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1,3-Dipolar Cycloadditions of Nitrones to α,β-Unsaturated γ-Lactams Derived from (*S*)-Pyroglutaminol[1]

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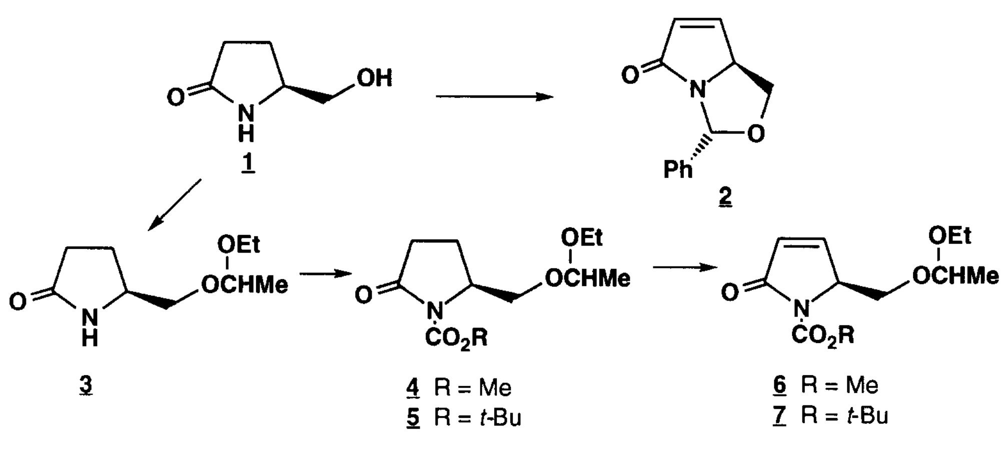
Abstract *: α,β-Unsaturated γ-lactams undergo regio- and stereoselective 1,3-dipolar cycloadditions with N-benzyl and N-methyl nitrones and can act as acceptors in conjugate addition of N-methylhydroxylamine. These reactions give access to highly functionalized pyrrolidones.*

Diastereoselective 1,3-dipolar cycloadditions of nitrones to dipolarophiles play an important role in organic synthesis.[2] The importance of optically pure substituted pyrrolidine units associated with various bioactive products led us to study the cycloaddition of nitrones to chiral protected α,β-unsaturated γ-lactams for the construction of highly functionalized heterocycles. The reactions were tested with lactams **2**, **6**, and **7** derived from (*S*)-pyroglutaminol **1**[3,4] by O,N-diprotection and phenylselenation followed by oxidative elimination.

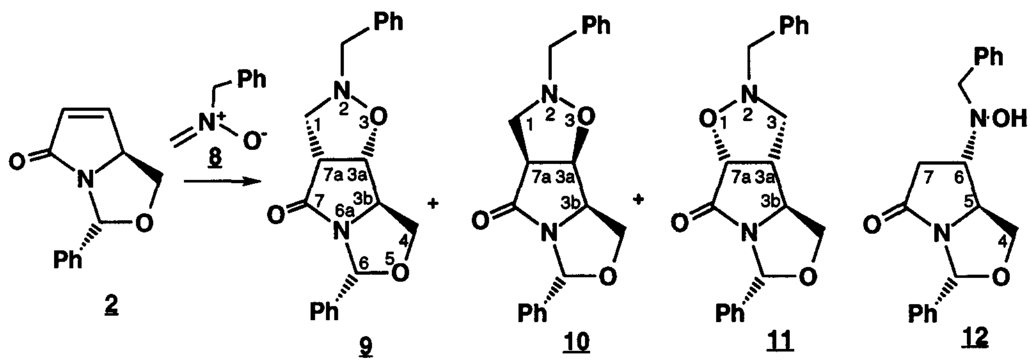


Scheme 1

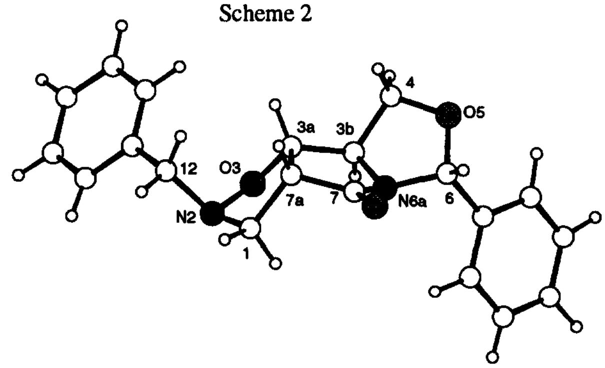
The lactam **2** was prepared with slight modifications[5] of the previously described procedure.[6] The pyrrolidones **4**[7,8] (95%) and **5** (93%) were readily obtained from the known acetal **3**[4,9-13] and converted to **6**[13] (79%) and **7** (75%) (Scheme 1).

a. N-Benzylnitrone **8**

The cycloaddition reaction of *N*-benzylnitrone **8** to the rigid bicyclic α,β-unsaturated lactam **2** was carried out in toluene at reflux to afford a major adduct **9** isolated in 75% yield (Scheme 2).[14] The regioselectivity observed with 1,2-disubstituted electron-deficient alkenes,[2] and particularly with α,β-unsaturated γ-lactones,[15] together with the consideration of steric factors, favour the structure **9** for this original 5,5,5-fused ring system. It could result from an attack of the convex face of the dipolarophile **2** with the anticipated regioselectivity. However, the stereostructure of **9** was rather difficult to ascertain by spectral analysis. In ^{1}H NMR, no significant coupling was observed between the proton NOCH of the isoxazolidine ring (C-3a-H, 4.61 ppm, J = 8 Hz) and the proton NCH of the pyrrolidone ring (C-3b-H, 4.06 ppm). In addition, the ^{1}H NMR spectrum showed very broad absorptions for the methylene α to N-2 (C-1-H_2), due to the relatively slow inversion of this isoxazolidine nitrogen.[16] Since few examples of nitrone cycloaddition to α,β-unsaturated amides have been studied[17] and related 1,3-dipolar cycloaddition of benzonitrile oxide to cinnamic esters and amides were reported to occur with different regioselectivities,[18] the structure **9** was proved by X-ray analysis (Fig).[19]



