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Reaction of Aldehydes with Stabilized Sulfur Ylides. Highly Stereoselective Synthesis of 2,3-Epoxy-amides.

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Abstract: Reaction of benzaldehyde (**1a**), 4-chloro-benzaldehyde (**1b**), or 3-nitro-benzaldehyde (**1c**), with N,N-dimethyl-2-(dimethylsulfuranylidene)acetamide (**2**), gives only the *trans*-3-phenyl-2,3-glycidamide derivatives **3a-c** in good yields. The same reaction with 2-nitro-benzaldehyde (**1d**), gives a 15:1 mixture (*trans-cis*) of analogous products **3d**. Reaction of **2** with 2,3-*O*-isopropylidene-D-glyceraldehyde (**4**) results in a highly stereoselective synthesis of (2S,3R,4R)- and (2R,3S,4R)-N,N-dimethyl-2,3-epoxy-4,5-*O*-isopropylidene-4,5-dihydroxypentanoamides (**5a**) and (**5b**), (86:14 at r.t., 96:4 at -5 to 0°C, **5a:5b**). Configurational analysis was made by three different methods: 1) ^{1}H-NMR coupling constants analysis; 2) comparison with the *cis-trans* analogous **15a,b** and **7a,b**, prepared by epoxidation of the *cis* or *trans* alkenes **13** and **12**; and 3) the transformation of the **5a, 7a** and **15a** (or **5b**, **7b** and **15b**) isomers into the known (3S,4R)-3,4,5-trihydroxypentanoic acid 1,4-lactone (**10a**) (or 3(R)-isomer, **10b** respectively).

INTRODUCTION

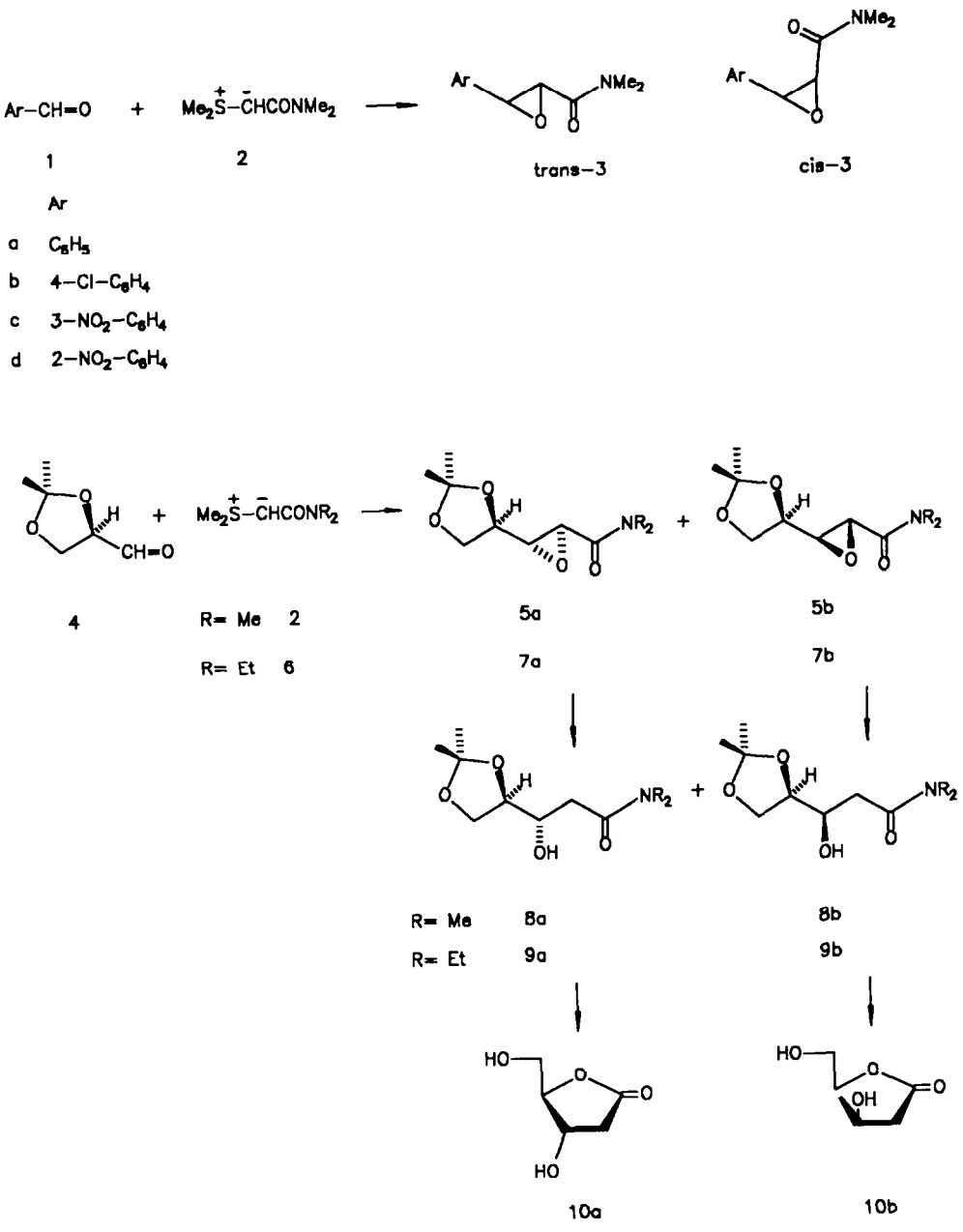
Epoxides are versatile intermediates in organic synthesis, because their electrophilic or nucleophilic opening leads to 1,2-difunctionalized systems or to the formation of new C-C bonds[1]. Thus, the synthesis of epoxides via condensation of aldehydes or ketones with sulfur ylides has become an important synthetic tool. Stereoselective synthesis of chiral epoxides is a significant and useful method for the preparation of several important kinds of natural or pharmaceutical products[1b].

