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Synthesis of *Pseudo*nucleosides containing Chiral *Sulfa*hydantoins as Aglycone (II) §

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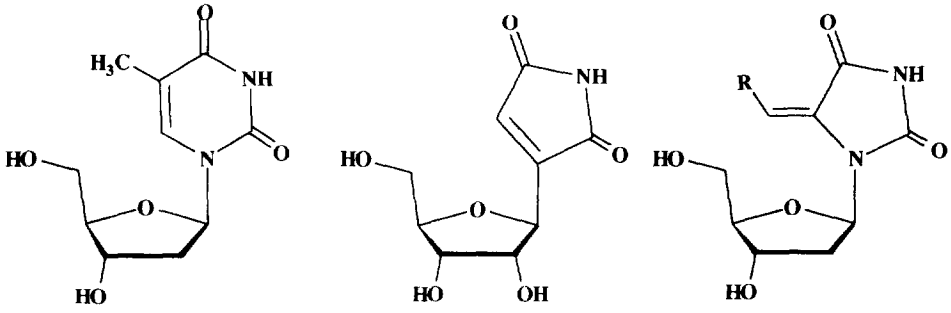
Abstract: A series of chiral *sulfahydantoins* have been synthesized by alkaline cyclization starting from N-sulfamylaminoacid methyl esters. Regioselective glycosylation of these *pseudo*pyrimidic heterocycles was carried out with a benzyl protecting group on the N-sulfonylcarbamic position. Best glycosylation results were obtained by preliminary silylation of sulfahydantoins, and their condensation with a tetraacylribofuranose which yielded the *pseudo*nucleosides in a ß-anomeric configuration.

Introduction

The modification of the heterocyclic aglycone is important for the preparation of new nucleosidic analogues used in antiviral and/or antitumoral chemotherapy [1]. In order for a pseudonucleoside to interfere with biological processes, it must be able to inhibit nucleoside biogenesis enzymes, or to selectively hybridize with natural nucleotides. This induces subsequent reactions that interfere with duplication and transcription mechanisms in the neosynthesized biopolymer.

The proven mode of action of compounds such as showdomycine **2** [2] or pseudonucleosides containing hydantoins **3** [3] results from the structural analogy between non-natural aglycones and pyrimidines (i.e. thymidine, **1**).



1 **2** **3**

- Fig 1-

§ part I : this journal (see ref. 4d).

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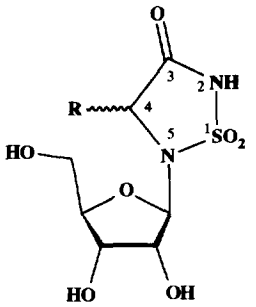
We describe here the preparation of a series of pseudo-nucleosides containing a sulfahydantoin (1,2,5-thiadiazolidin-3-one 1,1-dioxide) [4] as aglycone (Fig. 2). These *sulfa* analogues of nucleobases were derived from aminoacids by *insertion of a sulfamoyl group*, according to a previously reported approach [5]. Besides the interest that could have presented the introduction of this new heterocyclic base, the utilisation of natural aminoacids allows the variation of the size of the substituent R, the control of the chirality of the asymmetric carbon $*C_4$, and lastly the introduction of a functional group in the chain R (amine, carboxylic acid, thiol) able to react as bionucleophile.



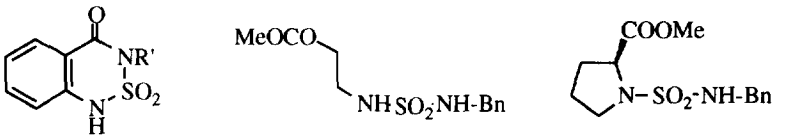
-Fig 2-

Chemistry

Preparation of heterocyclic compounds

Sulfahydantoins **8** were synthesized in four steps (Scheme 1) starting from L-aminoesters **4** and chlorosulfonyl isocyanate (CSI) [5]. Initial sulfamoylation was followed by benzylation under Mitsunobu conditions [6], and then acidic treatment. Alkaline cyclization of N-sulfamoylaminoesters **7** thus obtained gave the desired heterocyclic compounds without racemization [4d], with an overall yield of 35-55% starting from the aminoester. It was also possible to directly obtain unprotected aglycones **10b-e** by cyclization, starting from Boc-sulfamides **5b-e** *via* intermediates **9b-e.**

The structure of the reaction products was confirmed by the usual methods: IR, ^1H and ^{13}C NMR and mass spectrometry. Boc-sulfamides **5b-e** were characterized by the presence in IR spectroscopy of two elongation bands of carbamate and ester carbonyles. Both **NH** were easily distinguished in NMR by the chemical shift and multiplicity for each of these two signals. The most acidic SO_2-N**H**-COO proton appeared in the form of a singlet at 7-8 ppm. This signal disappears in alkylation compounds **6b-e**. Deprotection and cyclisation were equally followed in NMR by the disappearance of signals of the *tert*-butyl protons and methyl esters.



11 R'=Bn
12 R'=H

13

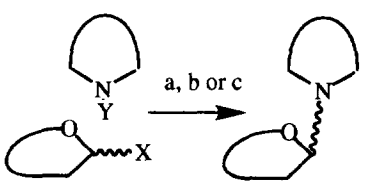
14

-fig 3-

Progressive increase in cyclization yields according to the steric bulk of R are observed. Surprisingly no cyclization was observed for compounds **13** and **14**, derived from ß-alanine and proline respectively. In the first case, the unsubstituted chain showed a further rotational level, whereas in the second case the rigidity of the proline structure entails a dihedral angle S-N-C-C(O) that prevented the bicyclic fusion.

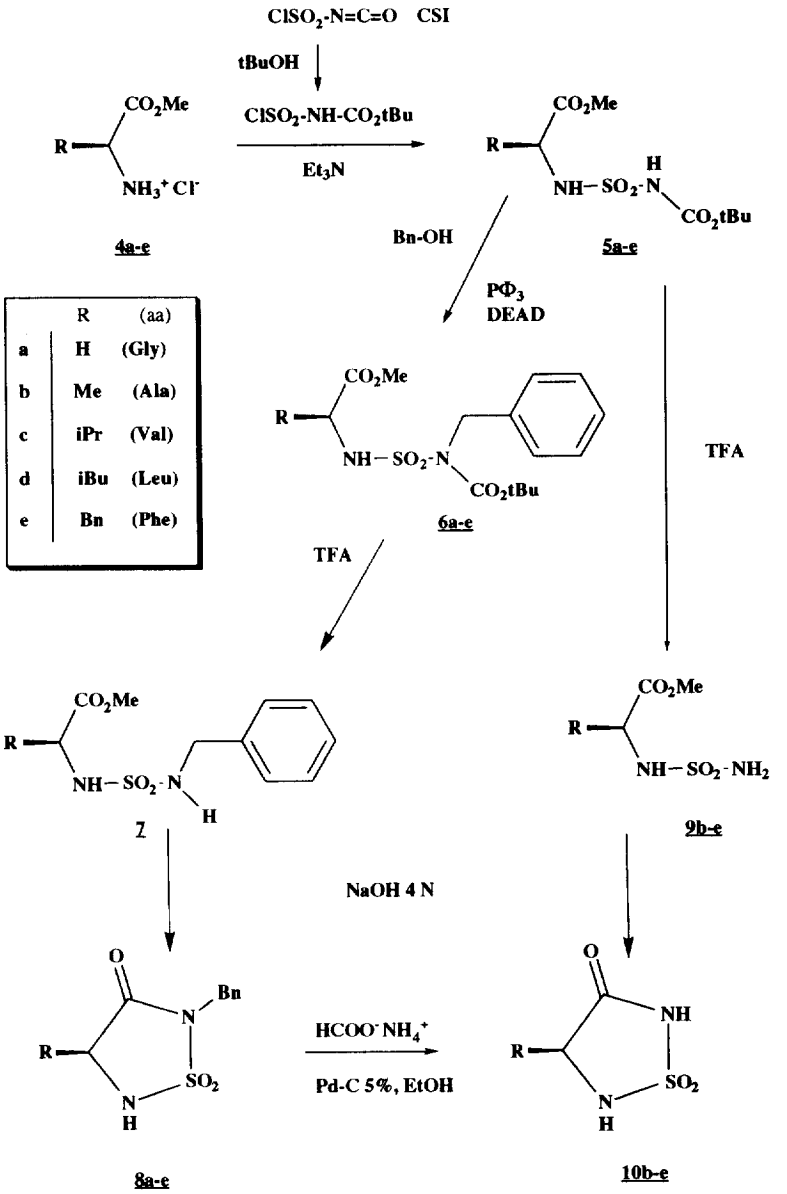
Glycosylation

Three methods of glycosylation (Fig. 4) were used: the Vorbrüggen method (c), requiring preliminary silylation of the base [7], the Hilbert-Johnson's process [8] starting from the halogenosugars (b), and the direct fusion method (a) in the presence of a catalytic amount of iodine [9]. All these methods have been reviewed [10].