Scheme 2



The reaction between **2** and *N*-benzylnitrone **8** also led to small amounts of two cycloadducts **10** (5%) and **11** (3%) and to **12** resulting from the 1,4-addition of *N*-benzylhydroxylamine (4%, structure of **12** will be discussed later with its *N*-methyl analog). The NMR analysis of **10** supported the diastereomeric structure, as comparison of chemical shifts of proton and carbon atoms at the ring junction (C-3a and C-7a, Table) in **9** and **10** excluded the alternate regioisomers. Furthermore, the coupling between C-3a-H and the vicinal C-3b-H in **10** (~ 6.5 Hz) agreed with a *cis* relationship. In the ^{13}C NMR spectrum of the minor cycloadduct **11**, the downfield shift of the carbon signal NO<u>C</u>H and the upfield shift of the adjacent methine signal (NCH_2<u>C</u>H) of the isoxazolidine ring, as compared to these resonances in **9** (Table), support the regioisomeric structure.[20] The configurations were attributed on the basis of the very small coupling (~1.5 Hz) between the protons NCH of the pyrrolidone ring and N-CH_2C<u>H</u> of the isoxazolidine, compatible with an expected dihedral angle near 110° in a *trans* relationship.

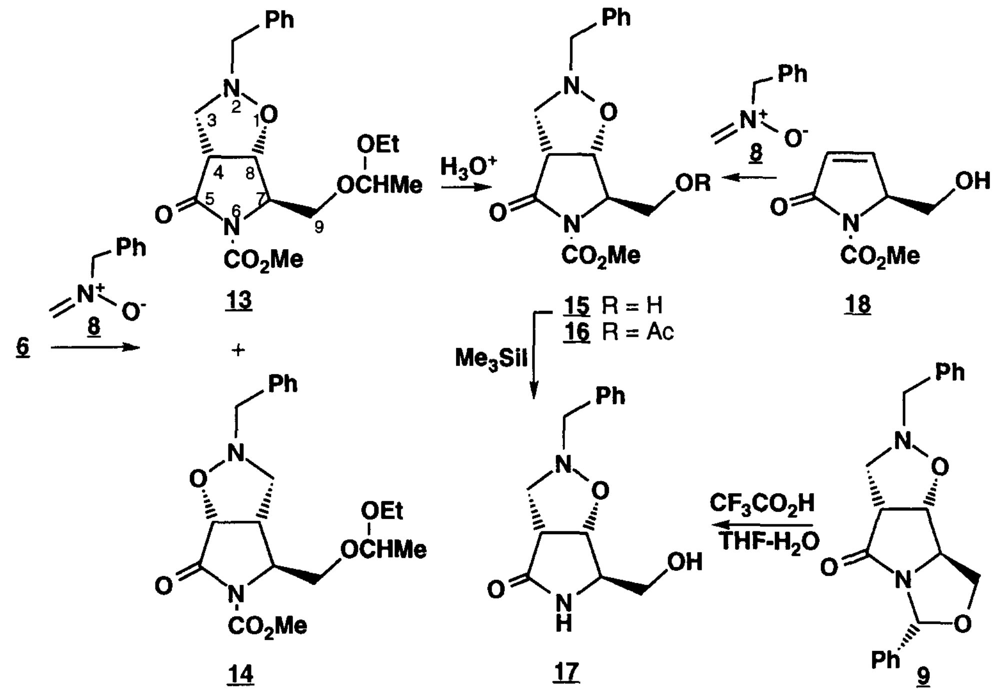
These results indicate very high regioselectivity and diastereoselectivity of this 1,3-dipolar cycloaddition.

Table : Comparison of relevant chemical shifts (^{1}H and ^{13}C) of isoxazolidine part of cycloadducts ($CDCl_3$, δ = 0, TMS)

δ / isoxazolidine	NOC<u>H</u>	NO<u>C</u>H	NCH_2C<u>H</u>	NCH_2<u>C</u>H
9	4.61	77.5	3.59	54.2
10	4.81	73.62	3.74	55.19
11	4.76	81.87	3.14	42.93
13	4.56	76.4 *	3.56	52.64
14	4.76	79.89	3.10	42.70
15	4.66	76.3*	3.63	52.64
16	4.54	76.0	3.56	52.4
17	4.55	78.91*	3.37	51.02
20	4.64	77.56	3.60	54.82
21	4.70	81.93	3.14	43.31
24	4.60	75.89	3.55	53.12
25	4.72	80.02	3.13	43.05
27	4.56	75.76	3.5	53.03
28	4.68	80.01	3.08	42.69

