$BnOCH_2$	47	-25.5 (90)	2S	3R
1b	H	p-$BrBnOCH_2$	71	-17.3 (99) [11]	2S	3R
1c	H	$tBuPh_2SiOCH_2$	51	-6.1 (98) [14a]	2S	3R
1d	p-$BrBnCH_2O$	H	70	-16.6 (96)	2S	3S
1e	$tBuPh_2SiOCH_2$	H	75	-13.8 (85) [14b]	2S	3S
1f	$tBuPh_2SiOCH_2$	H	83	+13.5 (83) [14b]	2R	3R

The oxidation reaction of epoxyalcohols to the corresponding aldehydes **2a-2f** has been optimised ; again the Doering procedure (pyridine/SO_3, DMSO, Et_3N) in our hands gave the best results compared with other methods (Swern, PDC, PCC oxidation reagents). The α,β-epoxyaldehydes thus obtained were allowed to react with various nucleophiles. In a typical run the metal nucleophile obtained at -78°C was added dropwise to an ethereal solution of the aldehyde at the same temperature. Acidic hydrolysis of the reaction mixture and the usual workup leads to a mixture of diastereosiomers (*anti/syn*) of the condensation products.



Reaction of *cis* α,β-epoxyaldehyde **2a** with lithium enolates in the presence or in the absence of other metals listed in table 2 was first considered.

Table 2. Reaction of the epoxyaldehyde **2a** with various enolates *

Entry	Enolate	Metal	Yield (**)	*anti : syn*	N° of compound
1		Li	44 (72)	80 : 20	**3 : 4**
2		Li	39 (47)	79 : 21	**5 : 6**
3		Li	61 (79)	80 : 20	**7 : 8**
4		Li	78 (87)	82 : 18	**9 : 10**
5		Li / ZnBr	50 (57)	87 : 13	**9 : 10**
6		Li / $Ti(OiPr)_3$	46 (60)	73 : 27	**9 : 10**
7		Li / BF_3	45 (66)	79 : 21	**9 : 10**

* Conditions : [2a] = [Enolate] ~ 0.4 M in Et_2O ; -78°C, 30 min.
** Yield calculated from effectively reacted aldehyde

When aldehyde **2a** was condensed with methyl or tert-butyllithium acetate (entries 3, 4) fairly good yields on condensation products were obtained. Reaction of **2a** with isobutyrate gave a modest yield (entry 2). Use *in situ* of Lewis acids (entries 5-7) leads also to moderate yields of the corresponding γ,δ-epoxy β-hydroxyesters along with secondary products.

The diastereoselectivity obtained in every case, whether we change the nucleophile or the metal, was always in favour of the *anti* diastereoisomer (*anti : syn* ~ 3-4 : 1). The results on the diastereoisomeric ratio thus obtained are in agreement with those reported in the literature for the condensation of α,β-epoxy-aldehydes with methyl lithium Grignard reagents and alkyl stannanes [9a] and of blocked α,β-alkoxyalde-hydes with lithium enolates ;[7] while they constitute a great improvement compared to those for the reaction of lithium acetates with α- or β-alkoxy aldehydes (*anti : syn* ~ 1 : 1).[7]

In order to improve the diastereoface preference we examined the reaction of α,β-epoxyaldehydes **2a-2f** with lithium tert-butylacetate by varying the experimental conditions. When the experiments were performed in conditions quite favorable to kinetic control (-110° or -78°C) with short reaction times (≤ 5 min) the same relative proportions of the two diastereoisomers **9/10** were obtained (~ 80/20) ; a result indicating that the preference for the *anti* isomer was almost identical in the earlier and final stages of the reaction at these temperatures (from t ≤ 5 min to ~ 5 h).

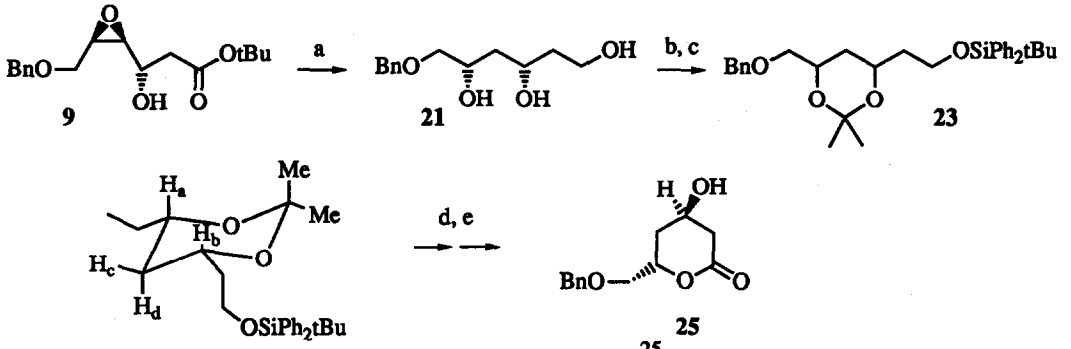
Variation of the temperature of the reaction when a 1:1 ratio of reactants was used did not provoke any change in selectivity, the diastereoisomeric ratio being 4:1 in favour of the *anti* adduct (table 3, entries 1-3). Whilst the same selectivity (~4:1) was obtained when using 2 equivalents of enolate at -78°C (table 3, entry 4), a great improvement was observed by varying **both** the temperature and the reactant equivalents. When 2 enolate equivalents were added to the *cis* α,β-epoxyaldehydes **2a**, **2b**, **2c** at -78°C and the mixture allowed to reach room temperature slowly, a 13-16:1 selectivity was obtained in favour of the *anti* diastereoisomer (table 3, entries 5, 7, 8). The best result on selectivity, but at the expense of the yield, was

achieved when increasing the temperature to the reflux temperature of the Et_2O (table 3, entry 6 *anti:syn* 97:3). Finally, when *trans* α,β-epoxyaldehydes **2d-2f** reacted under the same experimental conditions (table 3, entries 9, 10, 11) the aldol products were obtained in fairly good yields but with a selectivity similar to that obtained under non-optimal conditions.

Table 3. Selectivity of the reaction of lithium tert-butylacetate with aldehydes **2a-2f**

Entry	Aldehyde	ald. : enolate	T °C	Yield	*anti : syn*	N° compound
1	2a	1 : 1	-110	70	81 : 19	**9 : 10**
2	2a	1 : 1	-20	71	81 : 19	**9 : 10**
3	2a	1 : 1	-78 ↗ 25	77	82 : 18	**9 : 10**
4	2a	1 : 2	-78	78	78 : 22	**9 : 10**
5	2a	1 : 2	-78 ↗ 25	82	93 : 7	**9 : 10**
6	2a	1 : 2	-78 ↗ 35	62	97 : 3	**9 : 10**
7	2b	1 : 2	-78 ↗ 25	79	92 : 8	**11 : 12**
8	2c	1 : 2	-78 ↗ 25	85	94 : 6	**13 : 14**
9	2d	1 : 2	-78 ↗ 25	67	74 : 26	**15 : 16**
10	2e	1 : 2	-78 ↗ 25	80	72 : 28	**17 : 18**
11	2f	1 : 2	-78 ↗ 25	74	72 : 28	**19 : 20**

The stereochemical assignement of the aldol products was established for compound **9** by conversion to six membered ring acetal **23** followed by ^1H NMR analysis.



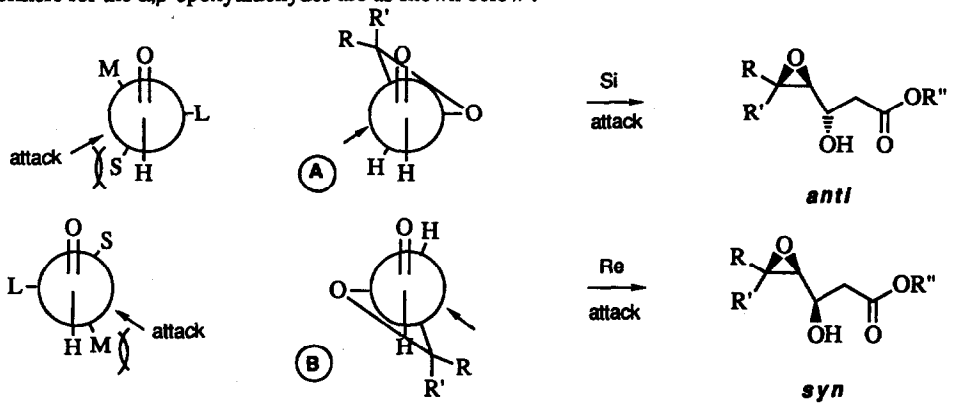
Jac = 2.5 ; Jbc = 2.2 ; Jad = 11.0 ; Jbd = 10.6 Hz ; $[\alpha]_D^{25}$ = +6.1 (9.3 x 10^{-2} ; $CHCl_3$)

a : Red.Al, THF 85% ; **b** : imidazole, $ClSiPh_2tBu$ 95% ; **c** : CSA, $(MeO)_2CMe_2$ 99% ; **d** : nBu_4NF, THF 90% ; **e** : i) PDC, DMF, ii) HCl, THF, iii) H^+, toluène 50%.