Sulfonium ylides form a class of nucleophilic reactants that have been extensively studied in the chemical literature[2]. Nonstabilized sulfonium ylides and the oxosulfonium methylides react with most carbonyl compounds to produce high yield of epoxides. Ylides stabilized by the presence of electron-withdrawing groups on the ylidic carbon normally condense only with exceptionally reactive carbonyl compounds.

In this paper, we report a highly stereoselective synthesis of 2,3-epoxyamides from aldehydes and amide-stabilized ylides. As preliminary experiments, several aromatic aldehydes were transformed to the corresponding 2,3-epoxyamides. Next, we examined the stereoselectivity of the reaction with 2,3-O-isopropylidene-D-glyceraldehyde, an α-chiral aldehyde which is a readily available C_3-synthon frequently used for stereocontrolled transformations[3].

RESULTS AND DISCUSSION

Reaction of the aromatic aldehydes **1a-d** with N,N-dimethyl-2-(dimethylsulfuranylidene) acetamide (**2**) gave the corresponding 2,3-epoxyamides **3a-d** , that showed exclusively the *trans* configuration about the oxiran ring[4]. Only the 2-nitrobenzaldehyde gave a diastereo-isomeric mixture of the *trans-cis* epoxide in a 15:1 ratio, determined by ^{1}H-NMR. Significant J values of the ^{1}H-NMR coupling constant are : *trans*-epoxide, $J_{2,3}$ = 2 Hz;


Ar–CH=O + Me2S+–C−HCONMe2
1
2
Ar
a C6H5
b 4–Cl–C6H4
c 3–NO2–C6H4
d 2–NO2–C6H4
trans–3
cis–3
4
R= Me 2
R= Et 6
5a
5b
7a
7b
8a
8b
9a
9b
R= Me
R= Et
10a
10b

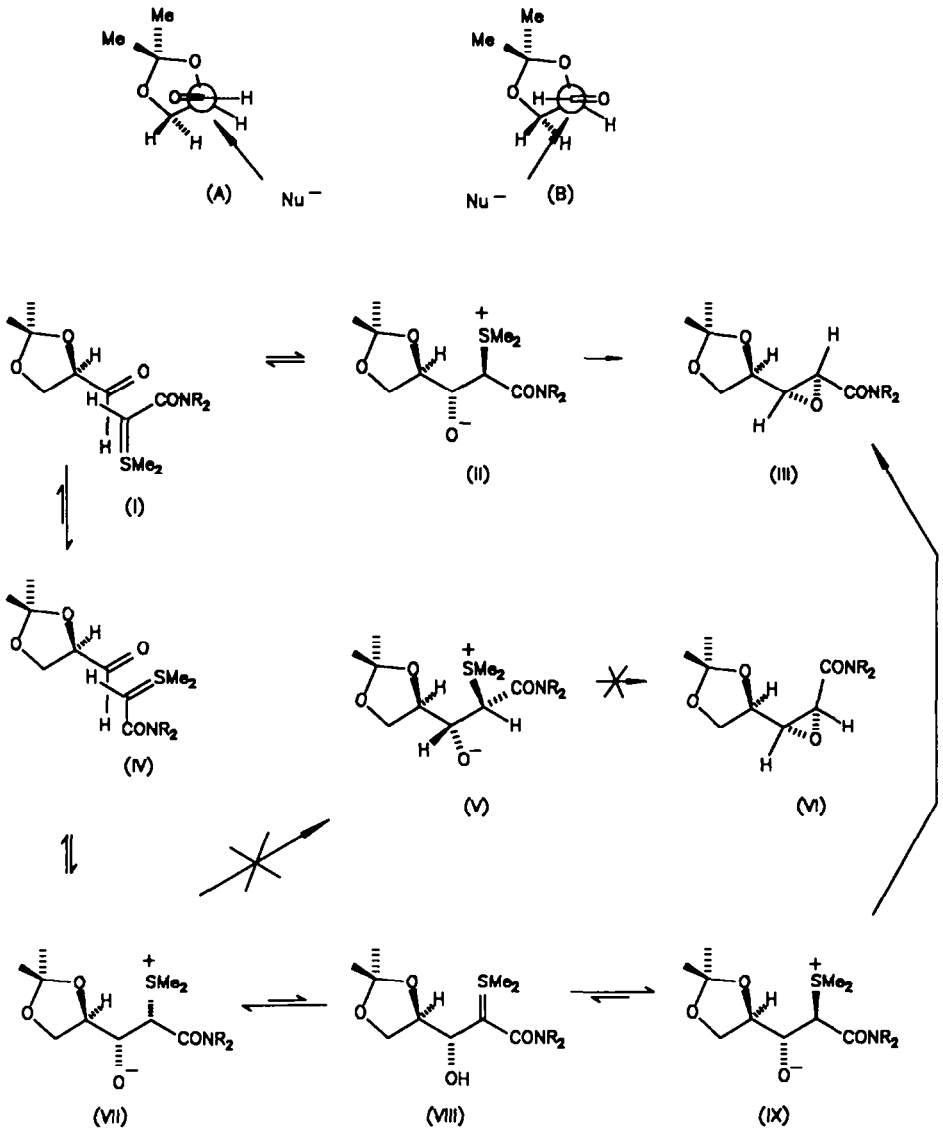
Scheme 1

cis-epoxide, $J_{2,3}$ = 4.6 Hz. This lower stereoselectivity may be the result of the higher reactivity of the carbonyl group of 2-nitrobenzaldehyde (higher electron affinity), which leads to a lower reversibility of the addition process, as well as to the participation of the nitro group in the departure of the dimethyl sulfonium group, preventing the epimerization at C-2. A similar situation has been observed in the Knoevenagel reaction of **4** with α-methylene-active carboxylic acids[5] (increasing the facility for decarboxilation of the adduct, increases the *cis/trans* relation), and in the Wittig reactions of aldehydes with stabilized phosphorus ylides[6].