*weak and broad signal

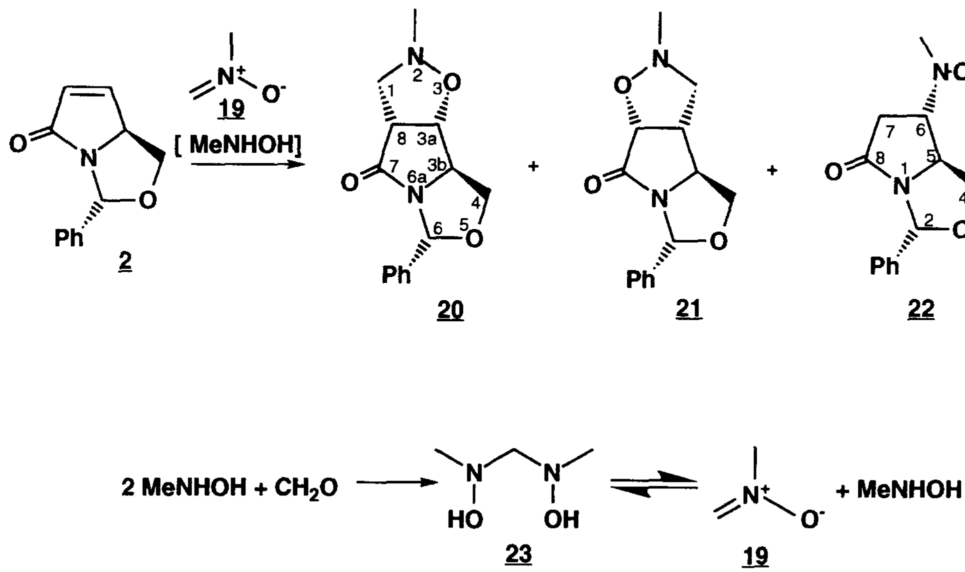
Similar experimental conditions applied to the *N*-methoxycarbonyl α,β-unsaturated γ-lactam **6** gave rise to the cycloadduct **13** (62%)[14] along with the regioisomer **14** (8%) but with incomplete conversion of the dipolarophile. Although the proton signal C-8-H is masked by the acetal proton, NMR data of the major adduct were compatible with the stereostructure **13** and were corroborated by those of derivatives **15** and **16**. Furthermore, the structure **13** was confirmed by a chemical correlation with the primary alcohol **17**, obtained by acid hydrolysis of **9** (Scheme 3). The deprotection of the primary alcohol function of **13** was achieved using very mild conditions to give **15** in 77% non optimized yield. This derivative was converted to **17** in poor yield (10%) by treatment with trimethylsilyl iodide. This correlation was carried out only to confirm the structural assignment. No effort was made to improve the yield, since the reverse sequence using the recently reported selective deprotection of amide carbamates[21](exemplified with the compound **24** in scheme 6) was more efficient.[22] The intermediate **15** could alternatively be obtained (31%) through the cycloaddition of *N*-benzylnitrone **8** to the α,β-unsaturated lactam **18**.[13]



Scheme 3

b. N-Methylnitrone **19**

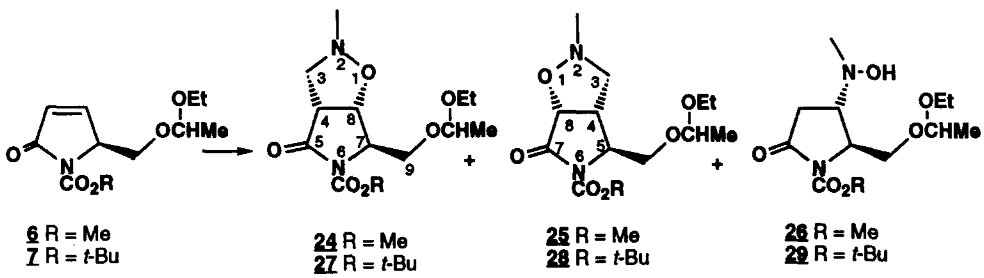
1,3-Dipolar cycloaddition with *N*-methylnitrone **19** gave more complex mixtures. The *N*-methyl nitrone was prepared from *N*-methylhydroxylamine hydrochloride and paraformaldehyde in the presence of powdered anhydrous K_2CO_3 in toluene, and used after filtration without purification, as previously described[23]. This mild method avoided alkaline reaction medium generally used to generate *N*-methylnitrone *in situ*.[24,25] The reaction of this nitrone with bicyclic lactam **2** afforded a mixture of three main compounds **20**, **21** and **22**, respectively isolated in 56, 5, and 35% yield by flash chromatography on silica gel (Scheme 4). ^1H and ^{13}C NMR data of **20** were compared with those of **9** and were found to be in full agreement with the same regio- and stereo-structures (Table). The relevant ^{13}C chemical shifts of **21**, closely related to those of *N*-benzyl cycloadduct **11** (Table) allowed us to assign the regioisomeric structure. The configurations were deduced from the coupling constants of the proton NCH of the pyrrolidone ring (3.90 ppm, J ~ 9.5, 6.5 and 1.5 Hz).