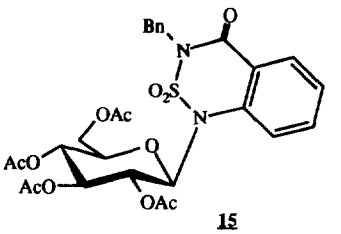
a. X= OAc; Y=H . Δ; I_2
b. X=Br; Y=H . DABCO
c. X=OAc; Y=Si(Me_3)$_3$. $SnCl_4$

-Fig 4-


ClSO2-N=C=O CSI
tBuOH
ClSO2-NH-CO2tBu
Et3N
CO2Me
R
NH3+ Cl-
4a-e
NH-SO2-N
H
CO2tBu
5a-e
Bn-OH
PΦ3
DEAD
TFA
6a-e
TFA
NH-SO2-N
H
7
NaOH 4 N
NH-SO2-NH2
9b-e
Bn
SO2
HCOO- NH4+
Pd-C 5%, EtOH
NH
8a-e
10b-e
R (aa)
a H (Gly)
b Me (Ala)
c iPr (Val)
d iBu (Leu)
e Bn (Phe)

-Scheme 1-

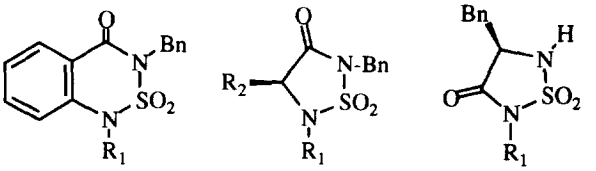
Route b has been previously applied using commercial acetobromoglucose and benzothiadiazinone **11**. Substitution was carried out in acetonitrile in the presence of diaza-[2.2.2]-bicyclooctane. The ß-anomer of the N-glucoside **15** was obtained in 35% yield (fig 5).
Nucleophilic condensation starting from sulfahydantoin **8a-e** and acetobromoglucose or triacetyl-1-chlororibose proved to be unsuccessful, due to thermal degradation of halosugars under the experimental conditions.



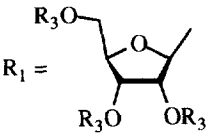
15

-Fig 5-

Condensation of peracylated D-ribose and aglycones **11**, **8a** and **8e** (route a) yielded the expected pseudonucleosides ß **16**, **17a** and **17e**. Starting from the unprotected sulfahydantoin **10e**, the only product was that resulting from the reaction at N^2 condensation, the most acidic reactive site. This regioselectivity was established by NMR study of compound **18** (*CH-NH signal appears as a doublet, that desappears after deuteration).



16 **17a-e** **18**

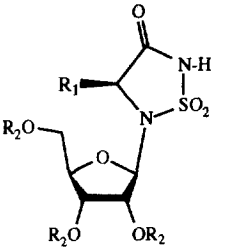


R_3 = Ac (**16**,**17c-e**)
= Bz (**17a-b**,**18**)

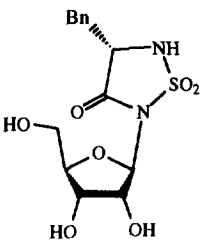
-Fig 6-

Route c proved to be a better method for glycosylation of sulfahydantoins. Compounds **8b-e** were first treated under anhydrous argon atmosphere by hexamethyldisilazane (HMDS) containing catalytic quantities of ammonium sulphate. Condensation on the tribenzoyl-1-acetyl-ß-D-ribofuranose (**a,b**) or the tetraacetyl-ß-D-ribofuranose (**c,d,e**) was carried out in acetonitrile in the presence of tin tetrachloride. ^1H NMR did not unambiguously confirm the anomeric configuration of the obtained pseudonucleosides ($J_{H1'H2}$ =7.3-7.8 Hz) but this method is known for its high stereoselectivity in the synthesis of ß-anomers.

Deprotection
Access to free *pseudo*nucleosides **20 d-e** -starting from their respective precursor **17**- requires both N-debenzylation and deacylation. The first step was carried out by hydrogenolysis using Pd-C 5% and ammonium formate as hydrogen donor in refluxing ethanol. Under ultrasonic irradiation at room temperature, with the same catalyst and cyclohexadiene, the reaction time was shortened 4-fold. The ester groups were then removed by treatment with ammonia-methanol. Further debenzylation of **18** gave the compound **21**, regioisomer of **20e**.

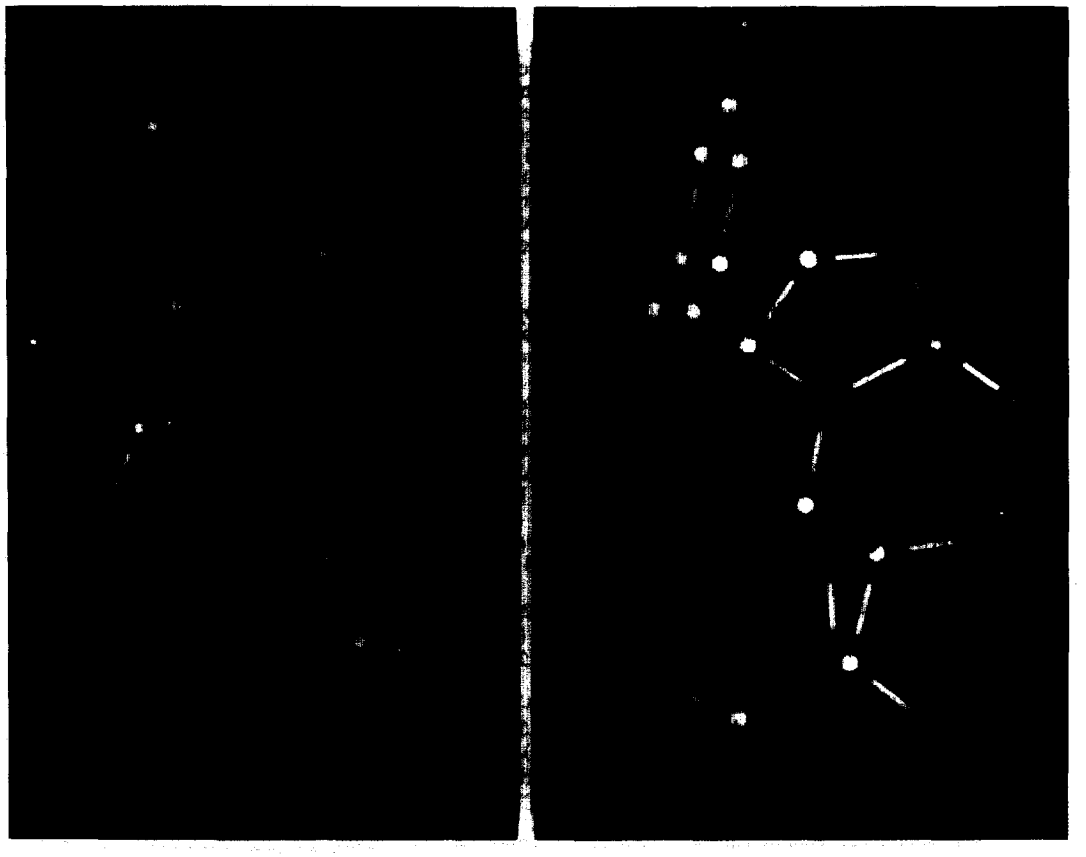


	R_1	R_2
19d	iBu	Ac
19e	Bn	Ac
20d	iBu	H
20e	Bn	H



21

-Fig 7-



-Fig 8-

Computerized minimization [11] of structural parameters for the *pseudo*nucleoside **20e** (Fig.8, left) determined the preferential position for aglycone, the lower conformation energy (-7.9 kcal.mol^{-1}) and the value of dipolar moment μ: 2.07u Debye. The dihedral angle H-C1'-C2'-H was 155° and the calculated $J_{H1'H2'}$ was approximately 9Hz, according to the hypothesis of ß configuration for the described series. For the hypothetical α-epimer (Fig.8, right) an analogous determination of $J_{H1'H2'}$ gave a value of 3.5 Hz.

Conclusion

We describe here the preparation of new pseudonucleosides containing sulfamylated derivatives of natural amino acids as aglycones. According to our previous report, ring closure was performed without racemization (in contrast with hydantoins) and the heterocyclization was dependent on the steric bulk on C*. Vorbrüggen's procedure proved to be well-suited for the N^5-glycosylation of benzyl-protected sulfahydantoins. The fusion method used for unprotected sulfahydantoins gave the N^2 regioisomer. In both cases only one of the two anomers was obtained; this would appear to be the ß configuration of this pseudoribonucleoside series, as suggested by previous reports and modeling calculations. The biological evaluation of the unprotected form of these congeners as antivirals, and their incorporation into synthetic RNA, are in progress.

Acknowledgements

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Experimental section

Melting points were determined in open capillary tubes on a thermotechnal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. Microanalysis were performed in the microanalysis laboratory of ENSCM (Montpellier). Ultraviolet spectra were recorded on a Cary 1186 spectrophotometer. Proton and Carbon Nuclear Magnetic Resonance were determined with a AC 250 Bruker spectrometer. Chemical shifts are expressed in parts per million, with TMS as reference. The multiplicity was indicated as: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) , l (large) and combination of these signals. Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive or negative mode on a JEOL DX 300 spectrometer using the G, GT or NOBA matrix. Optical rotations were mesured in a 1 cm cell on a Perkin-Elmer polarimeter. Thin Layer Chromatography (TLC) was performed on a precoated aluminium sheets of silicagel 60F_{254} (Merck). Column chromatography was performed with silicagel 60. All solvents used for the reactions were anhydrous.

Methyl esters of [N-(N'-*tert*-butyloxycarbonyl)-sulfamoyl] amino acids

The synthesis of these compounds, starting from chlorosulfonyl isocyanate (CSI), *tert*-butanol and natural aminoacids was carried out according a general procedure previously described [4d].

Methyl [N-(N'-tert-butyloxycarbonyl)-sulfamoyl]-glycinate **5a**

Yield=87%; **Rf=** 0,61 (CH_2Cl_2-MeOH 9-1); **mp=** 105-107°C **IR** (KBr, ν cm-1): 1748, 1716 (C=O, methyl and carb. esters); 1170, 1359 (SO_2). **1H NMR** ($CDCl_3$, δ ppm) 7.82 (s, 1H, NH-Boc); 5.90 (t, J=6.20 Hz, 1H, NH); 4.00 (d, J=6.20 Hz, 2H, CH_2); 1.45 (s, 9H, tBu). **MS** (FAB<0, NOBA): 267 ([M-H]-). **Anal.** ($C_8H_{16}N_2O_6S$) calc % C 35.82; H 5.97; N 10.44; S 11.94 found % C 35.76; H 6.02; N 10.37; S 11.89.