The reaction of 2,3-O-isopropylidene-D-glyceraldehyde (**4**) with the ylide **2**, in $CHCl_3$ at room temperature, proceeded with a high diastereoselectivity to give the *trans*-2,3-epoxyamides **5a,b** in 95% yield. ^{1}H-NMR of **5** indicated a ratio **5a**:**5b** of 86:14, and showed that both **5a** and **5b** have *trans* configuration about the oxiran ring ($J_{2,3}$ = 2.1 Hz). The reaction of **4** with ylide **6** under similar conditions gave the *trans*-2,3-epoxyamides **7a,b** in 90% yield. The ratio of stereoisomeric products was nearly always the same (Scheme 1). The configuration of the major isomers **5a** and **7a** was tentatively assigned as (2S,3R,4R)-N,N-dimethyl- and N,N-diethyl-2,3-epoxy-4,5-O-isopropylidene-4,5-dihydroxypentanoamide, assuming preferential approach of the ylide to the less sterically hindered *si*-face of the 2,3-O-isopropylidene-D-glyceraldehyde in its preferred Felkin-Ahn[7] conformation (**A**) (Scheme 2). The predominance of this conformation agrees with the observed $J_{1,2}$ coupling constant in ^{1}H-NMR[8]. An attack of the ylide to the opposite face is sterically hindered, thus explaining the low yield of **5b** and **7b**.

This model explains the high stereoselectivity reached at C-3 by 1,2-asymmetric induction, but not the *trans* stereospecifity observed in the reaction. The latter may be interpreted as the result of an internal induction, as shown in Scheme 2. Thus there are two possible initial interactions, the *si-si* or *lk*[9]-approach (**IV**) and the *si-re* or *ul*-approach (**I**) of the reactants (aldehyde-ylide). The first interaction (**IV**), a *lk,ul*-1,2 process, must be the preferred one if we take into consideration the mutual electrostatic stabilization of the developing charges over the carbonyl oxygen and the sulfur atom. Nevertheless, the resulting adduct (**VII**) must adopt the conformation indicated (**V**), with an *anti* relationship for the oxygen and sulfur atoms, to lead to the *cis*-epoxide (**VI**), which was not detected in the reaction mixture. A conformation like (**V**) is highly hindered because the ring-substituent at C-3 bisects the two higher substituents at C-2. Thus, the only way for the reaction to proceed is from the less favourable interaction (**I**), a *ul,ul*-1,2 process, which as shown in Scheme 2, leads to the adequate adduct (**II**) (*anti*-relationship), and finally to a *trans*-epoxide (**III**), the principal product of the reaction. Moreover, the higher stability of ylide **2** leads to a higher reversibility of adduct formation and thus, adduct (**VII**) may revert to the original products, giving then adduct (**II**), and finally to the *trans*-epoxide (**III**). Similar arguments have been used in the literature to account for preferent formation of *trans*-epoxides[10].

Nevertheless, recently[11] we have studied the reaction of alkyl diazoacetates with (**4**), finding that at room temperature, the first product isolable from the reaction is a new 2-substituted alkyl diazoacetate. These results suggest that we must consider now another route to the *trans*-epoxide from the adduct (**VII**). As Scheme 2 shows, the basic oxygen at C-3 of (**VII**) or the ylide present in the reaction media, could abstract the H-2 proton of (**VII**) to give a similar ylide (**VIII**). Protonation of ylide (**VIII**) could give (**IX**, the same as **II**), a 2-epimer of (**VII**), which can also account for the *trans*-epoxide isolated. Ylide (**VIII**) has not been detected nor isolated as in the case of the diazoacetate, but this can be easily explained because sulfur ylides are more basic and can be rapidly protonated in the presence of OH groups.

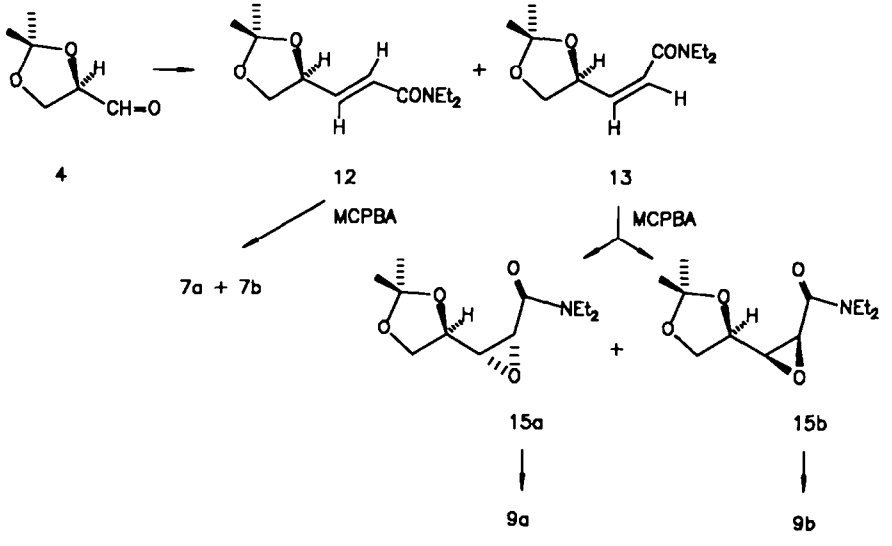


Scheme 2

In order to examine the effect of temperature on the stereoselectivity, the reaction was repeated at -5º - 0ºC, leading to a higher stereoselectivity with an increased ratio **5a**:**5b**, (96:4). Lower temperatures, below -5ºC, lead to sluggish epoxide formation.