The mevinic lactone, the active part of the compactin in the inhibition of the HMG-CoA reductase was also synthesized in two steps from the acetal **23** and the $[\alpha]_D^{25}$ measured was in good agreement with that reported in the literature.[15]

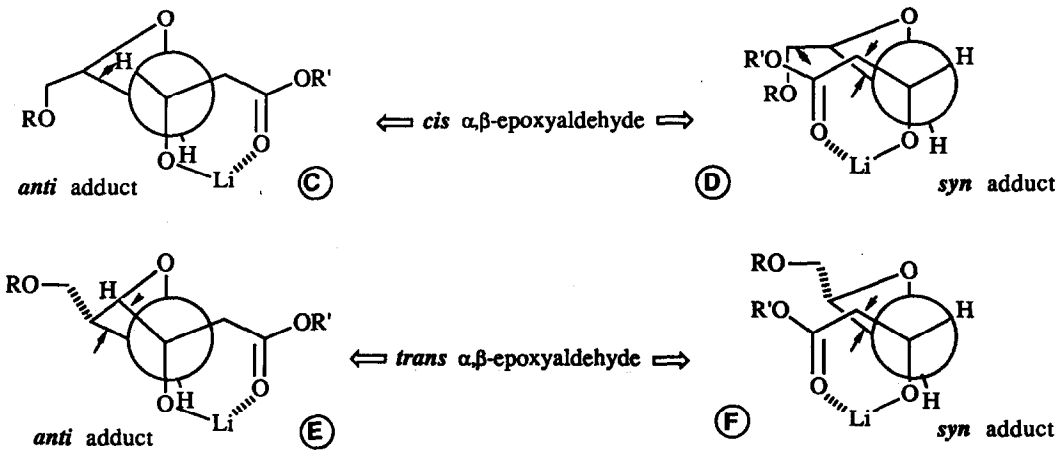
The diastereofacial preference in the addition of metal enolates to the chiral α,β-epoxyaldehydes **2a-2f** can be discussed if the aldolisation reaction is under kinetic control. The selectivity was found to be nearly independant of a variety of conditions indicating that the kinetic and the thermodynamic control were both in favor of the *anti* isomer ; it actually seems unlikely that the diastereoisomeric ratio observed at -110°

or -78°C for short reaction times was the result of an equilibration between the diastereoisomers. Thus, according to the Felkin-Anh model of asymmetric induction, the diastereoselectivity can be explained by the dominant interaction between the incoming nucleophile and the largest group attached to the aldehyde, so that the nucleophile attacks antiperiplanar to that group. In this case we can assume that the oxygen atom of the epoxide function is the large group. This is also in accordance with the Eisenstein proposals [16] based on frontier molecular orbital arguments, that is, the ligand with the lowest σ* orbital would be perpendicular to the carbonyl plane and *anti* to the attacking nucleophile. As carbon-heteroatom bonds the two possible conformers for the α,β-epoxyaldehydes are as shown below :

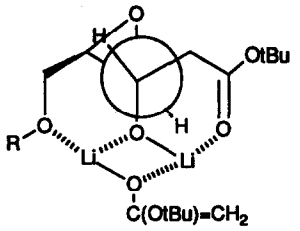


According to Ahn-Eisenstein the intrinsic energies of the two conformers are about equal and stereodifferentiation arises under kinetic control from different interactions between the aldehyde and the incoming nucleophile which is attacking through the Bürgi-Dunitz trajectory.[17] In this case the Si attack is favoured as gauche interactions between the nucleophile and the small (S) ligand of the aldehyde (H) are less than in the Re attack (nucleophile-Medium(M) ligand).

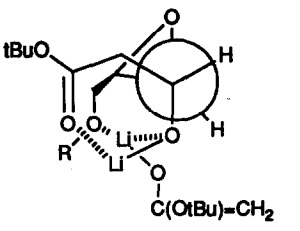
On the other hand, the thermodynamic control of the reaction leads to the same results. In fact, if we examine the possible conformations for the lithiated adducts issued from the *cis* and *trans* chiral α,β-epoxyaldehydes it appears clearly that conformers (C) and (E) develop less interactions than (D and (F) and thus are thermodynamically more stable.



An enhanced diastereoselectivity is observed in favour of the *anti* diastereoisomer in the case of *cis* α,β-epoxyaldehydes **2a-2c** when two lithium equivalents are added and the temperature rises from -78°C to +25°C. We suppose that by increasing the temperature new associative intermediate or exchange reactions could take place between the second equivalent of lithium enolate and conformers (C) and (D) leading to dilithioadducts (C') and (D').



(C') dilithiated adduct *anti*



(D') dilithiated adduct *syn*

In these adducts the oxygen atom of the ether function participates in complexation with the second lithium atom enhancing the stability of the conformer (C') versus (D') which is much more sterically hindered. As the aldolisation reaction is equilibrated this phenomenum may be favour the stabilization of the dilithiated *anti* isomer and thus increase the diastereofacial preference. This assumption is also in agreement with the fact that no increase in diastereoselectivity is observed when the aldolisation reaction is carried under the same experimental conditions whith the *trans* α,β-epoxyaldehydes. In this case there is no possibility of the ether oxygen atom participating in the formation of dilithiated adducts.

The study of the influence of the ether function on the aldolisation reaction is currently under progress.

In conclusion, the aldolisation reaction of lithium ester enolates with chiral α,β-epoxyaldehydes **2a-2f** proceeds with diastereofacial preference in favour of the *anti* isomer (*anti:syn* generally 4:1). The Felkin-Ahn model can explain these results. The diastereoselectivity of the reaction may be greatly enhanced (*anti:syn* 16:1) in the case of *cis* α,β-epoxyaldehydes **2a-2c** by a synergic effect of temperature and enolate excess. The high degree of asymmetric induction achieved may thus be reliable for synthetic approaches to optically active polyols and polyhydroxylated compounds.

EXPERIMENTAL

Products were purified by distillation, recrystallisation or by medium pressure liquid chromatography on a Jobin et Yvon Moduloprep apparatus by using Amicon 6-35 μm or Merck 15 μm silica. IR spectra were recorded with a Perkin-Elmer 883 spectrometer while for NMR spectra a Bruker AC-200 or AC-250 spectrometers were used (200 or 250 MHz for ^{1}H and 50.32 or 62.9 MHz for ^{13}C). Chemical shifts were referenced to the tetramethylsilane. Optical rotations were measured at 25°C with a Perkin-Elmer 141 apparatus. Mass spectra were recorded on a Nermag R10-10. All solvents were distilled and dried before use.

Epoxidation reaction. General procedure.[12] To a stirred suspension of activated powdered molecular sieves (3 Å, 30% of mass of alcohol) in anhydrous methylene chloride (5 mL/mmol of alcohol) under N_2 and at -23°C, was added titanium isopropoxide (0.2 eq.) and (+) or (-) diisopropyl tartrate (0.3 eq.). After 20 min of stirring tert-butylhydroperoxide (2 eq., 3M solution in isooctane) was added and after 30 min a solution of allylic alcohol in methylene chloride (0.4 mL/mmol of alcohol) was added dropwise. The reaction mixture was stirred at -20°C for 36 h. The reaction was quenched by water (1 mL/mmol of alcohol) and the mixture was stirred for 60 min while allowing it to warm to room temperature. Hydrolysis of the tartrate was then effected by adding a 30% aqueous solution of NaOH saturated with sodium chloride (0.40 mL/mmol of alcohol) and stirring vigorously for 30 min. After a first extraction the aqueous phase was washed with methylene chloride (three times). The combined organic phases were washed with saturated NaCl, filtered through celite, dried over $MgSO_4$ and the solvent evaporated. The epoxyalcohol was purified by HPLC chromatography, distillation or recrystallisation.