Scheme 4

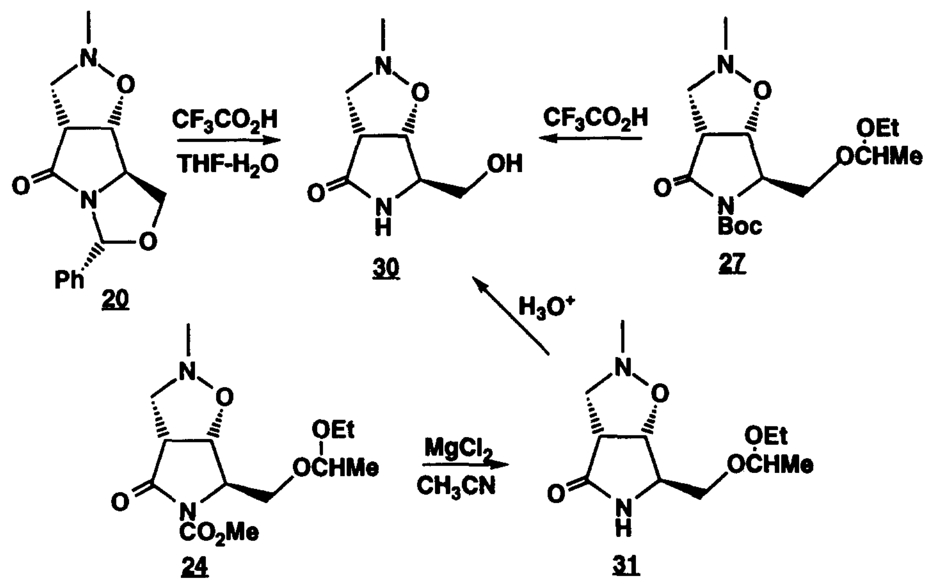
The compound **22** resulted from a conjugate addition of *N*-methylhydroxylamine to the α,β-unsaturated lactam **2,** as shown by the highest significant peak observed at m/z 248 in its mass spectrum. The ^1H NMR spectrum of **22**, very similar to that of **12**, indicated the presence of one proton exchangeable with D_2O at 6.55 ppm and the absence of an OCH resonance ; the signals at 2.85 and 2.59 ppm (partially masked by the NMe singlet) were coupled with the proton C-6-H at 3.28 ppm and could be related to a methylene $C\underline{H}_2CHN$ (C-7-H_2) but the corresponding peak was not well visible in the ^{13}C spectrum. On the other hand, two NCH carbon signals were observed at 69.69 and 62.76 ppm. The formation of **22** in significant amounts could be explained by the presence of *N*-methylhydroxylamine in the reaction medium, coming from the starting hydrochloride or from an aminal intermediate **23** ; it probably reflects the incomplete depolymerization of paraformaldehyde (Scheme 4). The lactam **2** and *N*-methylhydroxylamine hydrochloride upon heating in toluene in the presence of K_2CO_3 afforded the compound **22** (24%), together with starting compound **2**, whereas the conjugate addition of *N*-benzylhydroxylamine to the same α,β-unsaturated lactam gave rise to **12** in higher yield (75%). Only one diastereomer could be detected in these experiments. It is interesting to note that these 1,4 addition reactions proceeded with high stereoselectivity as the related conjugate addition of amines to (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one.[26] The configuration 6*S* was first assigned taking into consideration steric hindrance due to the oxazolidine methylene. Since the configuration at C-6 in such bicyclic systems are not deductible from the coupling constant between the protons C-6-H and C-5-H ($J \sim 5$ Hz), the structure **22** was confirmed by NOE observed between C-6-H (3.28 ppm) and one of the protons of the oxazolidine methylene (C-4-H) at 3.71 ppm. These diastereoselective 1,4 additions could be extended and applied to the synthesis of interesting chiral 3-amino substituted pyrrolidones and pyrrolidines.

The *N*-alkoxycarbonyl lactams **6** and **7** gave similar results, leading principally to 1,3-dipolar cycloadducts **24** (56%) and **27** (54%), along with small amounts of **25** (7%) and **28** (5%) and hydroxylamines **26** (25%) and **29** (15%) (Scheme 5).



Scheme 5

The compounds **20** and **27** were correlated through the deprotected primary alcohol **30** obtained by acidic treatment with CF_3CO_2H. The selective cleavage of amide carbamates with magnesium salts[21] was applied to **24** to afford **31**, which was converted to the same alcohol **30** by mild acid hydrolysis (Scheme 6).



Scheme 6

Thus, the 1,3-dipolar cycloaddition of the *N*-methylnitrone occurred also with high regio- and diastereoselectivity. The formation of a minor regioisomer has been already observed in the addition of cyclic nitrones to alkyl (*E*)-crotonates.[27]

On the other hand, the conjugate addition of *N*-methylhydroxylamine could be minimized or avoided by modification of the corresponding nitrone preparation and the yield of the major cycloadducts could probably be optimized. Thus, starting from the α,β-unsaturated lactam **2**, the generation of *N*-methylnitrone *in situ* using a two-fold excess of *N*-methylhydroxylamine hydrochloride and paraformaldehyde, led to the improved yield (75%) of the major adduct **20**.

In conclusion, cycloaddition of nitrones (or conjugate addition of amino nucleophiles) to conveniently protected α,β-unsaturated lactams, allowing the creation of two (or one) asymmetric centers on the pyrrolidone ring, constitutes an useful access to multifunctional pyrrolidones and pyrrolidines. The cycloadditions of more complex nitrones and other dipoles such as nitrile oxides, as well as synthetic potentialities of these methods, are under investigation in our laboratory.

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EXPERIMENTAL SECTION

Melting points were taken on a microscope Leitz. Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations in $CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, $\delta = 0$ ppm) from Bruker AC200, AC250, AM300 or AM400; coupling constants *J* values are given in Hertz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). ^{13}C NMR spectra were recorded on AC250 (62.5 MHz) or AM300 (75 MHz). Mass spectra and high resolution mass spectra were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Unless stated otherwise, all experiments were performed under argon atmosphere. Usual workup means that organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum.