[(S)(-)] Methyl [N-(N'-tert-butyloxycarbonyl)-sulfamoyl]-alaninate **5b**

Yield=90%; **Rf=** 0.59 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = -14 (c=1 MeOH); **mp=** 72-74°C. **IR** (KBr, ν cm-1):1762, 1708 (C=O, methyl and carb. esters); 1152, 1365 (SO_2). **1H NMR** ($CDCl_3$, δ ppm) 7.72-7.00 (sl, 1H, NH-Boc); 5.82 (d, J=6.78 Hz, 1H, NH); 4.40 (qd, J_1= 6.78, J_2 = 3.20 Hz, 1H, CH*); 3.80 (s, 3H, OCH_3); 1.55 (s, 9H, tBu); 1.45 (d, 6.76 Hz, 3H, CH_3). **MS** (FAB<0, NOBA): 281 ([M-H]-); 181 ([M-Boc]-, 40%). **Anal.** ($C_9H_{18}N_2O_6S$) calc % C 38.29; H 6.38; N 9.92; S 11.34 found % C 38.22; H 6.41; N 9.88; S 11.37.

[(S)(+)] Methyl [N-(N'-tert-butyloxycarbonyl)-sulfamoyl]-valinate **5c**

Yield=84%; **Rf=** 0.72 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = + 2.5 (c=1, MeOH); **mp=** 89-90°C. **IR** (KBr, ν cm-1): 1752, 1697 (C=O, methyl and carb. esters); 1357, 1152 (SO_2). **NMR** ($CDCl_3$, δ ppm) **1H** : 7-7.5 (sl, 1H, NH-Boc); 5.22 (s, 1H, NH); 4.15 (dd, 1H, CH*); 3.78 (s, 3H, OCH_3); 2.20 (m, 1H, CHß); 1.45 (s, 9H, tBu); 0.9 and 1.05 (2d, J=7.16Hz, 6H, 2 CH_3). **13C**: 24.0 (2CH_3); 24.5 (CH ß); 27.5 (CH_3-*t* Bu); 52.1 (CH_3O); 58.2 (C*); 84.4 (C-tBu); 152.8 (CO carbamate); 173.1 (CO ester). **MS** (FAB<0, matrix NOBA): 309 ([M-H]-); 235 ([M-OtBu]+). **Anal.** ($C_{11}H_{22}N_2O_6S$) calc % C 42.58; H 7.09; N 9.03; S 10.32. found % C 42. 73; H 7.22; N 9.14; S 10.18.

[(S)(-)] Methyl [N-(N'-tert-butyloxycarbonyl)-sulfamoyl]-leucinate **5d**

Yield=83%; **Rf=** 0.67 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = -14.5 (c=1 MeOH); **mp=** 67-68°C. **IR** (KBr, ν cm-1): 1753, 1702 (C=O, methyl and carb. esters); 1358, 1162 (SO_2); 3267, 2964 (NH). **NMR** ($CDCl_3$, δ ppm) **1H**: 7. 25 (s. 1H, NH); 5.80 (s, 1H, NH-C* exch); 4.25 (t, J=6.20 Hz, 1H, CH*); 3.64 (s, 3H, OCH_3); 1.85 (m, 1H, *i*pr); 1.55 (d, J=6.18 Hz, 2H, CH_2 ß); 1.48 (s, 9H, *t*Bu); 0.95 (2d, J=3.60Hz, 2CH_3).**13C** : 23.2 and 23.5 ([CH_3]2CH); 27.5 (CH_3-tBu); 42.2 (CH_2 ß) 52.2 (CH_3O); 57.9 (C*); 84.4 (C-tBu) ; 150.8 (CO carbamate); 172.2 (CO meth. ester). **MS** (FAB<0, matrix GT): 323 ([M-H]-); 249 ([M-OtBu]-); 223 ([M-Boc]-). **Anal.** ($C_{12}H_{24}N_2O_6S$) calc % C 44.44; H 7.50; N 8.64; S 9.87; found C 44.64; H 7.53; N 8.48; S 9.85.

[(S)(+)] Methyl [N-(N'-tert-butyloxycarbonyl)-sulfamoyl]-phenylalaninate **5e**

Yield 87%; **Rf=** 0.68 ($CHCl_3$-MeOH 9-1); $[\alpha]_D$ = +12 (c=1; MeOH); **mp=**131-132°C. **IR** (KBr, ν cm-1): 1753, 1702 (C=O methyl and carb. esters); 1358, 1162 (SO_2); 3267, 2964 (NH). **NMR** ($CDCl_3$, δ ppm) **1H**: 7.30 (m, 3H, Ar-H); 7.20 (m, 2H, Ar-H *ortho*); 7.10 (s, 1H, NH exch); 5.60 (d, J=8.2 Hz, 1H, NHα exch); 4.50 (m, 1H, CH*); 3.70 (s, 3H, OCH_3); 3.10 (2dd, J= 2.7 and 6Hz, 2H, CH_2 Bn); 1.45 (s, 9H, *t*Bu). **13C** : 27.2 (3 CH_3 tBu); 39.2 (CH_2 Bn); 51.8 (CH_3O); 57.5 (C*); 84.1 (C tBu); 127.3 (C-para); 128.8 (C-ortho); 130.0 (C meta); 135.7 (C-ipso); 152.7 (CO carbamate); 172.1 (CO ester). **MS** (NOBA, FAB<0): 357 ([M-H]-); 283 ([M-OtBu]-). **Anal.** ($C_{15}H_{22}N_2O_6S$) calc % C 50.27; H 6.14; N 7.82; S 8.93. found % C 50.21; H 6.13; N 7.78; S 8.90.

General procedure of Mitsunobu reaction

A solution of [Boc-sulfamide] aminoester (0.01M) **5a-e** and diethyl (isopropyl) azodicarboxylate (0.01M; 1.74g or 2.02 g) in THF (8mL) was added dropwise (15mn, 5°C) to a solution of equimolar quantities of triphenylphosphine (2.52g) and benzylic alcohol (1.08g; 1.06 mL) in THF (8mL). The reaction medium was stirred under atmosphere of dry nitrogen for about 45 min. TLC reveals the formation of substituted compound

(UV, ninhydrine) less polar than its precursor. Oxydoreduction compounds were removed by filtration after precipitation into diethylether. The filtrate was concentrated and the crude residue was purified by column chromatography eluted with dichloromethane. Benzylated sulfamides **6a-e** were recovered in 80-95 % yield.

Methyl [N-(N'- tert-butyloxycarbonyl,N'-benzyl)-sulfamoyl]-glycinate **6a**
Yield 82%; **Rf**= 0.63 ($CHCl_3$-MeOH 9-1); **mp**= 60-62°C. **IR** (KBr, ν cm^{-1}): 1746, 1704 (C=O methyl and carb. esters); 1362, 1169 (SO_2); **1H NMR** ($CDCl_3$, δ ppm) : 7.35 (m, 5H, Ar-**H**); 6.15 (t, J=5.89 Hz, 1H, **NH** exch); 4.65 (s, 2H, CH_2 Bn); 4.03 (d, J=5.89 Hz, 2H, CH_2); 3.70 (s, 3H, OCH_3); 1.48 (s, 9H, tBu). **MS** (FAB>0, NOBA): 359 ([M+H]+); 259 ([M-Boc]+). **Anal.** ($C_{15}H_{22}N_2O_6S$) calc % C 50.27; H 6.14; N 7.82; S 8.93 found % C 50.52; H 6.02; N 7.62; S 8.88.

[(S)(-)] Methyl [N-(N'-tert-butyloxycarbonyl, N'-benzyl)-sulfamoyl]-alaninate **6b**
Yield 88%; **Rf**= 0.68 ($CHCl_3$-MeOH 9-1);$[\alpha]_D$= -12 (c=1; MeOH); **mp**=54-55°C. **IR** (KBr, ν cm-1) 1754, 706 (C=O methyl and carb. esters); 1374, 1165 (SO_2); **1H NMR** ($CDCl_3$, δ ppm) 7.35 (m, 5H, Ar-**H**); 5.90 (d, J=7.20 Hz, 1H, **NH**); 4.70-4.90 (2d, J=15.57Hz, 2H, CH_2 Bn); 3.75 (s, 3H, OCH_3); 1.50 (s, 9H, tBu); 1.30 (d, J=7.15 Hz, 3H, CH_3). **MS** (FAB>0, NOBA) 373 ([M+H]+); 317 ([M-tBu]+); 273 ([M-Boc]+). **Anal.** ($C_{16}H_{24}N_2O_6S$) calc % C 51.61; H 6.45; N 7.52; S 8.60 found % C 51.52; H 6.41; N 7.49; S 8.64.

[(S)(-)] Methyl [N-(N'-tert-butyloxycarbonyl, N'-benzyl)-sulfamoyl]-valinate **6c.**
Yield 83%; **Rf**= 0.76 ($CHCl_3$-MeOH 9-1); $[\alpha]_D$= -9 (c=1; MeOH); **mp**=50°C. **IR** (KBr, ν cm-1) 3300, 3240 (NH) 1750, 1720 (C=O methyl and carb. esters); 1370, 1167 (SO_2); **1H NMR** ($CDCl_3$, δ ppm) 7.25 (m, 5H, Ar-**H**); 5.75 (d, J=8.80 Hz, 1H, **NH**); 4.70 (2d; Jgem= 15.5Hz, 2H, CH_2 Bn)); 3.60 (s, 3H, OCH_3); 3.55 (m, 1H, **CH***); 1.95 (m, 1H, **CH**α); 1.48 (s, 9H, tBu); 0.75- 0.85 (2d, J=6.45 Hz, 6H, $2CH_3$). **MS** (FAB>0, NOBA): 401 ([M+H]+); 301 ([M-Boc]+). **Anal.** ($C_{18}H_{28}N_2O_6S$) calc % C 54.00; H 7.00; N 7.00; S 8.00 found % C 54.14; H 7.07; N 6.92; S 7.92.