(2S,3R)-4-(benzyloxy)-2,3-epoxybutan-1-ol **(1a)**. The crude product was purified by HPLC chromatography (eluant petroleum ether : ethyl acetate 7:3, tlc : Rf = 0.2) to afford 4.25 g (21.9 mmol) of **1a** starting from 8.6 g (48 mmol) of allylic alcohol (yield : 45%). IR (Film) ν cm^{-1} : 3405, 3032, 1098. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.37-7.31 (m, 5H,), 4.61 and 4.53 (m, 2H, J = 11.8 Hz), 3.72 (m, 2H), 3.69 and 3.66 (m, 2H, J = 5.9 ; 4.9 ; 11 Hz), 3.28 (m, 1H, J = 4.4 ; 4.9 ; 5.9 Hz), 3.21 (m, 1H, J = 4.4 ; 5.5 ; 5.6 Hz), 2.4 (m, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 137.7 ; 128.6 ; 128.0 ; 127.9 ; 73.3 ; 68.1 ; 60.5 ; 56.1 ; 55.1. Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02 ; H, 7.26. Found : C, 67.99 ; H, 7.28. $[\alpha]_D^{25}$ = -25.5° (c = 0.8 ; $CHCl_3$).

(2S,3R)-4-(p-bromobenzyloxy)-2,3-epoxybutan-1-ol **(1b)**. Compound **1b** was obtained after crystallisation in petroleum ether - ether in 71% yield ; m.p. : 53°C. IR ($CHCl_3$) ν cm^{-1} : 3604, 3013, 1596-1488, 1103. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.50-7.46 (m, 2H, arom.), 7.23-7.20 (m, 2H, arom.) ; 4.59 and 4.44 (AB syst., 2H, J = 12 Hz, pBrPhC$\underline{H}_2$), 3.74 (m, 2H, C$\underline{H}_2$OH), 3.68 (d, 2H, OC$\underline{H}_2$), 3.26 (m, 2H, OCH_2C$\underline{H}$ and C$\underline{H}$CH_2OH), 2.17 (s, 1H, OH). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm : 136.6 ; 131.6 ; 129.4 ; 121.8 ; 72.6 ; 68.2 ; 60.6 ; 55.8 ; 54.9. MS (EI) : 272-274 (M, 1%), 211-213 (2%), 185-187 (100%), 169-171 (84%), 90 (78%), 77 (39%), 57 (44%). Anal. Calcd. for $C_{11}H_{13}O_3Br$: C, 48.37 ; H, 4.79 ; O, 17.57. Found : C, 48.32 ; H, 4.60 ; 0, 17.85. $[\alpha]_D^{25}$ = -17.3° (c = 1.2 ; $CHCl_3$).

(2S,3R)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-ol **(1c.)** Purification on silica gel (eluant ether : petroleum ether 8:2 ; tlc : R_f = 0.34). yield = 51%. IR (Film) ν cm^{-1} : 3421, 3073, 2935 and 2861, 1470, 1110. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.71-7.66 (m, 4H, arom., 7.46-7.38 (m, 6H, arom.), 3.91 and 3.76 (AB part of an ABX(Y) syst., 2H, J = 5.3 ; 5.6 ; 11.7 Hz, OC$\underline{H}_2$), 3.67 (m, 2H, C$\underline{H}_2$OH), 3.22 (m, 2H, OCH_2C$\underline{H}$ et C$\underline{H}$CH_2OH), 2.10 (m, 1H, OH), 1.07 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 135.6 ; 135.5 ; 133.0 ; 132.9 ; 130.0 ; 129.8 ; 127.9 ; 62.3 ; 60.8 ; 56.4 ; 56.2 ; 26.8 ; 19.2. MS (EI) : 269 (2.3%), 256 (1%), 241 (2.2%), 199 (98%), 105 (32.5%), 83 (100%). Anal. Calcd. for $C_{20}H_{26}O_3Si$: C, 70.13 ; H, 7.65. Found : C, 69.88 ; H, 7.60. $[\alpha]_D^{25}$ = -6° (c = 0.7 ; $CHCl_3$).

(2S,3S)-4-(p-bromobenzyloxy)-2,3-epoxybutan-1-ol **(1d)**. Compound **1d** was obtained in 70% yield after crystallisation in ether-petroleum ether. m.p. : 46-48°C. IR ($CHCl_3$) ν cm^{-1} : 3605, 3053 and 3013, 2926 and 2871, 1586, 1488, 1103. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.49-7.44 (m, 2H, arom.), 7.26-7.19 (m, 2H, arom.), 4.53 and 4.50 (AB syst., J = 12.2 Hz, 2H, pBrPh-C$\underline{H}_2$), 3.94 (A part of an ABXY(Z) syst., 1H, J = 2.4 ; 12.7 Hz, C$\underline{H}_2$OH), 3.78 (A' part of an A'B'X'(Y') syst. , 1H, J = 2.8 ; 11.5 Hz, -O-C$\underline{H}_2$), 3.65 (B part of an ABXY(Z) syst., 1H, J = 4 ; 12.7 Hz, C$\underline{H}_2$OH), 3.49 (B' part of an A'B'X'(Y') syst., 1H, J = 5.6 ; 11.5 Hz, O-C$\underline{H}_2$), 3.23 (ddd, 1H, J = 2.3 ; 2.8 ; 5.6 Hz, OCH_2C$\underline{H}$), 3.09 (ddd, 1H, J = 2.3 ; 2.4 ; 4 Hz, C$\underline{H}$CH_2OH), 1.96 (m, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 136.8 ; 131.6 ; 129.4 ; 121.7 ; 72.6 ; 69.7 ; 61.1 ;

55.6 ; 54.2. MS (DCI, NH_3) : 274 (M+1, 0.6%), 246 (0.8%), 211-213 (0.8%), 169-171 (48%), 89 (100%). Anal. Calcd. for $C_{11}H_{13}O_3Br$: C, 48.37 ; H, 4.79 ; O, 17.57. Found : C, 48.42 ; H, 4.78 ; O, 17.55. $[\alpha]_D^{25}$ = -16.6° (c = 0.7 ; $CHCl_3$).

(2S,3S)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-ol **(1e)**. The product was purified by HPLC chromatography (eluant petroleum ether : ether : ethylacetate 5:4:1 ; tlc : Rf = 0.34) to afford the epoxyalcohol **1e** in 85% yield. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.71-7.66 (m, 4H, arom.), 7.44-7.37 (m, 6H, arom.), 3.92 (m, 1H, CH_2OH), 3.89 and 3.78 (AB part of an ABX(Y) syst., 2H, J = 3.2 ; 4.3 ; 12 Hz, OCH_2), 3.30 (m, 1H, CH_2OH), 3.17 (m, 1H, OCH_2CH), 3.10 (m, 1H, $CHCH_2OH$), 1.80 (m, 1H, OH), 1.06 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 135.7 ; 135.6 ; 133.2 ; 133.1 ; 129.8 ; 127.8 ; 63.2 ; 61.2 ; 55.8 ; 55.7 ; 26.8 ; 19.3. MS (EI) : 285 (0.2%), 267 (0.6%), 255 (0.6%), 199 (26.1%), 163 (31%), 47 (35%). Anal. Calcd. for $C_{20}H_{26}O_3Si$: C, 70.13 ; H, 7.65. Found : C, 70.0 ; H, 7.71. $[\alpha]_D^{25}$ = -13.8° (c=0.75;$CHCl_3$).

(2R,3R)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-ol **(1f)**. Obtained in 83% yield. Spectroscopic assignements are identical with **1e**. Anal. Calcd. for $C_{20}H_{26}O_3Si$: C, 70.13 ; H, 7.65. Found : C, 70.35 ; H, 7.62. $[\alpha]_D^{25}$ = +13.5° (c = 0.9 ; $CHCl_3$).

General procedure for oxidation of epoxyalcohols 1a-1f to aldehydes 2a-2f : To a solution of epoxyalcohol in methylene chloride (1.5 mL/mmol) was added under N2 anhydrous dimethylsulfoxide (2 mL/mmol of epoxyalcohol), triethylamine (5 eq.) and then pyridine sulfur trioxide complex (5 eq.). The reaction mixture was stirred for 30 min., ether was added (7 times the volume of CH_2Cl_2) and then the reaction was quenched with water. The organic phase was washed three times with water dried over $MgSO_4$ and the solvent evaporated. The epoxyaldehyde was purified by distillation or silica gel chromatography.