The previous tentative stereochemical assignments of the epoxides **5a,b** and **7a,b** were confirmed by the conversion of **5a,7a** and **5b,7b** into the known (3S,4R)- and (3R,4R)-3,4,5-trihydroxypentanoic acid 1,4-lactones, **10a** and **10b**[12] respectively. Thus, when the epoxyamides **5** and **7** were treated with $NaBH_4$ in EtOH, the oxiran ring was regio and stereospecifically opened at the C-2 position to give ß-hydroxyamides **8** and **9**, respectively. (The ^{1}H-NMR of *β*-hydroxyamides included in Table 1 shows the same ABX patterns of the *α*-methylene protons of the analogous ethyl[13] and methyl[11] ester described). The crude *β*-hydroxyamides were treated with 50% aqueous TFA to give the corresponding lactones **10a** and **10b** (optical rotation and spectroscopic data identical with those of an authentic sample).

The *cis*-epoxyamides used for comparison purposes, were prepared by epoxidation with MCPBA, of the corresponding *cis*-alkene, prepared by a Wittig reaction (Scheme 3). Thus, the Wittig reaction of 2,3-O-isopropilidene-D-glyceraldehyde (**4**) with the N,N-diethylcarbamoylmethylenetriphenylphosphorane proceeded with a very low selectivity, and produced a mixture of the *trans*- and *cis*-olefines **12** and **13** in 90% yield in a 45:55 ratio. The same compounds were also prepared by the Knoevenagel reaction between the aldehyde **4** and the N,N-diethyl carbamoyl acetic acid (**14**). Nevertheless, now, the yield in olefine compounds was lower, owing to the formation of a greater proportion of a hydroxylated compounds mixture resulting from the single decarboxylation process[5].



Scheme 3

Both isomeric alkenes **12** and **13** were separated by flash chromatography and their structures were assigned from their ^{1}H-NMR data. Thus, the coupling constant between H-2 and H-3 of **12** is 15 Hz while that of **13** is 11.6 Hz. These results suggested that **12** is a *trans*-olefine whereas **13** is a *cis*-olefine.

Both the *trans*- and *cis*-alkenes, **12** and **13**, were epoxidated with MCPBA, showing a low stereoselectivity and a very low reaction speed, producing after 4-6 days a 58-62% yield of epoxides. Compound **12** gave the isomeric mixture **7a**:**7b** in a 2:1 ratio. Compound **13** gave the *cis*-epoxyamides **15a**:**15b** in a 3:2 ratio. ^{1}H-NMR

spectra of the later mixture indicated that both had a *cis* configuration about the oxirane ring ($J_{2,3}$ = 4.3 and 4.5 Hz respectively). Both isomers **15** were separated by preparative TLC, and the absolute stereochemistry in C-2 and C-3 for each isomer was determined by transformation into the β-hydroxyamide **9a** and **9b** respectively.

Table 1. ^{1}H NMR data for compounds 5a, 5b, 7a, 7b, 8a, 8b, 9a, 9b, 12, 13, 15a and 15b

	H-2 $J_{2,3}$	H-2' $J_{2,2'}$ $J_{2',3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{4,5'}$	H-5' $J_{5,5'}$	CH_2	CH_3	Isop.
5a	3.58 *d* 2.1 Hz		3.20 *dd* 5.4 Hz	3.95 *ddd* 5.0 Hz	3.96 *dd* 8.3 Hz	4.15 *dd* 10.5 Hz		3.14*s* 2.96*s*	1.41*s* 1.33*s*
5b	3.63 *d* 2.1 Hz		3.22 *dd* 3.5 Hz	4.20 *ddd* 6.1 Hz	3.89 *dd* 6.5 Hz	4.10 *dd* 8.2 Hz		3.13*s* 2.95*s*	1.38*s* 1.33*s*
7a	3.52 *d* 2.0 Hz		3.17 *dd* 5.4 Hz	3.95 *ddd* 5.1 Hz	3.92 *dd* 8.4 Hz	4.12 *dd* 10.4 Hz	3.43*q* 3.37*q* 7.2 Hz	1.21*t* 1.09*t*	1.38*s* 1.30*s*
7b	3.55 *d* 2.1 Hz		3.22 *dd* 3.5 Hz	4.13 *ddd* 6.2 Hz	3.87 *dd* 5.7 Hz	4.07 *dd* 8.0 Hz	3.47*q* 3.37*q* 7.2 Hz	1.20*t* 1.08*t*	1.35*s* 1.30*s*
8a	2.66 *dd* 2.5 16	2.34 *dd* 8.4 Hz	3.80 *m*	4.04 *dt* 3 and 8 Hz	<- 3.95-3.85 ->			2.93*s* 2.87*s*	1.30*s* 1.25*s*
8b	<-- 2.45 --> *d* 7 Hz		4.10 *m*	4.15 *dt* 6.5 Hz	3.89 *dd* 6.5 Hz	4.0 *dd* 8.4 Hz		2.98*s* 2.93*s*	1.42*s* 1.42*s*
9a	2.71 *dd* 2.5 16.2	2.37 *dd* 8.2 Hz	3.80 *ddd* 8.2 Hz	4.10 *dt* 5.0 Hz	3.89 *dd* 5.0 Hz	3.95 *dd* 10.0 Hz	3.34*q* 3.28*q* 7.1 Hz	1.15*t* 1.09*t*	1.35*s* 1.30*s*
9b	<-- 2.47 --> *d* 6.1 Hz		4.10 *m*	4.16 *dt* 6.5 Hz	3.92 *dd* 6.5 Hz	4.02 *dd* 8.1 Hz	3.45*q* 3.25*q* 7.1 Hz	1.16*t* 1.10*t*	1.44*s* 1.35*s*
12	6.48 *dd* 15.0 and 1.4* Hz		6.79 *dd* 5.4 Hz	4.66 *m* 6.5 Hz	3.64 *t* 7.3 Hz	4.15 *dd* 6.5 Hz	3.40*m* 3.35*m* 7.1 Hz	1.17*t* 1.12*t*	1.41*s* 1.39*s*
13	6.16 *d* 11.6 Hz		6.05 *d* 6.5 Hz	5.21 *dd* 7.0 Hz	3.64 *dd* 6.9 Hz	4.36 *dd* 8.3 Hz	3.35*m* 3.30*m* 7.0 Hz	1.16*t* 1.12*t*	1.43*s* 1.35*s*
15a	3.61 *d* 4.3 Hz		3.16 *dd* 7.9 Hz	3.78 *ddd* 4.6 Hz	3.93 *dd* 6.4 Hz	4.05 *dd* 8.7 Hz	3.40*m* 3.30*m* 7.1 Hz	1.17*t* 1.05*t*	1.36*s* 1.21*s*
15b	3.54 *d* 4.5 Hz		3.17 *dd* 7.7 Hz	3.75 *ddd* 6.5 Hz	3.84 *dd* 7.0 Hz	4.10 *dd* 6.5 Hz	3.40*q* 3.30*q* 7.1 Hz	1.17*t* 1.05*t*	1.41*s* 1.28*s*