(5*S*)-1-*tert*-Butoxycarbonyl-5-(1-ethoxy)ethoxymethyl pyrrolidin-2-one 5. To a stirred solution of (5*S*)-5-(1-ethoxy)ethoxymethyl pyrrolidin-2-one **3** (13.41 g, 71.7 mmol) in dry CH_2Cl_2 (21.5 mL) at room temperature were added successively triethylamine (10.0 mL, 71.7 mmol), a solution of di-*tert*-butyldicarbonate (31.30 g, 143.4 mmol) in CH_2Cl_2 (35 mL) and 4-dimethylaminopyridine (8.80g, 72.0 mmol). The mixture was stirred at room temperature for 0.25 h. prior to the removal of the solvent under reduced pressure. The residue was purified by flash chromatography (eluent : heptane-Et_2O 2 : 8). (5*S*)-1-*tert*-Butoxycarbonyl-5-(1-ethoxy)ethoxymethyl-1-pyrrolidin-2-one **5** (mixture of diastereomers) was obtained as a colorless oil (19.13 g, 93%). Analysis for $C_{14}H_{25}NO_5$: calcd.% : C = 58.51, H = 8.77, N = 4.87 ; found % : C = 58.43, H = 8.63, N = 4.93. MS : 288 $(M + H)^{+\cdot}$, 259, 257, 201, 185, 159, 142, 129 (100%), 98. IR : 2990, 1782, 1749, 1709, 1475, 1450. ^1H NMR (250 MHz) : 4.68 (m, 1H, OCHO), 4.26 (m, 1H, C-5-H), 3.85 -3.36 (2 OCH_2), 2.70 (m, 1H), 2.38 (m, 1H), 2.12 (m, 1H), 2.03 (m, 1H) : C-3-H_2 and C-4-H_2, 1.53 (s, 9H, *t*-Bu), 1.28 (2d, 3H, *J* = 5.5, $CH\underline{H}_3$), 1.19 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 174.66.(NCO), 149.78 (NCO_2), 99.69-99.33 (OCHO), 82.61 (C*, *t*-Bu), 65.49-65.12 (OCH_2), 61.11-60.72 (OCH_2), 57.27 (NCH), 31.97 (C-3), 27.95 (CH_3, *t*-Bu), 21.30 (C-4), 19.54-19.41 ($CH\underline{C}H_3$), 15.15 ($CH_2\underline{C}H_3$).

(5*S*)-5-(1-Ethoxy)ethoxymethyl-1-methoxycarbonyl-3-pyrrolin-2-one 6. To a stirred solution of LiHMDS (1M in cyclohexane-THF, 23.3 mL) in anhydrous THF (194.0 mL) was added at - 78°C a solution of (5*S*)-5-(1-ethoxy)ethoxymethyl-1-methoxycarbonyl pyrrolidin-2-one **4** (4.76 g, 19.4 mmol) in THF (27.0 mL). The mixture was stirred for 0.5 h. at -78°C before the addition of a solution of PhSeCl (3.75 g, 19.6 mmol) in THF (19.0 mL). A saturated aqueous solution of NH_4Cl (30 mL) was added to the mixture after being stirred at - 78°C for 1.5 h and the crude product was extracted with EtOAc. The residue obtained after usual workup was dissolved in CH_2Cl_2 (132 mL). To this solution were added at 0°C pyridine (4.7 mL) and H_2O_2 (30% w/v solution, 23.0 mL). The mixture was stirred for 2 h. at 0°C and extracted with CH_2Cl_2 after addition of aqueous solution of Na_2CO_3 (aqueous 10% w/v solution). The product obtained after usual workup was purified by flash chromatography (eluent : pentane-Et_2O 2 : 8) to give **6** as a pale yellow oil (3.73 g, 79%). HRMS : calcd for $C_{10}H_{14}NO_5$ (M-CH_3) : 228.0872, found : 228.0900. MS : 228 (M - CH_3)$^{+\cdot}$, 213, 198, 154 (100%), 141, 109, 73. IR : 1792, 1736. ^{1}H NMR (250 MHz) : 7.34 (m, 1H, C-4-H), 6.16 (dd, 1H, $J_{3,4}$ = 6 , J' = 1, C-3-H), 4.77 (m, 1H, C-5-H), 4.68 (m, 1H, OCHO), 3.91 (s, 3H, CO_2CH_3), 4.10 and 4.02 (2dd, 1H, J = 10, J' = 3.5), 3.68, 3.58 and 3.46 (3m, 3H) : 2 OCH_2, 1.29 (2d, 3H, J = 5.5, CHC$\underline{H}_3$), 1.19 (t, 3H, J = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (62.5 MHz) : 168.3 (CO), 151.2 (NCO_2), 149.9 and 126.3 (CH=CH), 99.5-99.3 (OCHO), 62.6 (OCH_2), 61.0-60.7 (OCH_2), 61.8-61.7 (NCH), 52.9 (OCH_3), 19.1 (CH$\underline{C}H_3$), 14.7 ($CH_2\underline{C}H_3$).

(5*S*)-1-*tert*-Butoxycarbonyl-5-(1-ethoxy)ethoxymethyl-3-pyrrolin-2-one 7. To a stirred solution of LDA (18.1 mmol) in anhydrous THF (70.0 mL) at -78°C was added a solution of the lactam **5** (4.34 g, 15.1 mmol) in THF (7.3 mL). The mixture was stirred for 0.5 h. at -78°C before the addition of a solution of PhSeCl (3.05 g, 15.9 mmol) in THF (7.3 mL). A saturated aqueous solution of NH_4Cl (50 mL) was added to the mixture after being stirred at - 78°C for 1 h. and the crude product was extracted with EtOAc. The residue obtained after usual workup was dissolved in CH_2Cl_2 (100 mL). To this solution were added at 0°C pyridine (3.2 mL) and H_2O_2 (30% w/v solution, 17.5mL). The mixture was stirred for 1.25 h. at 0°C and extracted with CH_2Cl_2 after addition of aqueous solution of Na_2CO_3 (10%, 45 mL). The product obtained after usual workup was purified by flash chromatography (eluent heptane-Et_2O : 2 : 8) to give **7** as a pale yellow oil (3.23 g, 75%). Analysis for $C_{14}H_{23}NO_5$: calcd.% : C = 58.93, H = 8.13, N = 4.91 ; found % : C = 58.62, H = 8.23, N = 4.78. IR : 2990, 1775, 1738, 1712, 1480, 1460. ^{1}H NMR (300 MHz) : 7.29 (m, 1H, C-4-H), 6.13 (dd, 1H, $J_{3,4}$ ~ 6 , J' ~ 1, C-3-H), 4.69 (2m, 2H, OCHO and C-5-H), 4.12 and 4.02 (2dd, 1H, J ~ 10, J' ~ 3.5), 3.71 (m, 2H), 3.44 (m, 1H) : 2 x OCH_2, 1.57 (s, 9H, *t*-Bu), 1.28 (2d, 3H, J = 5.5, CHC$\underline{H}_3$), 1.19 (t, 3H, J = 7, $CH_2C\underline{H}_3$).