(2R,3R)-4-(benzyloxy)-2,3-epoxybutan-1-al **(2a)**. Compound **2a** was obtained in 79% yield after HPLC chromatography (eluant petroleum ether : ethyl acetate 7:3 ; tlc, Rf = 0.25). IR ($CHCl_3$) ν cm^{-1} : 3065-3033, 2864, 1724, 1095. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 9.43 (d, 1H, J = 4.7 Hz, CHO), 7.37-7.28 (m, 5H, arom.), 4.55 (s, 2H, $PhCH_2$), 3.87 and 3.71 (AB part of an ABX(Y) syst., 2H, J = 3.5; 4.5 ; 11.5 Hz, OCH_2), 3.49 (m, 1H, CH_2-CH), 3.40 (t(dd), 1H, J = 4.7, 4.7 Hz, CHCHO). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 197.6 ; 137.2 ; 128.6 ; 128.1 ; 127.9 ; 73.6 ; 66.3 ; 58.0 ; 57.4. SM (DCI, NH_3) : 210 (M+18, 100%). Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73 ; H, 6.29. Found ; C, 68.41 ; H, 6.29. $[\alpha]_D^{25}$ = +104.3° (c = 0.94 ; $CHCl_3$).[18]

(2R,3R)-4-(p-bromobenzyloxy)-2,3-epoxybutan-1-al **(2b)**. The crude product was distilled under reduced pressure (105°, 0.3 Torr) to yield the epoxyaldehyde **2b** (87%). IR (Film) ν cm^{-1} : 2865, 1723, 1487, 1093. ^1H NMR (80 MHz, $CDCl_3$) δ ppm : 9.39 (d, 1H, J = 5 Hz, CHO), 7.44 (m, 2H, arom.), 7.13 (m, 2H, arom.), 4.46 (s, 2H, $PhCH_2$), 3.75 (m, 2H, O-CH_2), 3.42 (m, 2H, OCH_2CH et CHCHO). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 197.6 ; 136.3 ; 131.7 ; 129.4 ; 121.9 ; 72.8 ; 66.5 ; 57.9 ; 57.3. MS (EI) : 271-269 (M, 0.2%), 253-255 (0.6%), 169-171 (100%), 119 (39%). $[\alpha]_D^{25}$ = +78.5° (c = 1.5 ; $CHCl_3$).

(2R,3R)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-al **(2c)**. Compound **2c** was obtained in 85% yield after purification by HPLC chromatography (eluant ether : petroleum ether 8:2 ; tlc, Rf = 0.4). IR (Film) ν cm^{-1} : 3074, 1724, 1111. ^1H NMR (250 MHz, C_6D_6) δ ppm : 9.25 (d, 1H, J = 4.9 Hz, CHO), 7.71-7.64 (m, 4H, arom.), 7.23-7.18 (m, 6H, arom.), 3.59 and 3.53 (AB part of an ABX(Y)syst., 2H, J = 3.2 ; 4.3 ; 12.3 Hz, OCH_2), 2.87 (t(dd), 1H, J = 4.8 Hz, CHCHO), 2.76 (m, 1H, OCH_2CH), 1.07 (s, 9H, tBu). RMN ^{13}C (50 MHz, $CDCl_3$) δ ppm : 198.1 ; 135.6 ; 132.5 ; 132.4 ; 130.1 ; 128.0 ; 60.8 ; 59.8 ; 57.8 ; 26.8 ; 19.2. MS (DCI, NH_3) :m/z 283 (M-tBu, 14%), 253 (15%), 199 (65%), 163 (43%). $[\alpha]_D^{25}$ = +40.6° (c = 3.7 ; $CHCl_3$).

(2R,3S)-4-(p-bromobenzyloxy)-2,3-epoxybutan-1-ol **(2d).** Compound **2d** was obtained in 74% yield after purification by HPLC chromatography (eluant ether : petroleum ether 8:2 ; tlc, Rf = 0.21). IR ($CHCl_3$) ν cm^{-1} : 1731, 1597, 1488, 1100. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 9.05 (d, 1H, J = 6.2 Hz, C<u>H</u>O), 7.48 (m, 2H, arom.), 7.20 (m, 2H, arom.), 4.53 and 4.51 (AB syst., 2H, J = 12 Hz, PhC<u>H</u>$_2$), 3.86 and 3.55 (AB part of an ABX(Y) system, 2H, J = 2.3 ; 5.1 ; 11.6 Hz, OC<u>H</u>$_2$), 3.48 (m, 1H, OCH$_2$C<u>H</u>), 3.33 (dd, 1H, J = 1.9 ; 6.2 Hz, C<u>H</u>CHO). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 197.6 ; 136.4 ; 131.6 ; 129.4 ; 72.7 ; 68.4 ; 56.2 ; 55.1. MS (DCI, NH_3) : 288-290 (M+18, 100%). $[\alpha]_D^{25}$ = +20.1° (c = 1.1 ; $CHCl_3$).

(2R,3S)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-al **(2e).** Purification by HPLC chromatography (eluant ether : petroleum ether 6:4 ; tlc, Rf = 0.4). Yield 80%. IR ($CHCl_3$) ν cm^{-1} : 3075, 1730, 1111. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 9.07 (d, 1H, J = 6,1 Hz, C<u>H</u>O), 7.69-7.64 (m, 4H, arom.), 7.46-7.38 (m, 6H, arom.), 3.97 and 3.84 (AB part of an ABX(Y) syst., 2H, J = 2.4 ; 3.3 ; 12.3 Hz, OC<u>H</u>$_2$), 3.40 (m, 2H, OCH$_2$C<u>H</u> et C<u>H</u>CHO), 1.06 (s, 9H, tBu). RMN ^{13}C (63 MHz, $CDCl_3$) δ ppm : 198.1 ; 135.6 ; 135.5 ; 132.8 ; 132.6 ; 130.0 ; 127.9 ; 61.8 ; 56.6 ; 56.2 ; 26.7 ; 19.2. MS (DCI, NH_3) : 283 (M-tBu, 10%), 253 (20%), 199 (38%), 183 (18%), 163 (12%), 115 (17%), 45 (75%), 31 (100%). $[\alpha]_D^{25}$ = +34.8° (c=0.4; $CHCl_3$).

(2S,3R)-4-(tert-butyldiphenylsilyloxy)-2,3-epoxybutan-1-al **(2f)**
Purification and spectroscopic assignements as for **2e**. $[\alpha]_D^{25}$ = -34.3° (c = 2 ; $CHCl_3$).

Aldolisation reaction using 1 eq. of lithium enolate/aldehyde. Lithium diisopropylamine was prepared at 0°C by addition under argon of 1 eq. of n-butyllithium to an ethereal solution of anhydrous diisopropylamine (0.5M solution). The mixture was stirred for 15 min, then 1 eq. of the ester was added dropwise at -78°C. After 30 min the lithium enolate was transferred under argon to an ethereal solution of the aldehyde (final enolate concentration 0.4M). The mixture was hydrolysed 15 min later with a saturated solution of NH_4Cl. After extraction with diethyl ether the combined organic phases were dried over MgSO4 and the solvent evaporated to afford the crude product which was purified by HPLC chromatography.
Aldolisation reaction using 2 eq. of lithium enolate/aldehyde. Lithium enolate prepared as above was transferred to an ethereal solution of aldehyde (0.5 eq. 1.2 mL/mmol). The temperature was allowed to slowly rise to 20°C, then the mixture was hydrolysed and treated as before.