[(S)(-)] Methyl [N-(N'-tert-butyloxycarbonyl, N'-benzyl)-sulfamoyl]-leucinate **6d.**
Yield 84%; **Rf**= 0.73 ($CHCl_3$-MeOH 9-1); $[\alpha]_D$= -18 (c=1; MeOH); **mp**=50°C. **IR** (KBr, ν cm-1): 3290, 3220 (NH) 1754, 1722 (C=O methyl and carb. esters); 1368, 1160 (SO_2); **NMR** ($CDCl_3$, δ ppm) **1H**: 7.35 (m, 5H, Ar-**H**); 5.75 (d, J=8.80 Hz, 1H, **NH**); 4,70-4.90 (Jgem=15.36Hz, CH_2-N); 3.85 (q, J=8.78 Hz, 1H, **CH***); 3.60 (s, 3H, OCH_3); 1.75 (m, 1H, iPr); 1.52 (s, 9H, **tBu**); 0.95-0.85 (2d, J=3.86 Hz, 6H, $2CH_3$). **13C** 21.8, 22.9 (iPr); 27.5 (3 CH_3 tBu); 41.2 (**C**β); 50.4 (CH_2 Bn); 51.9 (CH_3O); 54.7 (**C***); 84 .2 (**C**-tBu); 126.5, 126.9, 128.0 (**C**-Ar); 135.8 (**C** Ar-ipso); 152.2 (CO carbamate); 172.6 (CO ester). **MS** (FAB>0, NOBA): 415 ([M+H]+); 359 ([M-tBu]+); 315 ([M-Boc]+). **Anal.** ($C_{19}H_{30}N_2O_6S$) calc % C 55.07; H 7.24; N 6.76; S 7.72 found % C 55.21; H 7.19; N 6.73; S 7.76.

[(S)(+)] Methyl [N-(N'-tert-butyloxycarbonyl, N'-benzyl)-sulfamoyl]-phenylalaninate **6e**
Yield 95%; **Rf**= 0.68 ($CHCl_3$-MeOH 9-1); $[\alpha]_D$= +3 (c=1; MeOH); **mp**=85-87°C. **IR** (KBr, ν cm-1): 3301, 3241 (NH) 1746, 1714 (C=O methyl and carb. esters); 1377, 1166 (SO_2); **NMR** ($CDCl_3$, δ ppm) **1H**: 7.35 (m, 10H, 2Ar-**H**); 5.75 (d, J=7.35 Hz, 1H, **NH**-exch); 4.72-4.90 (2d, Jgem=15.60Hz, CH_2 Bn), 4.00 (q, J=7.30 Hz, 1H, **CH***); 3.60 (s, 3H, OCH_3); 3.00 (2dd, Jvic= 5.77 Hz, Jgem=19Hz, 2H, CH_2-**C***); 1.48 (s, 9H, tBu).**13C**: 27.4 (3 CH_3-tBu); 38.7 (CH_2-Bn); 50.2 (CH_2 -N) 52.3 (CH_3O); 57 (**C***); 84.4 (**C**-*t* Bu); 126.8 ; 129.2 ; 129.2 ; 135.7 (**C**-Ar); 150.1 (**CO** carbamate); 172.3 (**CO** ester). **MS** (FAB>0, matrice NOBA): 449 ([M+H]+); 393 ([M-Isobutene]+); 393 ([M-Boc]+). **Anal.** ($C_{22}H_{28}N_2O_6S$) calc % C 58.93; H 6.25; N 6.25; S 7.14 found % C 58.69; H 6.19; H 6.29; S 7.10.

General procedure for acidic decarbamylation
A solution of trifluoroacetic acid (3 Eq) in dichloromethane (v/v) was added dropwise to the N-Boc (benzyl) sulfamides **6 (5) a-e** (5.10^{-3} M) dissolved in the same solvent (50 mL). The reaction medium was stirred for 2 hours, concentrated under reduced pressure and coevaporated with diethyl ether. Residue was recrystallized from dichloromethane; the deprotected sulfamides **7-9** were obtained in 85-95% yield.

Methyl [N-(N'-benzyl)-sulfamoyl]-glycinate **7a**
Yield= 89%; **Rf**=0.62 (CH_2Cl_2-MeOH 9-1); foam. **1H NMR** (DMSO D6, δ ppm) 7.42 (m, 5H, Ar-**H**); 5.75 (t, J=5,44 Hz, 1H, **NH**); 5.25 (sl, 1H, **NH**-Bn); 4.05 (d, 2H, CH_2 Bn); 3.70 (d, J=5.44 Hz, 2H, CH_2-N); 3.65 (s, 3H, OCH_3). **MS** (FAB>0, matrix NOBA): 259 ([M+H]+); 517 ([2M+H]+). **Anal.** ($C_{10}H_{14}N_2O_4S$) calc % C 46.51; H 5.42; N 10.85; S 12.40 found % C 46.44 ; H 5.60; N 10.78 ; S 12.68.

Methyl [N-(N'-benzyl)-sulfamoyl]-alaninate **7b**
Yield= 92%; **Rf**=0.68 (CH_2Cl_2-MeOH 95-5); foam, **NMR** ($CDCl_3$, δ ppm) **1H** 7.35 (s, 5H, Ar-**H**); 5.10 (d, J=9.98 Hz, 1H, **NH**α); 4.60 (s broad, 1H, NH-Bn); 4.15 (2d, Jgem=15.64 Hz, 2H, CH_2 Bn); 4.05 (q, J=7.06 Hz,

1H, CH*); 3.60 (s, 3H, OCH_3); 1.45 (d, J=7.06 Hz, 3H, CH_3 Ala). **MS** (FAB>0, matrix NOBA): 273 ([M+H]+). **Anal.** ($C_{11}H_{16}N_2O_4S$) calc % C 48.52; H 5.88; N 10.29; S 11.76 found % C 48.44; H 5.91; N 10.23; S 11.71.

Methyl [N-(N'-benzyl)-sulfamoyl]-valinate **7c**
Yield= 95%; **Rf**=0.65 (CH_2Cl_2-MeOH 95-5); foam; $[\alpha]_D$= -11 (c=1 MeOH). **1H NMR** ($CDCl_3$, δ ppm) 7.35 (m, 5H, Ar-H); 5.40 (s broad, 2H, 2NH); 4.15 (s, 2H, CH_2 Bn); 3.80 (d, J= 4.70 Hz, 1H, CH*); 3.65 (s, 3H, OCH_3); 2.10 (m, 1H, iPr); 0.85-0.95 (2d, J=6.80 Hz, 6H, $2CH_3$). **MS** (FAB>0, matrix NOBA): 301([M+H]+). **Anal.** ($C_{13}H_{20}N_2O_4S$) calc % C 52.00; H 6.66; N 9.33; S 10.66 found % C 51.89; H 6.69; N 9.28; S 10.63.

Methyl [N-(N'-benzyl)-sulfamoyl]-leucinate **7d**
Yield= 93%; **Rf**=0.64 (CH_2Cl_2-MeOH 9-1); foam, $[\alpha]_D$= -12 (c=1 MeOH); **NMR** ($CDCl_3$, δ ppm) **1H** 7.35 (m, 5H, Ar-H); 4.85 (d, J= 9.78 Hz, 1H, NHα); 4.45 (t, J= 6.03 Hz, 1H, NH-Bn); 4.15 (d, J=5.58 Hz, 2H, CH_2 Bn); 4.05 (m, 1H, CH*); 3.06 (s, 3H, OCH_3); 1.70-1.85 (m, 1H, *iso*but); 1.40-1.50 (m, 2H, CH_2 leu); 0.90-1.00 (2d, J=3.98 Hz, 6H, $2CH_3$). **13C** 21.7, 23.5 (iPr); 40.5 (Cb); 48.6 (CH_2-Bn); 52.6 (CH_3O); 55.1 (C*); 126.3, 126.8, 128.3 (C Ar,*o,m,p*); 137.0 (C ipso); 173.8 (CO ester). **MS** (FAB>0, matrix NOBA): 315 ([M+H]+); 629 ([2M+H]+). **Anal.** ($C_{14}H_{22}N_2O_4S$) calc % C 53.50; H 7.00; N 8.91; S 10.19 found % C 53.57; H 7.06; N 8.80; S 10.13.

Methyl [N-(N'-benzyl)-sulfamoyl]-phenylalaninate **7e**
Yield= 92%; **Rf**= 0.71 (CH_2Cl_2-MeOH 9-1); **mp**= 126-128°C. **1H NMR** ($CDCl_3$, δ ppm) : 7.35-7.15 (m, 10H, 2Ar-H); 4.90 (d, J=9.4Hz, 1H, NH exch), 4.45 (t, J=16.3 Hz, 1H, NH-Bn exch), 4.40 (m, 1H, CH*); 4.05 (2dd, Jvic=5.43 Hz, Jgem=16.25 Hz, 2H, CH_2 Bn); 3.70 (s, 3H, OCH_3); 3.25 (2dd, Jvic=5.86 Hz, Jgem=16.32 Hz, CH_2 β). **MS** (FAB>0, matrix NOBA) 349 ([M+H]+); 697 ([2M+H]+). **Anal.** ($C_{17}H_{20}N_2O_4S$) calc % C 58.62; H 5.74; N 8.04; S 9.19 found % C 58.72; H 5.69; N 8.01; S 9.16.