Reaction between the lactam 2 and *N*-benzyl-nitrone 8.

To a stirred solution of the lactam **2** (638 mg, 3.17 mmol) in anhydrous toluene (9.0 mL) at room temperature was added *N*-benzylnitrone **8** (472 mg, 3.50 mmol) in toluene (8.0 mL) and the mixture was heated at 110°C for 7 h. Flash chromatography of the residue obtained after removal of the solvent (eluent : heptane-Et_2O from 2 : 8 to 1 : 9) afforded the compounds **9** (800 mg, 75%), **10** (51 mg, 5%), **11** (32 mg, 3%) and **12** (40 mg, 4%).

(3a*S*, 3b*R*, 6*R*, 7a*R*)-2-Benzyl-6-phenyl-hexahydro-3,5-dioxa-2,6a-diazacyclopenta[*a*]pentalene-7-one 9. Colorless crystals. Mp : 110-2°C (Et_2O), $[\alpha]_D^{25}$ = + 153 (c = 1.14). Analysis for $C_{20}H_{20}N_2O_3$: calcd.% : C = 71.41, H = 5.99, N = 8.33 ; found % : C = 71.32, H = 5.87, N = 8.21. MS : 336 ($M^{+\cdot}$, 100%), 307, 229, 201, 173, 156, 131, 118, 105, 91, 77. IR : 3024, 2851, 1702, 1496, 1457. ^{1}H NMR (300 MHz) : 7.45, 7.35 and 7.29 (3m, 10H, ArH), 6.28 (s, 1H, OCHN), 4.61 (d, 1H, $J_{3a,7a}$ = 8, $J_{3a,3b}$ < 1, C-3a-H), 4.25 (dd, 1H, $J_{4a,4b}$ = 8, $J_{3b,4a}$ ~ 7, C-4-Ha), 4.06 (dd, 1H, $J_{3b,4a}$ ~ 7, $J_{3b,4b}$ ~ 9, C-3b-H), 3.96 (2H, C$\underline{H}_2$Ph), 3.59 (dd, 1H, $J_{3a,7a}$ ~ $J_{7a,1}$ ~ 8, C-7a-H), 3.52 (m, 1H, C-1-Ha), 3.44 (dd, 1H, $J_{4a,4b}$ = 8, $J_{3b,4b}$ ~ 9, C-4-Hb), 2.83 (m, 1H, C-1-Hb). ^{13}C NMR (62.5 MHz) : 177.6 (NCO), 138.4 and 136.7 (C*, Ar), 128.7, 128.6, 128.5, 127.6 and

126.0 (CH, Ar), 87.8 (OCHN), 77.5 (NOCH), 68.6 (OCH_2), 66.2 (NCH), 61.2 (N<u>C</u>H_2Ph), 58.7 (NCH_2), 54.2 (NCH_2<u>C</u>H).

(3a*R*, 3b*R*, 6*R*, 7a*S*)-2-Benzyl-6-phenyl-hexahydro-3,5-dioxa-2,6a-diazacyclopenta[*a*]pentalene-7-one 10. White crystals. Mp : 83-4°C (CH_2Cl_2-pentane), $[\alpha]^{25}_D$ = + 120 (c = 1.77). HRMS calcd for $C_{20}H_{20}N_2O_3$: 336.1474, found : 336.1462. MS : 336 ($M^{+\cdot}$), 172, 161, 160, 147, 134, 105, 91(100%), 77. IR : 3010, 1702, 1496, 1456, 1403. ^1H NMR (250 MHz) : 7.45, and 7.34 (2m, 10H, ArH), 6.36 (s, 1H, OCHN), 4.81 (bdd, 1H, $J_{3a,3b}$ ~ 6.5, $J_{3a,7a}$ ~ 7, C-3a-H), 4.17 (m, 1H, C-3b-H), 4.13-3.95 (C-4-H_2, C<u>H</u>Ph), 3.89 (d, 1H, J = 13, C<u>H</u>Ph), 3.74 (dd, 1H, $J_{3a,7a}$ ~ $J_{7a,1}$~ 7, C-7a-H), 3.68 (m, 1H, C-1-Ha), 2.68 (m, 1H, C-1-Hb). ^{13}C NMR (75 MHz) : 176.49 (NCO), 136.62 (C*, Ar), 128.89, 128.72, 128.56, 128.50, 127.69 and 126.02 (CH, Ar), 87.23 (OCHN), 73.62 (NOCH), 65.36 (OCH_2), 62.43 (NCH), 61.97 (NCH_2), 57.94 (NCH_2), 55.19 (NCH_2<u>C</u>H).