(3S,4S,5R)- and (3R,4S,5R)-Ethyl-[-6-(benzyloxy)-4,5-epoxy-3-hydroxy]hexanoate **(3 and 4).** The crude product was purified by HPLC chromatography (eluant HPLC or tlc methylene chloride-ethyl acetate 8:2). We obtained diastereoisomers **3** (153 mg ; tlc : R_f = 0.39) and **4** (38 mg ; tlc : R_f = 0.31) starting from 300 mg of aldehyde (yield 44%).
Compound 3 : IR (Film) ν cm^{-1} : 3448, 1732, 1102. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.35-7.31 (m, 5H, arom.), 4.60 and 4.54 (AB syst , 2H, J = 11.8 Hz, PhC<u>H</u>$_2$), 4.16 (2H, J = 7.1 Hz, C<u>H</u>$_2$CH$_3$), 3.94 (m, 1H, CHOH), 3.78 and 3.70 (AB part of an ABX(Y) syst., 2H, J = 5.1 ; 6.0 ; 11.1 Hz, O-C<u>H</u>$_2$), 3.30 (m, 1H, OH), 3.27 (ddd, 1H, J = 5.1 ; 6.0 ; 4.3 Hz, OCH$_2$C<u>H</u>), 3.00 (dd, 1H, J = 8.1 ; 4.3 Hz, C<u>H</u>CHOH), 2.61 and 2.71 (A'B' part of an A'B'X'(Y) syst., 2H, J = 3.9 ; 8.3 ; 16.2 Hz, C<u>H</u>$_2$CO), 1.26 (t, 3H, J = 7.1 Hz, CH$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 171.9 ; 137.5 ; 128.6 ; 128.0 ; 127.9 ; 73.6 ; 68.2 ; 66.5 ; 61.0 ; 57.2 ; 55.2 ; 39.3 ; 14.2. MS (EI) : 71, 91, 107, 187, 198, 215, 216, 244, 281 (M+1).
Compound 4 : IR : identical to **3**. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.35-7.31 (m, 5H, arom.), 4.60 and 4.52 (AB syst., 2H, J = 11.8 Hz, PhC<u>H</u>$_2$), 4.16 (2H, J = 7.2 Hz), 3.94 (m, 1H, C<u>H</u>OH), 3.68 (s, 1H, -OC<u>H</u>$_2$), 3.66 (s, 1H, -OC<u>H</u>$_2$), 3.29 (m, 1H, OCH$_2$C<u>H</u>), 3.06 (dd, 1H, J = 4.4 ; 7.5 Hz, C<u>H</u>CHOH), 2.60 and 2.57 (A'B' part of an A'B'X'(Y) degenerated syst., 2H, C<u>H</u>$_2$CO), 1.26 (t, 3H, J = 7.15 Hz, C<u>H</u>$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 171.3 ; 137.6 ; 128.5 ; 127.9 ; 127.8 ; 73.5 ; 68.1 ; 66.8 ; 61.0 ; 58.6 ; 55.4 ; 38.7 ; 14.2. MS : identical to **3**

(3S,4S,5R)- and (3R,4S,5R)-Ethyl-[-6-(benzyloxy)-4,5-epoxy-3-hydroxy-2,2-dimehyl]hexanoate (**5** and **6**). The crude product was purified by HPLC chromatography (eluant HPLC or tlc petroleum ether : methylene chloride : ethyl acetate 4:4.8:1.2) to afford diastereoisomers **5** (84 mg ; tlc, Rf = 0.24) and **6** (22 mg ; tlc, Rf = 0.29) starting from 170 mg of aldehyde **2a** (yield 47%).

Compound 5 : IR ($CHCl_3$) ν cm^{-1} : 3499, 1723, 1092. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.36-7.30 (m, 5H, arom.), 4.62 and 4.55 (AB syst., 2H, J = 11.8 Hz, $PhC\underline{H}_2$), 4.17 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 3,.79 and 3.73 (AB part of an ABX(Y) syst., 2H, J = 5.1 ; 6.2 ; 11.1 Hz, $O\text{-}C\underline{H}_2$), 3.42 (m, 1H, C<u>H</u>OH), 3.28 (d, 1H, J = 5.3 Hz, O<u>H</u>), 3.21 (ddd, 1H, J = 5.1 ; 6.2 ; 4.4 Hz, $CH_2C\underline{H}$), 3.09 (dd, 1H, J = 4.4 ; 8.4 Hz, C<u>H</u>CHOH), 1.29 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.26 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 177.0 ; 137.5 ; 128.5 ; 127.9 ; 75.1 ; 73.5 ; 68.6 ; 60.9 ; 54.9 ; 53.5 ; 46.3 ; 22.4 ; 19.9 ; 14.1. MS (DCI, NH_3) : 326 (M+18, 29%), 309 (M+1, 100%), 210 (21%), 164 (4%), 108 (4%).

Composé 6 : IR ($CHCl_3$) ν cm^{-1} : 3534, 1722, 1093. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.37-7.32 (m, 5H, arom.), 4.64 and 4.54 (AB syst., 2H, J = 11.8 Hz, $PhC\underline{H}_2$), 4.16 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 3.81 and 3.66 (AB part of an ABX(Y), syst., 2H, J = 3.7 ; 6.5 ; 11.4 Hz, $OC\underline{H}_2$), 3.65 (m, 1H, C<u>H</u>OH), 3.30 (ddd, 1H, J = 3.7 ; 6.5 ; 4.3 Hz, $OCH_2C\underline{H}$), 3.10 (dd, 1H, J = 4.3 ; 6.1 Hz, C<u>H</u>CHOH), 2.60 (m, 1H, OH), 1.29 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.26 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 176.3 ; 137.7 ; 128.5 ; 127.8 ; 73.4 ; 72.5 ; 68.0 ; 60.9 ; 56.6 ; 55.7 ; 46.4 ; 21.5 ; 20.8 ; 14.1. MS : identical to **5**

(3S,4S,5R)- and (3R,4S,5R)-Methyl-[6-(benzyloxy)-4,5-epoxy-3-hydroxy]hexanoate (**7** and **8**). The crude product was purified by HPLC chromatography (eluant HPLC or tlc methylene chloride : ethyl acetate 8:2) to afford compound **7** (119 mg ; tlc, Rf = 0.26) and **8** (30 mg ; tlc, Rf = 0.23) starting from 179 mg of aldehyde **2a** (yield 79%).

Compound 7a : IR ($CHCl_3$) ν cm^{-1} : 3519, 3038, 1731, 1095.^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.36-7.30 (m, 5H, arom.), 4.62 and 4.52 (AB syst., 2H, J = 11.9 Hz, $PhC\underline{H}_2$), 3.84 (m, 1H, C<u>H</u>OH), 3.77 and 3.69 (AB part of an ABX(Y) syst., 2H, J = 5.2 ; 6.0 ; 11.2 Hz, $OC\underline{H}_2$), 3.7 (s, 3H, CH_3), 3.30 (m, 1H, O<u>H</u>), 3.27 (m, 1H, $OCH_2C\underline{H}$), 2.99 (dd, 1H, J = 4.3 ; 8.1 Hz, C<u>H</u>CHOH), 2.77 and 2.57 (A'B' part of an A'B'X'(Y') syst., 2H, J = 3.8 ; 8.5 ; 16.1 Hz, $C\underline{H}_2CO$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 172.1 ; 137.5 ; 128.6 ; 128.0 ; 127.9 ; 73.5 ; 68.2 ; 66.4 ; 57.2 ; 55.2 ; 51.9 ; 39.1. MS (EI) : 267 (M+1, 23%), 230 (76%), 205 (47%), 181 (20%), 107 (30%), 91 (100%). Anal. Calcd. for $C_{14}H_{18}O_5$: C, 62.71 ; H, 6.74 . Found : C, 63.14 ; H, 6.81.

Compound 8a : IR : identical to **7a**. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.34-7.31 (m, 5H, arom.), 4.65 and 4.47 (AB syst., 2H, J = 11.8 Hz, $PhC\underline{H}_2$), 3.95 (m, 1H, C<u>H</u>OH), 3.71 (s, 3H, CH_3), 3.67 (m, 2H, $OC\underline{H}_2$), 3.20 (m, 1H, $OCH_2C\underline{H}$), 3.07 (dd, 1H, J = 4.4 ; 7.5 Hz, C<u>H</u>CHOH), 2.9 (m, 1H, OH), 2.81 (m, 2H, $C\underline{H}_2CO$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 171.7 ; 137.5 ; 128.5 ; 127.9 ; 127.8 ; 73.5 ; 68.0 ; 66.8 ; 58.6 ; 55.4 ; 52.0 ; 38.5.

(3S,4S,5R)- and (3R,4S,5R)-6-Tert-butyl-[-6-(benzyloxy)-4,5-epoxy-3-hydroxy]hexanoate (**9** and **10**). The crude product was purified by HPLC chromatography (eluant HPLC or tlc methylene chloride : petroleum ether : ethyl acetate 4.8:4:1.2) to afford compounds **9** (218 mg ; tlc, Rf = 0.21) and **10** (51 mg ; tlc, Rf = 0.16) starting from 216 mg of aldehyde **2a** (yield 87%).