* $J_{2,4}$

Table 2. ^{13}C NMR data for compounds 5a, 5b, 7a, 7b, 12, 13, 15a and 15b

Comp.	C=O	OCO	C-2	C-3	C-4	C-5	CH_2	CH_3	Isop.
5a	166.3	110.1	57.6	52.0	75.0	66.9		36.3 35.6	26.4 25.0
5b	166.7	110.0	57.1	50.8	73.8	66.0		36.1 35.9	26.1 25.6
7a	165.6	110.1	57.6	51.9	75.1	67.0	41.4 40.7	14.7 12.8	26.5 25.1
7b	165.6	110.0	57.0	51.0	74.1	66.1	41.4 40.7	14.7 12.8	26.0 25.5
12	165.2	109.9	141.6	121.7	75.5	69.0	42.3 40.9	14.8 13.1	26.4 25.8
13	165.4	109.3	142.5	122.6	73.9	69.7	42.6 40.0	14.3 13.0	26.6 25.3
15a	164.8	109.8	56.9	53.4	72.9	67.6	41.1 40.1	14.1 12.6	26.8 25.0
15b	165.3	110.1	58.4	52.9	75.7	66.3	41.5 40.1	14.4 12.6	26.7 25.3

EXPERIMENTAL

All mp's are uncorrected. IR spectra were recorded with a Perkin-Elmer 883 spectrometer. UV spectra were recorded with a HP-5482A spectrophotometer. Optical rotations were measured at 18-20°C with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a HP-5988. ^1H and ^{13}C-NMR spectra were recorded using a Bruker WP 200 SY spectrometer. Proton chemical shifts are referenced to the residual chloroform or acetone signals (δ 7.24 or 2.04) and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77ppm). The multiplicity of ^{13}C resonances was determined by INEPT experiments. The 2D NMR and NOE data were analyzed using Bruker's microprograms. TLC were performed on silica gel 60 F 254 plates and column chromatography was carried out on silica gel 60 (72-230 mesh).

Sulfonium salts: The sulfonium salts were prepared by direct reaction of dimethyl sulfide and the α-chloro carbonyl compounds.

N,N-Dimethylcarbamoylmethyl dimethylsulfonium chloride: Hygroscopic solid; IR (KBr) 1630 cm^{-1}; ^1H NMR ($CDCl_3$)δ 5.65 (s, 2H). 3.35 (s, 6H), 3.14 (s, 3H), 2.94 (s, 3H).

N,N-Diethylcarbamoylmethyl dimethylsulfonium chloride[14]**:** ^1H NMR ($CDCl_3$)δ 5.59 (s, 2H), 3.37 (s, 6H), 3.40 (q, 2H, J=7.1 Hz), 3.34 (q, 2H, J= 7.1 Hz), 1.28 (t, 3H, J= 7.1 Hz), 1.11 (t, 3H, J= 7.1 Hz).

Sulfur ylids: To a suspension of the sulfonium salts (0.05 mol) in acetonitrile (200 ml) was added sodium hydride (80% dispersion in mineral oil, 0.06 mol), in one portion. After stirring for 3 h. at room temperature the mixture was filtered to remove sodium chloride and the solution evaporated to a yellow oil. The

ylides were used without further purification because of instability.

N,N-Dimethyl-2-(dimethylsulfuranylidene) acetamide (2): yellowish oil; yield 89%; ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 7H), 2.50 (s, 6H).

N,N-Diethyl-2-(dimethylsulfuranylidene) acetamide (6)[14]: ^{1}H NMR ($CDCl_3$) δ 3.14 (q, J = 7.1 Hz, 4H), 2.70 (s, 7H), 0.98 (t, 6H, J = 7.1 Hz).

General procedure for the reactions of ylids with aldehydes:

1.- Synthesis of 3-arylglycidamides 3a-3d: To a solution of aldehyde (**1a-1d**, 1 mol) in $CHCl_3$ was added the ylide (**2**, 1.3 mol). The mixture was stirred at room temperature for a period 1-3 h, when all the starting aldehyde was consumed (TLC assay). The solvent was evaporated and the residue chromatographed on silica gel with hexane-ethyl acetate, 1:1.

trans-N,N-Dimethyl-3-phenylglycidamide (3a): colorless liquid; Rf 0.45 (AcOEt); yield 70%; IR (film) 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27-7.24 (m, 5H), 3.96 (d, 1H, J=2 Hz, H-3), 3.58 (d, 1H, J= 2 Hz, H-2), 3.01 and 2.91 (2s, 3H each, NMe_2); ^{13}C NMR ($CDCl_3$) δ 165.5 (CO), 136.0 (C-1'), 128.5 (3C), 126.0 (2C), 57.6, 57.0 (C-2, C-3), 36.5, 36.0 (NMe_2); MS, m/e (rel. int.) 191 (M^+, 17), 174 (2.5), 147 (5), 131 (4), 89 (21), 85 (47), 77 (20), 72 (100).