Synthesis of sulfahydantoins and their N^2-benzylderivatives; general procedure.
Headline cyclized compounds were obtained by addition of NaOH 4N (5mL) to N-sulfamoylaminoesters **9a-e** or their N-benzyl homologues **7a-e** (10^{-2} mole) in 50 mL of ethanol). After 1h stirring, HCl 10 N were added dropwise (up to pH1) then distilled water (50ml). The medium was extracted with dichloromethane, concentrated under vacuum and purified by chromatography. The first fraction afforded the expected products. The aqueous phase of the extraction contains the saponified sulfamoylamino acid in 10-30% yield.

N-2-benzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **8a**
Yield= 62%; **Rf**= 0.64 (CH_2Cl_2-MeOH 9-1); **mp**= **52**°C. **IR** (KBr, ν cm^{-1}): 1724 (C=O). **1H NMR** ($CDCl_3$, δ ppm): 7.35 (m, 5H, Ar-H); 4.75 (t, J=7.80 Hz,1H, NH); 4.65 (s, 2H, CH_2 Bn); 4.05 (d, J=7.80 Hz, 2H, CH_2). **MS** (FAB>0, matrix GT) 227 ([M+H]+). **Anal.** ($C_9H_{10}N_2O_3S$) calc % C 47.78; H 4.42; N 11.38; S 14.16 found % C 47.64; H 4.38; N 11.42; S 14.09.

(S)(-)] N-2-benzyl-4-methyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **8b**
Yield= 64%; **Rf**= 0.66 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-29.(c=1, $CHCl_3$); **mp**= 98-99°C. **IR** (KBr, ν cm^{-1}): 1721 (C=O). **1H NMR** ($CDCl_3$, δ ppm): 7.40 (m, 5H, Ar-H); 4.80 (s, 1H, NH exch); 4.75 (s, 2H, CH_2 Bn); 4.35 (m, 1H, CH*); 1.60 (d, J=6.88 Hz, 3H, CH_3). **MS** (FAB>0, matrix GT) 241 ([M+H]+). **Anal.** ($C_{10}H_{12}N_2O_3S$) calc % C 50.00; H 5.00; N 11.67; S 13.33 found % C 50.46; H 5.06; N 11.54; S 13.26.

[(S)(-)]N-2-benzyl-4-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **8c**
Yield= 71%; **Rf**= 0.65 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-112 (c=1, $CHCl_3$); **mp**= 63-65°C. **IR** (KBr, ν cm^{-1}): 1715 (C=O). **1H NMR** ($CDCl_3$, δ ppm): 7.55-7.35 (m, 6H, 5Ar-H, NH); 4.70 (s, 2H, CH_2 Bn); 4.15 (m, 1H, CH*); 2.30 (m, 1H, CH-*i*Pr); 0.90-1.10 (2d, J=6.96 Hz, 6H, $2CH_3$). **MS** (FAB>0, matrix GT) 269 ([M+H]+). **Anal.** ($C_{12}H_{16}N_2O_3S$) calc % C 53.73; H 5.97 ; N 10.44; S 11.94 found % C 53.62; H 5.96; N 10.38; S 11.89.

[(S)(-)] N-2-benzyl-4-isobutyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **8d**
Yield= 77%; **Rf**= 0.66 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-75 (c=1, $CHCl_3$); **mp**= 62-64°C. **IR** (KBr, ν cm^{-1}): 1724 (C=O). **NMR** ($CDCl_3$, δ ppm) **1H** 7.35 (m, 5H, Ar-H); 4.64 (s, 2H, CH_2 Bn); 4.05 (m, 1H, CH*); 1.75 (m, 2H, CH_2 β); 1.60 (m, 1H, CH); 0.70-0.80 (2d, J=6.50 Hz, 6H, $2CH_3$). **13C** 21.8 ($2CH_3$ iPr); 24.8 (CH iPr); 40.3 (CH_2 β); 44.7 (CH_2 Bn); 60.2 (C*); 126.6, 127.3, 127.9 (C Ar *o,p,m*); 135.2 (C Bn ipso); 171.6 (CO ester). **MS** (FAB>0, matrix GT) 283 ([M+H]+). **Anal.** ($C_{13}H_{18}N_2O_3S$) calc % C 55.31; H 6.38 ; N 9.92; S 11.34 found % C 55.17; H 6.43; N 9.85; S 11.39.

[(S)(+)] N-2,4-dibenzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **8e**
Yield= 82%; **Rf=** 0.70 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =+73 (c=1, $CHCl_3$); **mp=** 67-69°C. **IR** (KBr, ν cm^{-1}): 1722 (C=O). **1H NMR** ($CDCl_3$, δ ppm) 7.10-7.35 (m, 10H, Ar-**H**); 4.70 (2d, Jgem=14 Hz, 2H, CH_2 Bn); 4.60 (d, J=7.90 Hz, 1H, **NH**, exch); 4.30 (m, 1H, C***H**); 3.05 (2dd, Jgem=15 Hz, $Jvic_1$= 7.85, $Jvic_2$=4.55 Hz, 2H, CH_2 β). **MS** (FAB>0, matrix GT) 317 ([M+H]+). **Anal.** ($C_{16}H_{16}O_3N_2S$) calc % C 60.75; H 5.06 ; N 8.86; S 10.12 found % C 60.61; H 5.09; N 8.78; S 10.07.

[(S)(-)] Methyl [N-sulfamoyl]-alaninate **9b**
Yield=96%; **Rf=** 0.46 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = -18 (c=1 MeOH); **mp=** 67-68°C. **IR** (KBr, ν cm-1): 1746 (C=O); 1341, 1149 (SO_2); 3330, 3270, 3250 (NH). **NMR** ($CDCl_3$, δ ppm) **1H** : 7,05 (d, J=8,8Hz, **NH**); 6,62 (s, 2H, NH_2); 4.20 (dt,1H, J=8.8Hz et 7.2Hz, **CH***); 3.65 (s, 3H, OCH_3); 1.45 (d, J=7.2 Hz, 3H, CH_3). **13C** 17 (CH_3); 50.9 (**C***); 51.8 (OCH_3); 173 (CO) **MS** (FAB>0, NOBA): 183 ($[M+H]^+$). **Anal.** ($C_4H_{10}N_2O_4S$) calc C 26.37; H 5.49; N 15.38; S 17.58 found C 26.45; H 5.42; N 15.28; S 17.86.

[(S)(+)] Methyl [N-sulfamoyl]-valinate **9c**
Yield= 97%; **Rf=**0.46 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$= +9.5 (c=1 MeOH); **mp=** 58-60°C. **IR** (KBr, ν cm-1)**:** 1748 (C=O) ; 1352, 1158 (SO_2). **NMR** ($CDCl_3$, δ ppm) **1H**: 6.40 (d, J=8.25 Hz,1H, NH); 5.45 (s, 2H, NH_2); 4.15 (dd, J=7.13 Hz, 1H, **CH***); 3.78 (s, 3H, OCH_3); 2.20 (m, 1H, CHβ); 0.9 et 1.05 (2d, J=7.16Hz, 6H, 2 CH_3). **13C**: 23.7 (2 CH_3); 24.3 (CH β); 51.7 (CH_3O); 58.2 (**C***); 172.6 (CO methyl ester) **MS** (FAB<0, matrice NOBA): 209 ([M-H]-). **Anal.** ($C_6H_{14}N_2O_4S$) calc % C 34.28; H 6.66; N 13.33; S 15.23 found % C 34.42; H 6.72; N 13.02; S 15.03.

[(S)(-)] Methyl [N-sulfamoyl]-leucinate **9d**
Yield=96%; **Rf=**0.47 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = -21.5 (c=1 MeOH); **mp=** 62-64°C **IR** (KBr, ν cm-1): 1751 (C=O) ; 1348, 1154 (SO_2); 3310 and 2960 (NH). **NMR** ($CDCl_3$, δ ppm) **1H** : 5.80 (s, 1H, **NH** exch); 5.20 (s, 2H, NH_2); 4.25 (t, J=7.40 Hz, 1H, **CH***); 3.66 (s, 3H, OCH_3); 1.85 (m, 1H, *i*Pr); 1.55 (m, 2H, CH_2 β); 0.93 (2d, J=6.80 Hz, 6H, $2CH_3$). **13C**: 22.5 ($2CH_3$ iPr); 23.5 (CHγ); 41.9 (CH β), 52.0 (CH_3O); 57.4 (**C***); 172.8 (CO). **MS** (FAB>0, NOBA): 225 ([M+H]+, 45%). **Anal.** ($C_7H_{16}N_2O_4S$) calc % C 37.50; H 7.14; N 12.50; S 14.28 found % C 37.36; H 7.19; N 12.42; S 14.25.

[(S)(+)] Methyl [N-sulfamoyl]-phenylalaninate **9e**
Yield=97%; **Rf=**0.52 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ = +45 (c=1 MeOH); **mp=** 64°C. **IR** (KBr, ν cm-1): 3480 (NH); 1745 (CO). **NMR** ($CDCl_3$, δ ppm) **1H** : 7.25 (m, 5H, Ar-**H**); 5.50 (d, 1H, J=8.5Hz, NH); 5.00 (s, 2H, NH_2); 4.30 (dt, 1H, CHα); 3.65 (s, 3H, OCH_3); 3.00 (2dd, J_1=5.54Hz, J_2=6.71Hz, Jgem=19.31Hz, 2H, CH_2). **13C**: 39.7 (CH_2Bn); 52.5 (CH_3O); 58.6 (**C***); 127.7 (**C**-para); 129.8 (**C**-ortho); 129.9 (**C**-meta); 137.3 (**C**-ipso); 173.5 (CO ester). **MS** (FAB>0, NOBA): 259 ([M+H]+). **Anal.** ($C_{10}H_{14}N_2O_4S$) calc % C 46.51; H 5.42; N 10.85 S 12.40 found % C 46.42; H 5.37; N 10.78; S 12.30.