Compound 9 : IR (Film) ν cm^{-1} : 3448, 1726, 1093. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.37-7.30 (m, 5H, arom.), 4.63 et 4.52 (AB syst., 2H, J = 11.8 Hz, $PhC\underline{H}_2$), 3.80 and 3.68 (AB part of an ABX(Y) syst., 2H, J = 4.7 ; 6.3 ; 11.2 Hz, $OC\underline{H}_2$), 3.76 (m, 1H, C<u>H</u>OH), 3.38 (m, 1H, OH), 3.28 (ddd, 1H, J = 4.3 ; 4.4 ; 6.3 Hz, $CH_2C\underline{H}$), 2.98 (dd, 1H, J = 4.3 ; 8.2 Hz, C<u>H</u>CHOH), 2.64 and 2.53 (A'B' part of an A'B'X'(Y) syst., 2H, J = 3.8 ; 8.2 ; 16.3 Hz, $C\underline{H}_2CO$), 1.46 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 171.4 ; 137.5 ; 128.6 ; 128.0 ; 127.9 ; 81.6 ; 73.5 ; 68.3 ; 66.6 ; 57.2 ; 55.4 ; 40.2 ; 28.1. MS (DCI, NH_3) : 326 (M+18, 38%), 270 (100%), 210 (36%), 168 (56%). $[\alpha]_D^{25} = -25.4°$ (c = 2.1; $CHCl_3$).[18]

Composé 10 : IR : identical to **9**. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm : 7.36-7.30 (m, 5H, arom.), 4.66 and 4.47 (AB syst., 2H, J = 11.8 Hz, Ph-C$\underline{H}_2$), 3.88 (m, 1H, C$\underline{H}$OH), 3.69 (s, 1H, OC$\underline{H}_2$), 3.66 (s, 1H, OC$\underline{H}_2$), 3.28 (m, 1H, $OCH_2C\underline{H}$), 3.07 (m, 1H, OH), 3.04 (dd, 1H, J = 4.4 ; 7.5 Hz, C$\underline{H}$CHOH), 2.53 and 2.49 (A'B' part of an A'B'X'(Y) degenerated syst., 2H, $C\underline{H}_2CO$), 1.45 (s, 9H, tBu). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 170.8 ; 137.6 ; 128.5 ; 127.9 ; 127.8 ; 81.7 ; 73.5 ; 68.2 ; 66.9 ; 58.5 ; 55.4 ; 39.7 ; 28.1.

(3S,4S,5R)- and (3R,4S,5R)-Tert-butyl-[6-(p-bromobenzyloxy)-4,5-epoxy-3-hydroxy]hexanoate (**11** and **12**). The crude product was purified by HPLC chromatography (eluant HPLC or tlc petroleum ether : methylene chloride : ethyl acetate 2:6.4:1.6). We obtained diastereoisomers **11** (508 mg ; tlc, Rf = 0.38) and **12** (120 mg ; tlc, Rf = 0.33) starting from 620 mg of aldehyde **2b** (yield 79%).

Compound 11 : IR ($CHCl_3$) ν cm^{-1} : 3519, 3041, 1713, 1596, 1155. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm : 7.47 and 7.23 (A_2B_2, syst. 4H, J = 8.4 Hz, arom.), 4.56 and 4.51 (AB syst., 2H, J = 12 Hz, PhC$\underline{H}_2$), 3.82 and 3.66 (AB part of an ABX(Y) syst. , 2H, J = 4.3 ; 6.5 ; 11.3 Hz, OC$\underline{H}_2$), 3.77 (m, 1H, C$\underline{H}$OH), 3.36 (d, 1H, J = 3.5 Hz, OH), 3.27 (ddd, 1H, J = 4.3 ; 4.3 ; 6.5 Hz, $OCH_2C\underline{H}$), 2.99 (dd, 1H, J = 4,3 ; 8,1 Hz, C$\underline{H}$CHOH), 2.65 and 2.53 (A'B' part of an A'B'X'(Y) syst., 2H, J = 3.6 ; 8.4 ; 16.4 Hz, $C\underline{H}_2CO$), 1.46 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 171.5 ; 136.6 ; 131.6 ; 129.4 ; 121.8 ; 81.8 ; 72.6 ; 68.4 ; 66.6 ; 57.1 ; 55.4 ; 40.1 ; 28.1. MS (EI) : 330-332 (M-tBu, 3%), 185-187 (13%), 169-171 (34%), 57 (100%). Anal. Calcd. for $C_{17}H_{23}O_5Br$: C, 52.72 ; H, 5.98 . Found : C, 52.87 ; H, 6.02. $[\alpha]_D^{25}$ = -19.7° (c = 0.6 ; $CHCl_3$).

Compound 12 : IR ($CHCl_3$) ν cm^{-1} : 3600 3010, 1719. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm : 7.48-7.45 (m, 2H, arom.), 7.22-7.19 (m, 2H, arom.), 4.56 and 4.46 (AB syst., 2H, J = 12 Hz, PhC$\underline{H}_2$), 3.90 (m, 1H, C$\underline{H}$OH), 3.71 and 3.63 (AB part of an ABX(Y) syst., 2H, J = 7.7 ; 9.4 ; 12 Hz, OC$\underline{H}_2$), 3.27 (m, 1H, $OCH_2C\underline{H}$), 3.08 (d, 1H, J = 4 Hz, OH), 3.05 (dd, 1H, J = 4.5 ; 7.5 Hz, C$\underline{H}$CHOH), 2.50 (m, 2H, $C\underline{H}_2CO$), 1.45 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 170.7 ; 136.7 ; 131.6 ; 129.4 ; 121.8 ; 81.7 ; 72.6 ; 68.3 ; 66.8 ; 58.4 ; 55.4 ; 39.7 ; 28.1. $[\alpha]_D^{25}$ = -6.6° (c = 0.5 ; $CHCl_3$).

(3S,4S,5R)- and (3R,4S,5R)-Tert-butyl-[6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-hydroxy]hexanoate. (**13** and **14**). The crude product was purified by HPLC chromatography (eluant HPLC or tlc petroleum ether : methylene chloride : ethyl acetate 5:3.4:1.6). Starting from 630 mg of aldehyde **2c** we obtained compound **13** (609 mg ; tlc, Rf = 0.38) and **14** (145 mg ; tlc, Rf = 0.2) with a total yield of 90%.

Composé 13 : IR ($CHCl_3$) ν cm^{-1} : 3622, 3512, 3029, 1716, 1156, 1110. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm : 7.72-7.67 (m, 4H, arom.), 7.45-7.38 (m, 6H, arom.), 3.94 and 3.86 (AB part of an ABX(Y) syst., 2H, J = 5 ; 6.1 ; 11.8 Hz, SiO-C$\underline{H}_2$), 3.76 (dddd, 1H, J = 3.5 ; 3.8 ; 8.1 ; 8.3 Hz, C$\underline{H}$OH), 3.27 (d, 1H, J = 3.5 Hz, OH), 3.23 (m, 1H, $SiOCH_2$-C$\underline{H}$), 2.98 (dd, 1H, J = 4.2 ; 8.1 Hz, C$\underline{H}$CHOH), 2.62 and 2.53 (A'B' part of an A'B'X'(Y) syst., 2H, J = 3.8 ; 8.3 ; 16.3 Hz, CH_2CO), 1.46 (s, 9H, OtBu), 1.07 (s, 9H, SitBu). RMN ^{13}C (63 MHz, $CDCl_3$) δ ppm : 171.4 ; 135.6 ; 132.9 ; 130.0 ; 127.9 ; 81.6 ; 66.5 ; 62.4 ; 57.6 ; 56.9 ; 40.2 ; 28.1 ; 26.8 ; 19.2. MS (EI) : 383 (M-OtBu, 0.7%), 325 (1%), 283 (1.7%), 199 (54%), 163 (26%), 57 (100%). Anal. Calcd. for $C_{26}H_{36}O_5Si$: C, 68.38 ; H, 7.94 . Found : C, 68.05 ; H, 7.92. $[\alpha]_D^{25}$ = -6.7° (c = 0.6 ; $CHCl_3$).