Cycloadduct 11 : (3a*R*, 3b*S*, 6*R*, 7a*R*)-2-Benzyl-6-phenyl-hexahydro-1,5-dioxa-2,6a-diazacyclopenta[*a*] pentalene-7-one. Colorless oil. $[\alpha]^{23}_D$ = + 87 (c = 0.59). HRMS calcd for $C_{20}H_{20}N_2O_3$: 336.1474, found : 336.1463. MS : 336 ($M^{+\cdot}$), 202, 120, 105, 91 (100%), 77. IR : 3040, 2854, 1715, 1497, 1455. ^1H NMR (300 MHz) : 7.48, and 7.33 (2m, 10H, ArH), 6.30 (s, 1H, OCHN), 4.76 (d, 1H, J = 8, NOCH, (C-7a-H)), 4.31 (dd, 1H, $J_{4a,4b}$ = 8, $J_{3b,4a}$ = 6.3, C-4-Ha), 4.22 and 3.88 (masked C<u>H</u>$_2$Ph), 3.88 (m, $J_{3b,4a}$ = 6.3, $J_{3b,4b}$ = 9.4, $J_{3a,3b}$ ~1.5, C-3b-H), 3.39 (dd, 1H, $J_{4a,4b}$ = 8, $J_{3b,4b}$ = 9.4, C-4-Hb), 3.14 (2m, 2H, NCH_2C<u>H</u> (C-3a-H) and BnNC<u>Ha</u>), 2.74 (m, 1H, BnNC<u>Hb</u>). ^{13}C NMR (75 MHz) : 138.39 and 136.24 (C*, Ar), 128.96, 128.75, 128.54, 128.48, 127.61 and 125.99 (CH, Ar), 87.50 (OCHN), 81.87 (NOCH), 71.00 (OCH_2), 63.52 (NCH), 61.41 (NCH_2), 61.07 (NCH_2), 42.93 (NCH_2<u>C</u>H).

(2*R*, 5*S*, 6*S*)-6-(*N*-Benzyl-*N*-hydroxy)amino-2-phenyl-3-oxa-1-azabicyclo[3.3.0]-octane-8-one 12. $[\alpha]^{23}_D$ = + 154 (c = 0.74). MS(CI) : 325 $(M+H)^+$, 279, 202 (100%), 165, 124, 107. IR : 3580, 3388, 3007, 1705, 1499, 1454. ^1H NMR (300 MHz) : 7.43 and 7.33 (2m, 10H, ArH), 6.32 (s, 1H, OCHN), 5.26 (bs, 1H, OH), 4.22 (m, 2H, C-4-Ha and C-5-H), 3.83 (d, 1H, J = 13.0) and 3.64 (d, 1H, J = 13.0) : NC<u>H</u>$_2$Ph, 3.73 (dd, 1H, J = 11, J' = 10, C-4-Hb), 3.48 (m, 1H, $J_{6,7a}$ = 10.0, $J_{6,7b}$ = 8.3, $J_{5,6}$ ~ 5, C-6-H), 3.00 (dd, 1H, $J_{7a,7b}$ = 16.2, $J_{6,7a}$ = 10.0, C-7-Ha), 2.64 (dd, 1H, $J_{7a,7b}$ = 16.2, $J_{6,7b}$ = 8.3, C-7-Hb). ^{13}C NMR (75 MHz) : 174.87 (CO), 138.21 and 136.51 (C*, Ar), 129.53, 128.74, 128.60, 128.54, 127.88 and 126.09 (CH, Ar), 86.96 (OCHN), 71.18 (OCH_2), 67.88 (NCH), 62.82 (NCH_2), 62.70 (NCH), 38.03 (CH_2).

Reaction between the lactam 2 and *N*-benzyl-hydroxylamine : (2*R*, 5*S*, 6*S*)-6-(*N*-benzyl-*N*-hydroxy) amino-2-phenyl-3-oxa-1-azabicyclo[3.3.0]-octane-8-one 12. A solution of *N*-benzyl-hydroxylamine (30.0 mg, 0.24 mmol) in anhydrous toluene (1.2 mL) was added at room temperature to the α,β-unsaturated lactam **2** (42.8 mg, 0.21 mmol) and the mixture was stirred at 110°C for 7 h. The solvent was evaporated under reduced pressure and the product was purified by preparative TLC (eluent : Et_2O) to give the compound **12** (52.0 mg, 75%).

Reaction between the lactam 6 and *N*-benzylnitrone 8.

To a stirred solution of the lactam **6** (493 mg, 2.0 mmol) in anhydrous toluene (15 mL) at room temperature was added *N*-benzylnitrone **8** (270 mg, 2.0 mmol) in toluene (10 mL) and the mixture was heated at 110°C for 5.25 h. Flash chromatography of the residue obtained after removal of the solvent (eluent : heptane-Et_2O

1 : 9 and Et_2O) afforded the cycloadducts **13** (476 mg, 62%) and **14** (64 mg, 8%) and the starting lactam **6** (113 mg, 23%)

(4*R*, 7*R*, 8*S*)-2-Benzyl-7-(1-ethoxy)ethoxymethyl-6-methoxycarbonyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-5-one 13. Colorless oil. HRMS calcd for $C_{19}H_{26}N_2O_6$: 378.1790, found : 378.1799. MS : 378 ($M^{+\cdot}$), 289, 236, 176, 160, 154, 150, 136, 91 (100%), 73. IR : 1795, 1730, 1723, 1448, 1376, 1311. ^1H NMR (200 MHz) : 4.63 (m 1H, OCHO), 4.56 (m, 1H, C-8-H), 4.34 (m, 1H, C-7-H), 3.88 (s, CO_2CH_3), 4.1-3.2 ((OCH_2, NCH_2), 3.56 (m, 1H, C-4-H), 1.25 (2d, 3H, $CHC\underline{H}_3$), 1.18 (t, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 174.19 (NCO), 151.76 (NCO_2), 136.47 (C*, Ar), 128.84, 128.49, 127.65 (CH, Ar), 99.89-99.48 (OCHO), [76.4 (NOCH) and 63.93 (NCH) weak and broad signals], 63.60-63.26 (OCH_2), 61.98-61.59 (CH_2,), 61.11 (CH_2), 58.67 (CH_2), 53.73 (OCH_3), 52.71-52.64 ($NCH_2\underline{C}H$), 19.71-19.44 ($CH\underline{C}H_3$), 15.25 ($CH_2\underline{C}H_3$).