Anal. calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.60; H, 7.01; N, 7.35.

trans-N,N-Dimethyl-3(4-chlorophenyl)glycidamide (3b): colorless liquid; yield 62%; IR (film) 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, J= 8.67 Hz), 7.15 (d, 2H, J= 8.67 Hz), 3.93 (d, 1H, J=2 Hz, H-3), 3.53 (d, 1H, J= 2 Hz, H-2), 3.02 and 2.89 (2s, 3H each, NMe_2); ^{13}C NMR ($CDCl_3$) δ 165.9 (CO), 134.3, 134.0 (C-1',C-4'), 128.0 (2C), 126.0 (2C), 57.0, 56.7 (C-2, C-3), 36.1, 35.4 (NMe_2); MS, m/e (rel. int.) 225 (M^+, 9.5), 208 (4.5), 165 (9.5), 125 (18), 89 (32.5), 85 (45.5), 72 (100).

Anal. calcd. for $C_{11}H_{12}NO_2Cl$: C, 58.45; H, 5.36; N, 6.21. Found: C, 58.73; H, 5.18; N, 6.20.

trans-N,N-Dimethyl-3(3-nitrophenyl)glycidamide (3c): white solid; mp 100ºC (benzene); yield 95%; IR (film) 1655 (C=O), 1526 and 1351 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (ddd, 1H, J= 8.1, 2.3 and 1.2 Hz, H-4'), 8.05 (ddd, 1H, J= 2.3, 1.6 and 0.9 Hz, H-2'), 7.60 (ddd, 1H, J=7.5, 1.2 and 1.6 Hz, H-6') , 7.47 (ddd, 1H, J= 7.5, 8.1 and 0.9 Hz, H-5'), 4.10 (d, 1H, J=1.9 Hz, H-3), 3.60 (d, 1H, J= 1.9 Hz, H-2), 3.07 and 2.92 (2s, 3H each, NMe_2); ^{13}C NMR ($CDCl_3$) δ 165.2 (CO), 148.1 (C-3'), 137.0 (C-1'),131.0 (C-6'), 129.2 (C-5'), 123.0 (C-4'), 120.0 (C-2'), 56.8, 56.0 (C-2, C-3), 36.1, 35.4 (NMe_2); MS, m/e (rel. int.) 236 (M^+, 4.5), 219 (4), 89 (18.5), 85 (29.5), 72 (100).

Anal. calcd. for $C_{11}H_{12}N_2O_4$: C, 59.93; H, 5.12; N, 11.86. Found: C, 59.62; H, 5.22; N, 11.94.

trans-N,N-Dimethyl-3(2-nitrophenyl)glycidamide (3d): white solid; mp 130-132ºC (benzene); yield 60%; IR (film) 1664 (C=O), 1519 and 1344 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (dd, 1H, J= 8.1 and 1.3 Hz, H-3'), 7.64 (ddd, 1H, J= 7.8, 1.3 and 6.6 Hz, H-5'), 7.57 (dd, 1H, J=7.8 and 2.3 Hz, H-6'), 7.46 (ddd, 1H, J= 8.1, 6.6 and 2.3 Hz, H-4'), 4.40 (d, 1H, J=2.13 Hz, H-3), 3.53 (d, 1H, J= 2.13 Hz, H-2), 3.03 and 2.97 (2s, 3H each, NMe_2); ^{13}C NMR ($CDCl_3$) δ 165 (CO), 147 (C-2'), 134, 132 (C-5', C-1'),129 (C-4'), 127 (C-6'), 124 (C-3'), 55.9, 55.5 (C-2, C-3), 36.3, 35.6 (NMe_2); MS, m/e (rel. int.) 236 (M^+, 1.5), 102 (29), 89 (5), 85 (2), 72 (100).

Anal. calcd. for $C_{11}H_{12}N_2O_4$: C, 59.93; H, 5.12; N, 11.86. Found: C, 59.75; H, 5.18; N, 11.91.

cis-N,N-Dimethyl-3(2-nitrophenyl)glycidamide (cis-3d): was isolated as white solid; mp ; yield <4%; ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, 1H, J= 8.2 and 1.4 Hz, H-3'), 7.80 (dd, 1H, J= 7.8 and 1.6 Hz, H-6'), 7.64 (ddd, 1H, J=7.8, 7.5 and 1.4 Hz, H-5'), 7.45 (ddd, 1H, J= 7.5, 8.2 and 1.6 Hz, H-4'), 4.77 (d, 1H, J=4.6 Hz, H-3), 4.13 (d, 1H, J= 4.6 Hz, H-2), 3.04 and 2.70 (2s, 3H each, NMe_2).

2.- Synthesis of (2S,3R,4R)- and (2R,3S,4R)-N,N-dimethyl-2,3-epoxy-4,5-O-isopropylidene-4,5-dihydroxypentanoamide (5a and 5b).

N,N-dimethyl-2-(dimethylsulfuranylidene)acetamide (**2**, 1.4 g, 0.0095 mol) was added to a solution of 2,3-O-isopropylidene-*D*-glyceraldehyde (**4**, 1 g, 0.0077 mol) in $CHCl_3$ (10 ml) at room temperature. The reaction was monitored by TLC and was complete in a few minutes. The solvent was evaporated and the residue chromatographed on silica gel with ethyl acetate, to give a colorless liquid (**5a,5b**, 1.52 g, 92%). ^1H NMR spectrum of the mixture showed a ratio of isomers **5a:5b**, 86:14. When the reaction was carried out at -5ºC - 0ºC, the ratio **5a:5b** was 96:4. TLC Rf 0.26 ethyl acetate; IR (film) 1645, 1385, 1360, 1260 cm^{-1}. MS m/e (rel. int.) 200 (86, M-15), 114 (50), 102 (33), 101 (10), 72 (100), 43 (62.5).

Anal. calcd. for $C_{10}H_{17}NO_4$: C, 55.08, H, 7.96; N, 6.51. Found: C, 55.83; H, 8.09; N, 6.22.