[(S)(-)] 4-methyl-1,2,5-thiadiazolidin-3-one dioxide **10b**
Yield= 56%; **Rf=** 0.38 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-12 (c=1, $CHCl_3$); **mp=** 86-87°C. **IR** (KBr, ν cm^{-1}): 1720 (C=O). **NMR 1H** ($CDCl_3$, δ ppm): 8.50 (s, 1H, **NH**, exch); 4.32 (m, 1H, **CH***); 1.50 (d, J=7.2 Hz, 3H, CH_3). **13C**: 17 (CH_3); 59 (**C***), 174 (**CO**). **MS** (FAB>0, matrix GT) 149 ([M+H]+). **Anal.**($C_3H_6N_2O_3S$) calc % C 24.00; H 4.00; N 18.66; S 21.33 found % C 24. 06; H 4.03; N 18.43; S 21.17.

[(S)(-)] 4-isopropyl-1,2,5-thiadiazolidin-3-one dioxide **10c**
Yield= 61%; **Rf=** 0.32 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-18 (c=1, $CHCl_3$); **mp=** 108-110°C. **IR** (KBr, ν cm^{-1}): 1721 (C=O). **1H NMR** ($CDCl_3$, δ ppm): 8.48 (s, 1H, NH); 5.25 (d, J=7.80 Hz, 1H, NH-C*); 4.15 (m, 1H, **CH***); 2.35 (m, 1H, **CH** iPr); 0.9-1.1 (2d, J=6.90 Hz, 6H, $2CH_3$). **MS** (FAB>0, matrix GT) 179 ([M+H]+). **Anal.** ($C_5H_{10}O_3N_2S$) calc % C 33.70; H 5.61; N 15.73; S 17.97 found % C 33.54; H 5.55; N 15.59; S 17.83.

[(S)(-)] 4-isobutyl-1,2,5-thiadiazolidin-3-one dioxide **10d**
Yield= 80%; **Rf=** 0.45 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =-25 (c=1, $CHCl_3$); **mp=** 122°C. **IR** (KBr, ν cm^{-1}): 1718 (C=O). **1H NMR** (DMSO D_6, δ ppm): 8.50 (s, 1H, NH-CO); 5.35 (d, J=7.20 Hz, 1H, NH); 4.50 (m, 1H, **CH***); 0.85-0.95 (2d, J=6.42 Hz, 6H, $2CH_3$); 1.75 (m, 1H, *i*Pr); 1.55 (m, 2H, CH_2β). **MS** (FAB>0, matrix GT) 191 ([M+H]+). **Anal.** ($C_6H_{12}N_2O_3S$) calc % C 37.50; H 6.25; N 14.58; S 16.66 found % C 37.43; H 6.22; N 14.63; S 16.69.

[(S)(+)] 4-benzylthia-2.5-diazolidin-3-one 1,1-dioxide **10e**
Yield= 78%; **Rf**= 0.42 (CH_2Cl_2-MeOH 9-1); $[\alpha]_D$ =+89 (c=1, $CHCl_3$); **mp**= 197-198°C. **IR** (KBr, ν cm^{-1}): 1719 (C=O). **NMR** (DMSO D_6, δ ppm) **1H**: 8.20 (sl, 1H, NH, exch); 7.32 (m, 6H, 5 Ar-**H** and NHβ); 4.42 (m, 1H, C***H**); 3.10 and 2.80 (2dd, Jg=14 Hz; Jv=4 Hz; CH_2 ß). **13C** ($CDCl_3$, δ ppm): 37.2 (CH_2); 61.9 (C*); 127.7, 128.3, 128.7, 136.2 (C-Ar); 171.5 (CO). **MS** (FAB>0, matrix GT) 225 ([M+H]+). **Anal.** ($C_9H_{10}N_2O_3S$) calc % C 47.78; H 4.42; N 12.4; S 14.15 found % C 47.54; H 4.38; N 12.56; S 14.08.

N^{-2}-Benzyl-benzothiadiazolidinone **11**
Yield= 80%; **Rf**= 0,42 (CH_2Cl_2-MeOH 9-1); **mp**= 184-186°C. **IR** (KBr, ν cm^{-1}): 1705 (C=O). **1H NMR** ($CDCl_3$, δ ppm): 8.10 (d, J=6.40 Hz, 1H, Hd); 7.70 (t, J=6.32 Hz, 1H, Hc); 7.35 (m, 6H, Ar (Bn)+Hd); 7.15 (d, 1H, J=7.6 Hz, Ha), 5.05 (s, 2H, CH_2 Bn). **MS** (FAB>0, matrix GT) 289 ([M+H]+). **Anal.** ($C_{14}H_{12}N_2O_3S$) calc % C 58.33; H 4.16; N 9.72; S 11.11 found % C 58.17; H 4.23; N 9.65; S 11.05.

Benzothiadiazinone **12**
Yield= 71%; **Rf**= 0.34 (CH_2Cl_2-MeOH 9-1); **mp**= 229-230°C. **IR** (KBr, ν cm^{-1}): 1679 (C=O). **1H NMR** (DMSO D6, δ ppm): 10.70 (s, 1H, NH-CO); 7.90 (d, J=6.40 Hz,1H, Hd); 7.65 (d, J=6.60 Hz, 1H, Ha); 7.50 (t, J=7.60 Hz, 1H, Hb); 7.20 (t, J=6.60 Hz, 1H, Hc); 6.65 (s, 1H, NH). **MS** (FAB>0, matrix GT) 197 ([M+H]+). **Anal.** ($C_7H_6N_2O_3S$) calc % C 42.42; H 3.03; N 14.14 ; S 16.16 found % C 42.54; H 3.09; N 14.02; S 16.11.

General procedure for nucleosidic condensation
way a An equimolar mixture of solid sulfahydantoin (or its N-benzyl homologue) and 1,2,3,5-tetra-O-acyl-(β,D)-ribofuranose was heated (155°C) with 0.4 % iodine *in vacuo* (20 mm Hg) for 30 mn. The resulting residue was purified by column chromatography (eluent: dichloromethane:MeOH 9:1) to give the nucleoside.
way b A solution of equimolar quantities of sulfahydantoin (1mmole) and acetobromoglucose in acetonitrile was refluxing with DABCO (2Eq) during 4 hours. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane. The organic layer was washed with water and dried with anhydrous sodium sulphate. Purification step was identical to the above described procedure.
way c Sulfahydantoin (5.10-3 M) in hexamethyldisilazane (HMDS) as solvent was refluxing 24h under argon atmosphere. Then the silylating agent was removed *in vacuo* and a solution of acylated sugar (1 Eq) and tin tetrachloride (2 Eq) in 10 mL acetonitrile were successively added. The reaction medium was heating to 60°C during 24h and finally concentrated, washed with a hydrogencarbonate solution, dried and purified in the same conditions as previous procedures.

N^{-2}-benzyl-N^{-6}-[2,3,4,6-tetra-O-acetyl-(β-D)-glucopyranos-1-yl]-benzo-1,2,6-thiadiazin-3-one 1,1-dioxide **15**
(way b) **Yield**= 23%; **Rf**= 0.72 (CH_2Cl_2 -MeOH 9-1); **mp**= 64-65°C; **1H NMR** ($CDCl_3$, δ ppm): 8.15 (d, J=6.32 Hz, 1H, Hd); 7.70 (t, J=7.70 Hz, 1H, Hb); 7.5-7.1 (m, 7H, Ar-**H**); 5.40 (d, 1H, J=10.8 Hz, $H_{1'}$); 5.9 (m, 1H, $H_{4'}$); 5.15 (dd, J=10.80 Hz, 1H, $H_{2'}$); 5.00 (dd, 1H, $H_{3'}$); 4.95 (2d, J=15 Hz, 2H, CH_2 Bn); 3.80-4 (2dd, 2H, $H_{6'}$ et $H_{6''}$); 3.55 (td, 1H, $H_{5'}$); 2.00-2.10 (3s, 9H, $3CH_3$ Ac). **MS** (FAB>0, matrix NOBA): 619 ([M+H]+). **Anal.** ($C_{28}H_{30}N_2O_{12}S$) calc % C 54.36; H 4.85; N 4.53; S=5.17 found % C 54.28; H 4.81; N 4.59; S 5.21.

N^{-2}-benzyl-N^{-6}-[2,3,5-tri-O-acetyl-(β-D)-ribofuranos-1-yl]-benzo-1,2,6-thiadiazin-3-one 1,1-dioxide **16**
(way a) **Rf**= 0.76 (MeOH- CH_2Cl_2 95-5). **1H NMR** ($CDCl_3$, δ ppm) : 8.10 (dd, J=1.58 and 7.75 Hz,1H, Ar-Hd), 7.65-7.60 (td, J=1.62 and 7.72 Hz, 1H, Hb Ar); 7.50-7.2 (m, 7H, Ar-**H**); 5.75 (d, J=7.41Hz, 1H, $H_{1'}$ β); 5.20 (dd, J=15.22 Hz, CH_2 Bn); 5.15 (dd, 1H, $H_{2'}$); 4.85 (dt, J=2.80 and 5.53Hz, 1H, $H_{4'}$); 4,00 (dd, $J_{3'-2'}$-$J_{3'-4'}$ 2.8 and 7.00 Hz,1H, $H_{3'}$); 3.70 (d, 2H, $H_{5'}$ $H_{5''}$); 2-2.05 (2s, 6H, 2 CH_3 OAc); 1.85 (s, 3H, CH_3 OAc 5').