Composé 14 : IR ($CHCl_3$) ν cm^{-1} : 3624, 3049, 1723, 1155-1110. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm : 7.70-7.64 (m, 4H, arom.), 7.45-7.37 (m, 6H, arom.), 3.91 and 3.72 (AB part of an ABX(Y) syst., 2H, J = 5.6; 5.8 ; 11.6 Hz, SiOC$\underline{H}_2$), 3.89 (m, 1H, C$\underline{H}$OH), 3.22 (m, 1H, SJ = 15.5 Hz, $OCH_2C\underline{H}$), 3.13 (d, 1H, J = 3.8 Hz, OH), 3.06 (dd, 1H, J = 4.4 ; 7.6 Hz, C$\underline{H}$CHOH), 2.59 and 2.54 (A'B' part of an A'B'X'(Y) syst., 2H, J = 4.5 ; 8 ; 16.7 Hz, $C\underline{H}_2CO$), 1.44 (s, 9H, OtBu), 1.06 (s, 9H, SitBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 170.9 ; 135.5 ; 132.9 ; 130.1 ; 130.0 ; 127.9 ; 81.6 ; 66.9 ; 62.2 ; 59.0 ; 56.3 ; 39.5 ; 28.1 ; 26.8 ; 19.2. $[\alpha]_D^{25}$ = +10.2° (c = 0.9 ; $CHCl_3$).

(3S,4S,5S)- and (3R,4S,5S)-Tert-butyl-[6-(p-bromobenzyloxy)-4,5-epoxy-3-hydroxy]hexanoate **(15 and 16)** The crude product was purified by HPLC chromatography (eluant methylene chloride : ethyl acetate 8:2) to give 910 mg of non separable diastereoisomers **15** and **16** (tlc, Rf = 0.44) starting from 1 g of aldehyde **2d** (yield 67%).

(3S,4S,5S)- and (3S,4S,5S)-Tert-butyl-[6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-hydroxy]hexanoate **(17 and 18).** The crude product was purified by HPLC chromatography (eluant HPLC or tlc petroleum ether : methylene chloride : ethyl acetate 6:3.2:0.8). We obtained compound **17** (1.35 g ; tlc, Rf = 0.33) and **18** (553 mg ; tlc, Rf = 0.28) starting from 1.78 g of aldehyde **2e** (yield 80%).

Compound 17 : IR ($CHCl_3$) ν cm^{-1} : 3626 and 3472, 1723, 1111 and 1048. ^1H NMR (250 MHz, C_6D_6) δ ppm : 7.80-7.75 (m, 4H, arom.), 7.24-7.22 (m, 6H, arom.), 3.92 (m, 1H, C<u>H</u>OH), 3.76 and 3.54 (AB part of an ABX(Y) syst., 2H, J = 2.7 ; 4.7 ; 12 Hz, OC<u>H</u>$_2$), 3.01 (ddd, 1H, J = 2.7 ; 4.7 ; 2.1 Hz, OCH$_2$C<u>H</u>), 2.90 (dd, 1H, J = 2,1 ; 4.5 Hz, C<u>H</u>CHOH), 2.87 (d, 1H, J = 4 Hz, OH), 2.35 (s, 1H, C<u>H</u>$_2$CO), 2.32 (s, 1H, C<u>H</u>$_2$CO), 1.32 (s, 9H, OtBu), 1.14 (s, 9H, SitBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 171.2 ; 136.1 ; 136.0; 133.8 ; 133.7 ; 130.1 ; 128.2 ; 80.8 ; 67.4 ; 63.8 ; 57.1 ; 56.4 ; 39.5 ; 28.0 ; 27.0 ; 19.5. MS (DCI, NH_3) : 474 (M+18, 100%), 418 (28%), 130 (19%), 102 (19%). Anal. Calcd. for $C_{26}H_{36}O_5Si$: C, 68.38 ; H, 7.94 . Found : C, 67.81 ; H, 8.19. $[\alpha]_D^{25}$ = -14.7° (c = 0.6 ; $CHCl_3$).

Compound 18 : IR (Film) ν cm^{-1} : 3434, 3073, 1728, 1155-1111. ^1H NMR (250 MHz, C_6D_6) δ ppm : 7.80-7.75 (m, 4H, arom.), 7.25-7.22 (m, 6H, arom.), 3.91 (m, 1H, C<u>H</u>OH), 3.75 and 3.52 (AB part of anABX(Y) syst., 2H, J = 2.7 ; 4.8 ; 11.9 Hz, SiOC<u>H</u>$_2$), 3.08 (ddd, 1H, J = 2.3 ; 2.7 ; 4.8 Hz, OCH$_2$-C<u>H</u>). 2.83 (dd, 1H, J = 2.3 ; 4 Hz, C<u>H</u>CHOH), 2.60 (m, 1H, OH), 2.39 and 2.27 (A'B' part of anA'B'X'(Y) syst., 2H, J = 7.9 ; 5.1 ; 15.7 Hz, C<u>H</u>$_2$CO), 1.33 (s, 9H, OtBu), 1.14 (s, 9H, SitBu). ^{13}C NMR (63 MHz, C_6D_6) δ ppm : 170.7 ; 136.1 ; 136.0 ; 133.8 ; 133.7 ; 130.1 ; 128.2 ; 80.7 ; 67.4 ; 63.6 ; 57.7 ; 56.0 ; 40.2 ; 28.0 ; 27.0; 19.5.

(3R,4R,5R)- and (3S,4R,5R)-Tert-butyl-[6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-hydroxy]hexanoate **(19 and 20).** The crude product was purified by HPLC chromatography (eluant HPLC or tlc petroleum ether : methylene chloride : ethyl acetate 6:3.2:0.8). We obtained diastereoisomers **19** (1.06 g ; tlc, Rf = 0.33) and **20** (425 mg ; tlc, Rf = 0.28) starting from 1.5 g of aldehyde **2f** (yield 74%).

Compound 19 : Spectroscopic assignements are identical to **17**. Anal. Calcd. for $C_{26}H_{36}O_5Si$: C, 68.38 ; H, 7.94. Found : C, 68.32 ; H, 8.09. $[\alpha]_D^{25}$ = +14.5° (c = 0.7 ; $CHCl_3$).

Compound 20 : Spectroscopic assignements are identical to **18**.

(3S,5S)-6-(benzyloxy)-3,5-dihydroxyhexan-1-ol **(21).** A solution of γ,δ-epoxy-β-hydroxyester **9** (394 mg, 1.28 mmol) in THF (15 ml) under argon and stirring was treated with RedAl (0.79 mL, 2.7 mmol). The mixture was stirred for 1 h, two more equivalents were additionned and stirring was maintened for another 3 h. The mixture was then diluted with ether (10 mL) and hydrolysed by dropwise addition of water (10 mL) then acidified to pH = 3. The organic phases were washed with water (2 mL) saturated $NaHCO_3$ (2 mL and saturated NaCl (2 mL). The combined aqueous phases were acidified and submitted to continuous extraction with ether for 12 h. All organic phases were then combined dried over $MgSO_4$ and solvent evaporated. The crude product was purified by HPLC chromatography (eluant acetone : ether 2:8) to afford 261 mg (yield 85%) of triol **21** (tlc, Rf = 0.2). IR (Film) ν cm^{-1} : 3360, 3090, 1105. ^1H NMR 200 MHz, $CDCl_3$) δ ppm : 7.34-7.30 (m, 5H, arom.), 4.52 (s, 2H, PhC<u>H</u>$_2$), 4.26 (m, 2H, C<u>H</u>OH), 3.76 (m, 2H, C<u>H</u>$_2$OH), 3.61 (m, 3H, OH), 3.43 and 3.37 (AB part of an ABX(Y) syst., 2H, J = 4.3 ; 9.5 ; 6.7 Hz, OC<u>H</u>$_2$), 1.70-1.55 (m, 4H, HCC<u>H</u>$_2$CH andC<u>H</u>$_2$CH$_2$OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 137.8 ; 128.5 ; 127.9 ; 74.4 ; 73.4 ; 71.3 ; 71.0 ; 60.7 ; 39.5 ; 38.8. SM (DCI, NH_3) : 241 (M+1), 176, 160, 101, 91 (100%), 75, 56.