Flash chromatography (silica gel) in 1:1 hexane/ethyl acetate, yielded pure diastereoisomer **5a**, and a mixture **5a**:**5b** enriched in **5b**.

5a: [α] -4.53 (c 0.84, $CHCl_3$). ^1H NMR and ^{13}C NMR data are given in Tables 1 and 2.

The spectral data of the diastereoisomer **5b** was deduced from the spectra of the mixture and of pure **5a** isomer obtained.

3.- *Synthesis of* (2S,3R,4R)- and (2R,3S,4R)-N,N-diethyl-2,3-epoxy-4,5-O-isopropylidene-4,5-dihydroxypentanoamide (7a and 7b).

Compounds **7a** and **7b** (87:13, 90% overall yield) were prepared from **4** and the ylide **6**, as described above for the compounds **5a** and **5b**. TLC Rf 0.55 ethyl acetate; IR (film) 1662, 1395, 1375, 1275 cm^{-1}. MS m/e (rel. int.) 228 (14.5, M-15), 142 (33), 101 (7), 100 (18.3), 85 (6), 72 (63), 43 (100).

Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.31; H, 8.73, N, 5.71.

Flash chromatography (silica gel) in 3:1 hexane/acetone, yielded pure diastereoisomer **7a**, and a mixture **7a**:**7b** enriched in **7b**.

7a: [α] -1.41 (c 1.2, $CHCl_3$). ^1H NMR and ^{13}C NMR data are given in Tables 1 and 2.

The spectral data of the diastereoisomer **7b** was deduced from the spectra of the mixture and of pure **7a** isomer obtained.

Synthesis of (3S,4R)- and (3R,4R)-3,4,5-Trihydroxypentanoic acid 1,4-lactone (10a and 10b)

General procedure: To a stirred solution of epoxide (2 mmol) in absolute EtOH (10 ml) was added $NaBH_4$ (189 mg, 5 mmol), and the mixture was refluxed for 2h. The solvent was removed, H_2O (20 ml) was added to the residue and the product was extracted with $CHCl_3$ (3x10 ml). The organic layer was dried and the solvent evaporated, to provide the ß-hydroxyamides. Thus the epoxides **5a** and **5b** given the β-hydroxyamides **8a** and **8b**, the epoxides **7a** and **15a** given the β-hydroxyamide **9a** and the epoxides **7b** and **15b** the β-hydroxyamide **9b**. (^1H NMR are given in Table 1). The crude ß-hydroxyamide was treated with TFA-H_2O (1:1, 2 ml) at 90 ºC for 2 h, and concentrated under reduced pressure. In order to complete the lactonization to the residue was added benzene and evaporated three times, to afford a brown syrup. The crude product was chromatographed on silica gel with ethyl acetate-hexane, 1:1 to give the lactones **10a** or **10b** with a nearly 80% of yield.

10a: colorless syrup. [α] -1.5 (c 1, EtOH). ^1H NMR ($CDCl_3$ - $(CD_3)_2CO$, 1:2) δ 4.48 (ddd, 1H, J= 6.8, 2.8 and 2.2 Hz, H-3), 4.35 (ddd, 1H, J= 3.4, 3.5 and 2.2 Hz, H-4), 3.76 (dd, 1H, J= 12.3 and 3.4 Hz, H-5'), 3.68 (dd, 1H, J= 12.3 and 3.5 Hz, H-5), 2.83 (dd, 1H, J= 17.9 and 6.8 Hz, H-2'), 2.34 (dd, 1H, J= 17.9 and 2.8 Hz). ^{13}C NMR ($(CD_3)_2CO$) δ 176.3 (CO), 88.9 (C-4), 69.3 (C-3), 62.4 (C-5), 38.8 (C-2).

10b: colorless syrup. [α] +49.3 (c 0.56, MeOH). ^1H NMR ($CDCl_3$ - $(CD_3)_2CO$, 1:2) δ 4.67 (ddd,

1H, J= 6.3, 2.7 and 4.8 Hz, H-3), 4.43 (ddd, 1H, J= 4.8, 4.4 and 5.1 Hz, H-4), 4.02 (dd, 1H, J= 12.3 and 4.4 Hz, H-5'), 3.95 (dd, 1H, J= 12.3 and 5.1 Hz, H-5), 2.74 (dd, 1H, J= 17.8 and 6.3 Hz, H-2'), 2.52 (dd, 1H, J= 17.8 and 2.7 Hz). ^{13}C NMR (D_2O) δ 179.2 (CO), 85.4 (C-4), 68.1 (C-3), 59.7 (C-5), 38.2 (C-2).

Synthesis of trans- and cis-N,N-diethyl-4,5-O-isopropylidene-4(S),5-dihydroxypentenamide (12 and 13)

1.- From 2,3-O-isopropylidene-D-glyceraldehyde (4) and N,N-diethylcarbamoylmethyl triphenylphosphonium chloride (11).

Preparation of phosphonium salt **11**: a mixture of N,N-diethylchloroacetamide (3 g, 0.02 mol) and triphenylphosphine (5.2 g, 0.02 mol) was refluxed in nitromethane (50 ml) for 30 h. The solvent was evaporated and the yellowish residue chromatographed on silica gel with ethyl acetate to give a white solid (5.02 g, 60% yield); m.p. 172-174°C; IR (KBr) 1626 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.0 - 7.5 (m, 15H), 5.53 (d, 2H, J= 12.9 Hz), 3.76 (q, 2H, J= 7.1 Hz), 3.19 (q, 2H, J= 7.1 Hz), 1.18 (t, 3H, J= 7.1 Hz), 0.94 (t, 3H, J= 7.1).