N^{-2}-benzyl-N^{-5}-[2,3,5-tri-O-benzoyl-(β-D)-ribofuranos-1-yl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide **17a**
(way a) **Yield**= 31%; **Rf**= 0.80 (CH_2Cl_2-MeOH 95-5). $[\alpha]_D$ =-17 (c=1, $CHCl_3$); **1H NMR** ($CDCl_3$, δ ppm): 7.35 (m, 20H, 4 Ar-**H**); 6.45 (d, J=7.3 Hz,1H, $H_{1'}$), 5.95 (dd,1H, $H_{3'}$); 5.80 (dd, 1H, $H_{2'}$); 4.85 (m, 2H, $H_{5'}H_{5''}$); 4.5 (m, 1H, $H_{4'}$); 4.65 (dd, J=15.20 Hz, 2H, CH_2 Bn); 4.00 (s, 2H, CH_2 Gly). **MS** (FAB>0, matrix NOBA) 671 (M+H]+), 445 (Osid.Cleav). **Anal.** ($C_{35}H_{30}N_2O_{10}S$) calc % C 62.68; H 4.47; N 4.17; S 4.77 found % C 62.55; H 4.39; N 4.21; S 4.88.

N^{-2}-benzyl-N^{-5}-[2,3,5-tri-O-benzoyl-(β-D)-ribofuranos-1-yl]-4-methyl-1,2,5-thiadiazolidin-3-one1,1-dioxide **17b**
(way c) **Yield**= 49%; **Rf**= 0.85 (CH_2Cl_2-MeOH 97:3); $[\alpha]_D$ =-32 (c=1, $CHCl_3$). **1H NMR** ($CDCl_3$, δ ppm): 7.30-8.20 (m, 20H, Ar); 5.95 (d, J=7.40Hz, 1H, $H_{1'}$β); 5.75 (d, 1H, $H_{3'}$); 5.70 (d, 1H, $H_{2'}$); 4.70 (m, 2H, $H_{5'}$ $H_{5''}$); 4.65 (dd, J= 15.20 Hz, 2H, CH_2 Bn); 4.50 (q, J=7.30 Hz, 1H, C***H**); 4.10 (dd, 1H, $H_{4'}$); 1.35 (d, 3H, CH_3 Ala). **MS** (FAB>0, matrix NOBA) 685 (M+H]+), 445 (Osid.Cleav). **Anal.** ($C_{36}H_{32}N_2O_{10}S$) calc % C 63.15; H 4.67; N 4.09; S 4.67 found % C 63.41; H 4.74; N 4.13; S 4.68.

N^{-2}-benzyl-N^{-5}-[2,3,5-tri-O-benzoyl-(β-D)-ribofuranos-1-yl]-4-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **17c**

(way c) **Yield**= 52%; **Rf**= 0.63 (MeOH-CH_2Cl_2 95-5); $[\alpha]_D$ =-10 (c=1, $CHCl_3$). **1H NMR** ($CDCl_3$, δ ppm): 5.75 (d, J=6.18 Hz, 1H, $H_{1'}$); 5.6 (dd, 1H, $H_{2'}$); 5.2 (dd, $J_{3'-2'}$, $J_{3'-4'}$= 5.89 et 8.32 Hz, 1H, $H_{3'}$); 4.65 (2d, J=15.32Hz, 2H, CH_2 Bn); 4.45 (dd, 1H, H'_4); 4.20-4.30 (2dd, Jgem=13 et Jvic=7.12 Hz, 2H, $H_{5'}$ $H_{5''}$); 4.10 (d, J=3.90 Hz, 1H, CH*); 2.00 (2s, 9H, $3CH_3$ OAc); 1.10 (m, 1H, iPr); 0.95-1.10 (2d, J=6.80 Hz,6H, $2CH_3$). **MS** (FAB>0, matrix NOBA) 527 (M+H]+), 253 (Osid.Cleav). **Anal.** ($C_{23}H_{30}N_2O_{10}S$) calc % C 52.47; H 5.70; N 5.32; S 6.08 found % C 52.65; H 5.76; N5.18; S 6.00.

N^{-2}-benzyl-N^{-5}-[2,3,5-tri-O-acetyl-(β-D)-ribofuranos-1-yl]-4-isobutyl-1,2,5-thiadiazolidin-3-one1,1-dioxide **17d**.

(way c) **Yield**= 67%; **Rf**= 0.56 (CH_2Cl_2-MeOH 95-5); $[\alpha]_D$ =-72 (c=1, $CHCl_3$). **NMR** ($CDCl_3$, δ ppm) **1H**: 7.45-7.28 (m, 5H, Ar-H); 5.60 (d, J=7.82 Hz, 1H, $H_{1'}$); 5.20 (dd, J=6.18 Hz, 1H, $H_{3'}$); 5.08 (dd, 1H, $H_{2'}$); 4.65 (2d, 15.21Hz, 2H, CH_2 Bn); 4.35 (dd, 1H, $H_{5'}$); 4.30 (m, 3H, $H_{4'}$); 4.25 (m, 1H, CH*); 4.10 (dd, 1H, $H_{5''}$); 2.15-1.90 (3s, 9H, 3 OAc); 1.75 (m, 2H, CH_2 β); 1.60 (m, 1H, CH); 0.70-0.80 (2d, J=6.50 Hz, 6H, $2CH_3$). **13C:** 19.2, 20.4, 21.6, 22.7, 23.6 (CH[CH_3]$_2$ and 3xCH_3 OAc); 40.4 (Cβ); 45.9 (CH_2 Bn); 58.9 (C*); 70.3 (C_5); 77.3, 80.2, 82.0 (sug. C_2,C_3,C_4); 88.2 (sug.C_1); 126.8, 128.1, 128.3 (C *o,m,p* Ar); 137.2 (C ipso); 170.8, 174.5 (CO Ac and CO heterocycl). **MS** (FAB>0, matrix NOBA) 541 (M+H]+), 259 (Osid.Cleav). **Anal.** ($C_{24}H_{32}N_2O_{10}S$) calc % C 53.33; H 5.92; N 5.18; S 5.92 found % C 53.56; H 5.98; N 5.12; S 5.88.

N^{-2},4-dibenzyl-N^{-5}-[2,3,5-tri-O-acetyl-(β-D)-ribofuranos-1-yl]-1,2,5-thiadiazolidin-3-one dioxide **17e**.

(way c) **Yield**= 70%; **Rf**= 0,67 (CH_2Cl_2-MeOH 9-1); $\alpha]_D$ =-32 (c=1, $CHCl_3$). **NMR** ($CDCl_3$, δ ppm) **1H**: 7.25-7.35 (m, 10H, 2 Ar-H); 5.50 (d, J=7.82 Hz, 1H, $H_{1'}$); 5.45 (dd, J=6.18 Hz, 1H, $H_{3'}$); 5.15 (dd, 1H, $H_{2'}$); 4.65 (dd, 15.21Hz, 2H, CH_2 Bn); 4.50 (m,1H, C*H); 3.90-4.10 (m, 3H, $H_{5'}$, $H_{5''}$, $H_{4'}$); 3.10-3.3O (2dd, 2H, CH_2 Phe); 2.10-1.95 (2s, 9H, 3 OAc). **13C**: 21.5, 21.8 (3CH_3; OAc); 35.5 (Cβ); 54.8 (CH_2 Bn); 59.8 (Cα); 64.2 (sug.C_5); 69.7, 71.3, 72.4 (sug. C_4 C_3 and C_2); 80.7 (C_1); 128-130 (C Ar *o,m,p*); 135-137 (2 C ipso); 171.0-172.0, 174.5 (CO aglyc. and 3 CO Ac). **MS** (FAB>0, matrix NOBA) 575 (M+H]+), 259 (Osid.Cleav). **Anal.** ($C_{27}H_{30}N_2O_{10}S$) calc % C 56.44; H 5.22; N 4.87; S 5.57 found % C 56.65; H 5.17; N 4.78; S 5.48.

N^{-2}-benzyl-N^{-5}-[2,3,5-tri-O-benzoyl-(β-D)-ribofuranos-1-yl]-4-benzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **18**

(way a) **Yield**= 35%; **Rf**= 0.62 (CH_2Cl_2-MeOH 9-1); $\alpha]_D$ = -111 (c=1, MeOH). **1H NMR** ($CDCl_3$, δ ppm): 7.20-8.20 (m, 20H, 4 Ar-H); 6.25 (t, 1H, J= 5.24Hz, $H_{1'}$); 6.00 (dd, J= 5.29 Hz ,1H, $H_{2'}$); 5.95 (dd, 1H, $H_{3'}$); 5.15 (d broad, 1H, NH, exch); 4.50-4.70 (m, 3H, $H_{5'}$, $H_{5''}$ et $H_{4'}$); 4.40 (m, 1H, CH*); 3.20 (2d, 2H, CH_2 Bn). **MS** (FAB>0, matrix NOBA): 671 ([M+H]+); 445 (osidic cleavage). **Anal.** ($C_{35}H_{30}N_2O_{10}S$) calc % C 62.68; H 4.47; N 4.17; S 4.77 found % C 62.55; H 4.40; N 4.21; S 4.88.

Hydrogenolysis.

To an ethanolic solution of nucleoside (0.1 mM in 3 mL) were added 15 mg Palladium on charcoal (5 %) and ammonium formate (3Eq). The reaction was heating 30-45 mn to 60°C in a ballon equiped with a condenser. Alternatively the same quantity of N-benzylnucleoside can be hydrogenolyzed under ultrasonic irradiation by cyclohexadiene (5 Eq) and Pd-C in a pear-shaped ballon cooled in a water bath. Vibracell 600W transmitter fitted with a microhorn was required; in that case the reaction time was 10 min. The reaction medium was filtered through celite and evaporated under reduced pressure; then the crude debenzylated compound was purified by column chromatography with dichloromethane as eluent.