(3S,5S)-6-(benzyloxy)-1-(tert-butyldiphenylsilyloxy)-3,5-dihydroxyhexane **(22)**. A solution of triol **21** (100 mg, 0.41 mmol) in anhydrous DMF (2 mL) was treated under stirring and argon with imidazole (118 mg, 1.75 mmol) and tert-butyldiphenylsilylchloride (113 µL, 0.41 mmol). The mixture was stirred for 12 h, then hydrolysed with 1 mL of saturated NH_4Cl solution and extracted with ether (3 x 10 mL). The organic phases were dried over $MgSO_4$ and solvent evaporated. HPLC purification of the crude product (eluant petroleum ether : ethyl acetate 7:3 ; tlc, Rf = 0.25) afford 188 mg of compound **22** (yield 95%). IR (Film) ν cm^{-1} : 3414 3070, 1110. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.70-7.65 (m, 4H, arom., 7.44-7.31(m, 11H, arom.), 4.57 (s, 2H, $PhC\underline{H}_2$), 4.21-3.90 (m, 2H, $C\underline{H}OH$), 3.90-3.77 (m, 2H, $C\underline{H}_2$-OSi), 3.44 (d, 2H, $PhCH_2OC\underline{H}_2$), 3.40 (m, 2H, OH), 1.86-1.60 (m, 4H, $CH(O)C\underline{H}_2CH(O)$ et $C\underline{H}_2CH_2$-OSi), 1.05 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 138.1 ; 135.6 ; 133.1 ; 133.0 ; 129.9 ; 128.5 ; 127.8 ; 74.4; 73.4 ; 71.7 ; 70.9 ; 39.9 ; 38.9 ; 26.8 ; 19.1 ; 15.3. MS (DCI, NH_3) : 490 (46%), 479 (M+1, 100%).

(3S,5S)-6-[(benzyloxy)methyl]-4-[1-(tert-butyldiphenylsilyl-oxy)ethyl]-2,2-dimethyl-1,3-dioxacyclohexane **(23)**. To a solution of compound **22** (130 mg, 0.27 mmol) in 2,2-dimethoxypropane (2 mL) under argon, was added camphor sulphonic acid (1.5 mg). The mixture was stirred for 1 h, hydrolysed with saturated $NaHCO_3$ solution (1 mL) extracted with ether (2 x 10 mL), dried over $MgSO_4$ and solvent evaporated to afford 140 mg (yield 100%) of compound **23** (tlc, eluant petroleum ether : ether 8:2, Rf = 0.35). IR ($CHCl_3$) ν cm^{-1} : 3072 and 3003, 1109. ^1H NMR (200 MHz, $CDCl_3$) δ ppm : 7.71-7.65 (m, 4H, arom., 7.43-7.35 (m, 11H, arom.), 4.65-4.51 (AB, 2H, J = 12.2 Hz, CH_2Ph), 4.24-4.12 (m, 1H, J = 2.2 ; 10.6 Hz, $BnOCH_2C\underline{H}(O)$), 4.17-4.05 (m, 1H, J = 2.5 ; 11.0 Hz, $C\underline{H}(O)CH_2CH_2OSi$), 3.90-3.63 (m, 2H, J = 10.2 ; 7.4 ; 5.6 ; 5.5 ; 5.2 Hz, $C\underline{H}_2$-O-$SiPh_2tBu$) 3.54 and 3.3 (AB part of an ABX(Y) syst., 2H, J = 9.9 ; 5.8 ; 4.9 Hz, $BnOCH_2$), 1.76-1.62 (m, 2H, $C\underline{H}_2$-CH_2-$OSiPh_2tBu$), 1.55-1.47 (m, 1H, J = 2.5, ;2.2 ; 12.5 Hz, $CH(O)C\underline{H}_2CH(O)$, eq), 1.47 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.35-1.20 (m, 1H, J = 11.0 ; 10.6 ; 12.5 Hz, $CH(O)C\underline{H}_2CH(O)$, ax), 1.05 (s, 9H, tBu). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 138.4 ; 135.6 ; 134.0 ; 133.9 ; 129.7 ; 128.5 ; 127.9 ; 127.7 ; 98.7 ; 73.8 ; 73.5 ; 68.7 ; 65.4 ; 59.7 ; 39.5 ; 34.1 ; 30.3 ; 27.0 ; 19.9 ; 19.3. MS (DCI, NH_3) : 536 (M+18, 100%), 519 (M+1, 51%), 293 (20%), 210 (17%).

(4S,6S)-6-[(benzyloxy)methyl]-4-(1-hydroxyethyl)-1,3-dioxacyclohexane **(24)**. To a solution of compound **23** (110 mg, 0.21 mmol) in THF (2 mL) was added n-BuNF (233 µL, 1.1 eq.). The mixture was stirred for 3 h, concentrated and purified by HPLC chromatography (eluant petroleum ether : ether 2:8 ; tlc, Rf = 0.2) to afford 53 mg pf compound **24** (yield 90%). IR ($CHCl_3$) ν cm^{-1} : 3627 and 3529, 3041, 1110. ^1H NMR (250 MHz, C_6D_6) δ ppm : 7.35-7.15 (m, 5H, arom.), 4.43 and 4.40 (AB syst., 2H, J = 12.2 Hz, $PhC\underline{H}_2$), 4.03-3.93 (m, 1H, $C\underline{H}CH_2CH_2OH$), 3.90-3.80 (m, 1H, $PhCH_2$-$OCH_2C\underline{H}$), 3.77-3.60 (m, 2H, $C\underline{H}_2$-OSi), 3.50 and 3.31 (AB part of an ABX(Y) syst., 2H, J = 5.2 ; 5.5 ; 9.7 Hz, $PhCH_2OC\underline{H}_2$), 2.22 (m, 1H, OH), 1.75-1.42 (m, 2H, $C\underline{H}_2CH_2OSi$), 1.47 (s, 3H, Me), 1.31 (s, 3H, Me), 1.29-1.19 (m, 2H, $CHOC\underline{H}_2CHO$). ^{13}C NMR (63 MHz, C_6D_6) δ ppm : 139.1 ; 128.6 ; 128.5 ; 127.8 ; 127.7 ; 98.7 ; 74.1 ; 73.6 ; 68.9 ; 66.2 ; 60.1 ; 39.1 ; 34.2 ; 30.4 ; 19.8. MS (DCI, NH_3) : 298 (M+18, 100%), 281 (M+1, 54%), 223 (27%).

(4R,6S)-6-[(bezyloxy)methyl]-4-hydroxy-2-oxocyclohexane **(25)**. .A solution of monoalcohol **24** (93 mg, 0.33 mmol) in anhydrous DMF (2 mL) was treated with pyridinium dichromate (435 mg, 3.5 eq.). The mixture was stirred under argon for 9 h, then hydrolysed (5 mL) and extracted with ether (3 x 10 mL). The organic phase was dried over $MgSO_4$ and coevaporated with CCl_4. The crude product was then treated with a HCl 1N : THF solution (1:1 ; 5 mL) for 2 h. After extraction with ether (5 x 10 mL) the organic phases were dried over $MgSO_4$ and solvent evaporated. The crude product was diluted in toluene (2 mL) and heated under reflux for 1 h in presence of a catalytic amount of camphor sulphonic acid. The solvent eliminated under vacuo and the crude product was purified by HPLC chromatography (eluant ethanol : ether 5:95) to afford 35 mg of compound **25** (yield 50%). IR ($CHCl_3$) ν cm^{-1} : 3616, 3044, 1736, 1108. ^1H NMR (250 MHz, $CDCl_3$) δ ppm : 7.39-7.28 (m, 5H, arom.), 4.86 (m, 1H, J = 4 ; 4 ; 4.2 Hz, $OCH_2C\underline{H}$), 4.60 and 4.55

(AB syst., 2H, J = 12 Hz, $PhC\underline{H}_2$), 4.43 (m, 1H, $C\underline{H}OH$), 3.70 and 3.61 (AB part of an ABX(Y) syst., 2H, J = 4 ; 4.2 ; 10.5 Hz, $OC\underline{H}_2CH$), 2.71 and 2.61 (A'B' part of anA'B'X'(Y') syst., 2H, J = 4 ; 4.5 ; 18 Hz, $C\underline{H}_2CO$), 2.12 (m, 1H, OH), 1.97 (m, 2H, $C\underline{H}_2CHOH$). ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm : 169.9 ; 137.8 ; 128.5 ; 127.8 ; 127.7 ; 74.9 ; 73.6 ; 71.6 ; 62.7 ; 38.7 ; 32.3. MS (DCI, NH_3) : 254 (M+18, 100%), 237 (22%). $[\alpha]_D^{25}$ = +6.1° (c = $9.3.10^{-2}$; $CHCl_3$).

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18. We correct here the two errors that have been slipped in our paper of ref. 9 concerning the $[\alpha]_D^{25}$ values of compounds **2a**, **9** (**1**, **7** respectively in Ref. 9).