Reaction of **4** with **11**: To a mixture of phosphonium salt (1.73 g, 0.004 mol) in water (7.5 ml) and 2,3-O-isopropylidene-D-glyceraldehyde (0.5 g, 0.0038 mol) in chloroform (5 ml), was added dropwise a solution of NaOH (0.2 g, 0.005 mol) in water (5 ml). The mixture was stirred for a few minutes and the organic layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated. The resulting residue was passed through a silica gel column (EtOAc-hexane, 1:1) to remove the triphenylphosphine oxide. Evaporation of solvents gave a colorless liquid (0.8 g, 90%) of the mixture *trans* and *cis* isomers. The ^1H NMR of the unseparated mixture corresponded to a ratio o *trans/cis* (**12/13**), 45:55. The two isomers were separated by flash chromatography on silica gel (EtOAc:hexane, 1:2).

12: colorless liquid (340 mg); Rf 0.36 (EtOAc:hexane, 1:1); [α] +10 (c 0.1, $CHCl_3$); IR (film) 1659 (C=O), 1612 (C=C) cm^{-1}. MS, m/e (rel. int.) 227 (M^+, 14.6), 212 (16.6), 169 (7.3), 156 (26.7), 152 (100), 140 (20.2), 126 (43.4), 124 (31.2), 100 (22.6), 98 (36.8), 97 (59.8), 72 (83), 43 (44.5).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.44; H, 9.25; N, 6.17. Found: C, 63.08; H, 9.31; N, 6.22.

13: colorless liquid (405 mg); Rf 0.55 (EtOAc/hexane, 1:1); [α] +122° (c 0.1, $CHCl_3$); IR (film) 1645 (C=O), 1614 (C=C) cm^{-1}. MS, m/e (rel. int.) 227 (M^+, 0.5), 212 (13.2), 169 (68.3), 156 (8.6), 152 (100), 140 (81.4), 126 (75), 124 (39), 100 (15), 97 (54.2), 72 (53.1), 43 (76.9).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.44; H, 9.25; N, 6.17. Found: C, 63.24; H, 9.26; N, 6.40.

^1H NMR and ^{13}C NMR data for compound **12** and **13** are given in Tables 1 and 2.

2.- From 2,3-O-isopropylidene-D-glyceraldehyde (4) and N,N-diethylcarbamoyl acetic acid (14)

Preparation of **14**: To a solution of N,N-diethylamine (16.4 g, 0.224 mol) in benzene (11.7 ml) at 0° C, was added dropwise malonyl chloride methyl ester (10.18 g, 0.075 mol) in benzene (10 ml). After stirring few minutes the mixture was washed with water (2 x 20 ml) and the aqueous phase was extracted with ether (3 x 20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give the N,N,-diethylcarbamoyl methyl acetate as a dark yellow liquid (9.15g, 70.9 %). Molecular distillation gave the analytical sample as clear liquid (150° C/1 mmHg). ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.38 (s, 2H), 3.33 (q, 2H, J = 7.0 Hz), 3.24 (q, 2H, J = 7.0 Hz), 1.13 (t, 3H, J = 7.0 Hz), 1.08 (t, 3H, J = 7.0 Hz). A solution of N,N,diethylcarbamoyl methyl acetate (7.5 g, 0.043 mol) in MeOH (27.5 ml) was treated with solution of KOH (3.5 g, 0.063 mol) in MeOH (27.5 ml) added dropwise, and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the solid residue was dissolved in water, acidulated with 2.5% aqueous hydrochloric acid and extracted with Cl_3CH. The organic layer was dried over anhydrous sodium sulfate and

concentrated to give the a white solid (5.5 g, 80 %). Recrystallization from benzene give the N,N-diethylcarbamoyl acetic acid as white needles (**14**): mp 72-74° C, IR (KBr) 1725 (C=O acid), 1594 (C=O amide) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.33 (s, 2H), 3.41 (q, 2H, J = 7.2 Hz), 3.29 (q, 2H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.2 Hz).

Reaction of **4** with **14**: A mixture of **4** (0.66 g, 0.0051 mol), **14** (0.81 g, 0.0051 mol) in pyridine (1.7 ml) and two drops of piperidine, were stirred at room temperature overnight. The solvent were removed in vacuo and the residue purified by flash chromatography on silica gel (AcOEt-hexane, 2:3) giving in order to elution: **13** (30.4 mg, 2.68%), **9a** (192 mg, 15.7%), **12** (436.7 mg, 38.5%) and **9b** (40 mg, 3.26%).

Synthesis of 7a, 7b, (2R,3R,4R)- and (2S,3S,4R)-N,N-diethyl-2,3-epoxy-4,5-O-isopropylidene-4,5-dihydroxypentanoamides (15a) and (15b) by epoxidation of alkenes 12 and 13.

To a solution of alkenes (0.1 mol) in CH_2Cl_2 was added m-chloroperbenzoic acid (0.14 mol) dissolved in CH_2Cl_2. The mixture was refluxed for several days (4-6), cooled, and shaken with a 10% solution of sodium sulfite to destroy excess peroxide. The organic layer then was shaken with 5% aqueous $NaHCO_3$ to remove m-chlorobenzoic acid and dried over anhydrous sodium sulfate. The solvent was evaporated and the mixture purified by column chromatography.

A mixture of *trans*-epoxides (**7a/7b**, 2:1, 58% yield) was obtained from *trans*-alkene **12**.

A mixture of *cis*-epoxides (**15a/15b**, 3:2, 62% yield) was obtained from the *cis*-alkene **13**. Rf 0.6 (AcOEt); IR (film) 1637, 1375, 1365, 1255 cm^{-1}.

Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.37; H, 8.61, N, 5.72.

The two isomers **15a** and **15b** were separated by preparative TLC (silica gel, AcOEt-hexane, 1:3). **15b** (the faster moving isomer on TLC), colorless liquid, [α] -16.6 (c 0.3, $CHCl_3$); **15a** (the slower moving isomer) [α] +12.3 (c 0.6, $CHCl_3$)

^1H NMR and ^{13}C NMR data for compounds **15a** and **15b** are given in Tables 1 and 2.

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