N^{-5}-[2,3,5-tri-O-acetyl-(β,D)-ribofuranos-1-yl]-4-isobutyl-1,2,5-thiadiazolidin-3-one **19d**

Yield= 75%; **Rf**= 0.55 (CH_2Cl_2-MeOH 95-5). **1HNMR** ($CDCl_3$, δ ppm): 5.55 (d, $J_{1'-2'}$= 7.80 Hz, 1H, $H_{1'}$β); 5.35 (dd, $J_{3'-2'}$= 5.8Hz, $J_{3'-4'}$=2.5Hz, 1H, $H_{3'}$); 5.10 (dd, J=7.75 and 5.80Hz, 1H, $H_{2'}$); 4.35 (dd, J=3.00 et 12.34 Hz, 2H, $H_{5'}$ et $H_{5''}$); 4.15 (t d, J=2.70 et 12.20 Hz, $H_{4'}$); 4.05 (dd, J=12.66 et 2.70 Hz, 1H, CH*); ; 2.05-2.10 (2s, 9H, 3 CH_3 Ac); 2.08 (m, 2H, CH_2 Leu); 1.68 (m, 1H, iPr); 1.10- 0.95 (2d, J=6.00 Hz, 6H, $2CH_3$Leu). **MS** (FAB>0, matrix NOBA) 451 (M+H]+), 259 (Osid.Cleav). **Anal.** ($C_{17}H_{26}N_2O_{10}S$) calc % C 45.33; H 5.77; N 6.22; S 7.11 found % C 45.12; H 5.64; N 6.25; S 7.02.

N^{-5}-[2,3,5-tri-O-benzoyl-(β-D)-ribofuranos-1-yl]-4-benzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **19e**

Yield= 68%; **Rf**= 0.58 (CH_2Cl_2-MeOH 95-5) **1H NMR** ($CDCl_3$, δ ppm): 7.25-7.35 (m, 5H, Ar-H); 5.35 (d, J_{1-2} 7.54Hz, 1H, $H_{1'}$); 5.45 (dd, J=5.28 Hz, 1H, $H_{3'}$); 5.12 (dd, J=5.30Hz, 1H, $H_{2'}$); 4.50 (dd,1H, C*H); 3.90-4.10 (m, 3H, $H_{5'}$, $H_{5''}$, $H_{4'}$); 3.10-3.30 (2dd, Jgem=7.95 and Jvic=16 Hz, 2H, CH_2 Phe); 2.08 (2s, 9H, 3OAc). **MS** (FAB>0, matrix NOBA) 485 (M+H]+), 259 (Osid.Cleav). **Anal.** ($C_{20}H_{24}N_2O_{10}S$) calc % C 49.58; H 4.95; N 5.78; S 6.61 found % C 49.67; H 5.02; N 5.85; S 6.54.

Ammonolysis

The tri-O-acyl nucleosides **18-19** were added at 0°C to a saturated solution of methanolic ammonia. The reaction was stirred overnight and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent dichloromethane with methanol gradient 0-15%.

N^5-[(β–D)-ribofuranos-1-yl)-4-isobutyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **20d**

Yield= 85%; **Rf**= 0.48 (CH_2Cl_2-MeOH 85-15); $[\alpha]_D$=-44 (c=1 MeOH). **1H NMR** (DMSO d6, δ ppm): 6.35 (s, 1H, N-H exch); 5.25 (d, J= 7.60 Hz, 1H, $H_{1'}$, β); 5.05 (mb, 3H, OH osid, exch); 4.30 (dd, J= 5.8Hz and =2.50 Hz, 1H, $H_{3'}$); 4.25 (dd,1H, $H_{2'}$); 4.25 (m, 2H, $H_{5'}$ et $H_{5''}$); 3.85 (m, $H_{4'}$); 4.00 (dd,1H, CH*); 2.08 (m, 2H, CH_2 Leu); 1.65 (m, 1H, *i*Pr); 0.95- 0.90 (2d, 6H, 2 CH_3 Leu). **MS** (FAB>0, matrix NOBA) 325 (M+H]+), 133 (Osid. Cleav). **Anal.** ($C_{11}H_{20}N_2O_7S$) calc % C 40.74; H6.17; N 8.64; S 9.88 found % C 40.45; H 6.13; N 8.65; S 9.74.

N^5-[(β–D)-ribofuranos-1-yl)-4-benzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **20e**

Yield= 88%; **Rf**= 0.52 (CH_2Cl_2-MeOH 85-15) $[\alpha]_D$=-47 (c=1 MeOH) **1H NMR** (DMSO d6, δ ppm): 7.25-7.35 (m, 6H, Ar-H and NH); 5.72 (t, 1H, 5'-OH, exch); 5.08 (d, $J_{1'-2'}$=7.02 Hz, 1H, $H_{1'}$); 4.35 (dd, J= 5.00 Hz, 1H, $H_{3'}$); 5.12-5.06 (2 d, broad, 2H, 2'OH, 3'OH, exch), 4.17 (dd, J=5.30 Hz,1H, $H_{2'}$), 4.50 (dd,1H, C*H); 3.50-3.90 (m, 3H, $H_{5'}$, $H_{5''}$, $H_{4'}$); 3.10-3.30 (2dd, J_1=8.45 and J_2=4.68 Hz, 2H, CH_2 Phe). **MS** (FAB>0, matrix NOBA) 359 (M+H]+), 133 (Osid.Cleav). **Anal.** ($C_{14}H_{18}N_2O_7S$) calc % C 46.92; H5.02; N 7.82; S 8.93 found % C 48.67; H 4.89; N 7.91; S 8.84.

N^2-[(β–D)-ribofuranos-1-yl)-4-benzyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide **21**

Yield= 84%; **Rf**= 0.54 (CH_2Cl_2-MeOH 85-15); $[\alpha]_D$=-17 (c=1, MeOH). **1H NMR** (DMSO d6, δ ppm): 7.25-7.35 (m, 5H, Ar-H); 6.02 (t, 1H, $J_{1',2'}$= 7Hz, $H_{1'}$); 5.25-5.00 (m broad, 4H, OH, NH, exch); 4.80 (dd, J= 5.29 Hz, 1H, $H_{2'}$); 4.60 (dd, J=5.34 Hz, 1H, $H_{3'}$); 3.55-3.90 (m, 3H, $H_{5'}$, $H_{5''}$ et $H_{4'}$); 4.35 (q, 1H, CH*); 3.15 (2dd, Jgem=8.32 and Jvic=4.70 Hz, 2H, CH_2 Bn). **MS** (FAB>0, matrix NOBA) 359 (M+H]+), 133 (Osid.Cleav). **Anal.** ($C_{14}H_{18}N_2O_7S$) calc % C 46.92; H5.02; N 7.82; S 8.93 found % C 47.10; H 5.13; N 7.65; S 8.74.

references

1. a.Harmon E.H, Robins R.K, Townsend L.B. *Chemistry and Biology of nucleosides and nucleotides* Academic Press N.Y. **1978.** b.Périgaud C.; Gosselin G.; Imbach J-L. *Nucleosides Nucleotides* ; **1992**, *11*, 903.
2. Nishimura H.; Mayama M.; Komatsu Y.; Shimaoka N.; Tanaka Y. *J.Antibiot* **1964**, *17*, 148.
3. El Barbary A.; Khodair A.I.; Pedersen E.B.*J.Org.Chem* **1993**, *58*, 5994-5999. El Barbary A.; Khodair A.I.; Pedersen E.B.*Arch. Pharm.* **1994**, *327*, 653. for a review concerning the hydantoins see Lopez C.A.; Trigo G.C. *Adv.Heterocycl.Chem.* **1985**, *38*, 177. Concerning the chemistry of the sulfamides see: Benson G.A.; Spillane W.J.*Chem. Rev.* **1980**, *80*, 151.
4. a. Aouf N.; Dewynter G.; Montero J-L.*Tetrahedron Lett.* **1991**, *32*, 6545. b. Coker J.N.; Kohlhase W.L.; Martens T.F.; Rogers A.; Allan G.G. *J.Org.Chem* **1962**, *27*, 3201. c. Maki Y.; Masugi T.; Ozeki K.*Chem.Pharm. Bull.Jap* **1973**, *21*, 2466. d. Dewynter G.; Aouf N.; Criton M.; Montero J-L. *Tetrahedron* **1993**, *49*, 65.
5. Dewynter.G.; Montero, J-L. *C.R.Acad.Sci. Paris ; série II,* **1992**, *315,* 1675-1692
6. Mitsunobu O.*Synthesis* **1981**,1.
7. a. Niedballa U.; Vorbrüggen H. *Angew. Chem. Int.Ed.* **1970**, *9*, 461. b.Niedballa U.; Vorbrüggen H. *J. Org. Chem.* **1974**, *39*, 3654; 3660; 3668; 3672. c.Vorbrüggen H.; Bennua B. *Chem. Ber.* **1981**, *114*, 1279. d.Vorbrüggen H.; Krolikiewicz K.; Bennua B. *Chem. Ber.* **1981**, *114*, 1234
8. a. Hilbert G.E.; Johnson,T.B. *J.Amer. Chem. Soc.* **1930**, *52*, 2001 and 4489. b. Pliml J.; Prystas M. *Adv. Heteroyclic Chem.* **1967**, *8*, 115.
9. a. Sato T.; Shimadate T.; Ishido Y. *Nippon Kagaku Zasshi* **1960**, *81*, 1440. b. Imai K.; Nohara H.; Honjo M. *Chem. Pharm. Bull* . **1966**, *14*, 1377.
10. a. Gosselin G.; Barrascut J-L; Imbach J-L. *L'actualité Chimique* **1979**, *3,* 7 and *4*, 13 .b. Ueda T. *Chemistry of Nucleosides and Nucleotides;* Townsend L.B. Ed; Plenum Press, New York , **1988.**
11. The modeling calculations were made with the *GenMol* Program: Pèpe G.; Siri D. *Stud. Phys. Theor. Chem.* **1990**, *71*, 93.

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