Cycloadduct 14 : (4*R* , 5*S* , 8*R*)-2-Benzyl-5-(1-ethoxy)ethoxymethyl-6-methoxycarbonyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-7-one. Colorless oil. HRMS calcd for $C_{19}H_{26}N_2O_6$: 378.1791, found : 378.1799. MS : 378 ($M^{+\cdot}$), 333, 305, 203, 198, 154, 141, 91(100%), 73. IR : 2975, 1796, 1757, 1724, 1499, 1441. ^1H NMR (200 MHz) : 7.30 (5H, ArH), 4.76 (1H, J = 8.5, J' ~ 1.5, NOCH (C-8-H)), 4.66 (1H, OCHO), 4.24, (m, 1H, NCH (C-5-H)), 3.91 (s, CO_2CH_3), 4.0-3.3 (2 OCH_2), 3.10 (m, $NCH_2C\underline{H}$), 1.25 (3H, $CHC\underline{H}_3$), 1.17 (t, 3H, J = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 136.25 (C*, Ar), 128.90, 128.49 and 127.58 (CH, Ar), 100.01-99.58 (OCHO), 79.89 (NOCH), 64.84-64.54 (CH_2), 61.82 (CH_2), 61.15 (CH_2), 53.82 (OCH_3), 42.70 ($NCH_2\underline{C}H$), 19.81-19.53 ($CH\underline{C}H_3$), 15.28 ($CH_2\underline{C}H_3$).

(4*R*, 7*R*, 8*S*)-2-Benzyl-7-hydroxymethyl-6-methoxycarbonyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one 15. To a solution of the cycloadduct **13** (222.3 mg, 0.6 mmol) in THF (1.9 mL) was added HCl (0.01N, 1.9 mL). The mixture was stirred at room temperature for 6 days, basified with a dilute aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 to give, after usual workup, the alcohol **15** which was purified by preparative TLC (eluent : Et_2O). Colorless oil (139.2 mg, 77%). $[\alpha]_D^{25}$ = - 69 (c = 0.57). HRMS calcd for $C_{15}H_{18}N_2O_5$: 306.1215, found : 306.1238. MS : 306 ($M^{+\cdot}$, 100%), 248, 231, 188, 160, 120, 118, 106, 104, 92, 91, 77, 65. IR : 3641, 3475, 3010, 2957, 1790, 1733 (sh), 1725. ^1H NMR (300 MHz) : 7.30 (5H, ArH), 4.66 (m, 1H, C-8-H), 4.23 (m, 1H, C-7-H), 4.06 (dd, 1H, $J_{9a,9b}$ = 11.8, $J_{7,9a}$ = 2.5, C-9-Ha), 3.94 (NCH_2Ph), 3.81 (s, CO_2CH_3), 3.75 (dd, 1H, $J_{9a,9b}$ = 11.8, $J_{7,9b}$ = 2, C-9-Hb), 3.63 (m, 1H, C-4-H), 3.43 (bm, C-3-Ha), 2.97 (bm, C-3-Hb). ^{13}C NMR (75 MHz) : 175.42 (NCO), 151.61 (NCO_2), 136.37 (C*, Ar), 128.84, 128.45 and 127.63 (CH, Ar), [76.3 (NOCH) and 65.63 (NCH) weak and broad signals], 61.83 (OCH_2), 58.36 (NCH_2), 53.43 (OCH_3), 52.64 ($NCH_2\underline{C}H$).

(4*R*, 7*R*, 8*S*)-7-Acetoxymethyl-2-benzyl-6-methoxycarbonyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one 16. To a stirred solution of the alcohol **15** (87mg, 0.28 mmol) in dry pyridine (2 mL) at room temperature, was added acetic anhydride in excess (0.9 mL). After being stirred for 24 h. at room temperature, the mixture was cooled to 0°C before slow addition of methanol (2 mL). After 30 min at room temperature, the solvents were evaporated under vacuum. The residue was dissolved in CH_2Cl_2, a dilute aqueous Na_2CO_3 solution was added and the acetate **16** was extracted with CH_2Cl_2 and purified after usual workup by preparative TLC (eluent : Et_2O) to give the compound **16** . Colorless oil (79mg, 80%). $[\alpha]_D^{25}$ = - 66 (c = 1.00). HRMS calcd for $C_{17}H_{20}N_2O_6$: 348.1321, found : 348.1310. MS : 349 $(M + H)^{+\cdot}$, 348 ($M^{+\cdot}$, 100%), 331, 306, 290, 289, 275, 271, 188, 160, 154, 91, 65, 55. IR : 1795, 1742, 1443, 1370, 1304. ^{1}H NMR (400 MHz) : 7.36 (m, 5H, ArH), 4.56 (dd, 1H, $J_{9a,9b}$ = 12, $J_{7,9a}$ ~ 3, C-9-Ha), 4.54 (m, 1H, C-8-H), 4.43 (dd, 1H, $J_{7,9a}$ ~ 3, $J_{7,9b}$ ~2, C-7-H), 4.19 (dd, 1H, $J_{9a,9b}$ = 12, $J_{7,9b}$ ~ 2, C-9-Hb), 3.95 (bm, 2H, C<u>H</u>$_2$Ph), 3.92 (s, 3H, CO_2CH_3), 3.56 (m, 1H, C-4-H,+ bm, 1H, C-3-Ha), 2.9 (bm, 1H, C-3-Hb), 2.05 (s, 3H, $COCH_3$). ^{13}C NMR (62.5 MHz) : 173.5 (NCO), 170.3 (OCO), 151.5 (NCO_2), 136.3 (C*, Ar), 128.9, 128.6 and 127.8 (CH, Ar), 76.0 (NOCH), 63.4 (OCH_2), 62.0 (NCH_2), 58.8 (NCH_2), 54.0 (OCH_3), 52.4 (NCH_2<u>C</u>H), 20.8 ($COCH_3$).

(4*R*, 7*R*, 8*S*)-2-Benzyl-7-hydroxymethyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one <u>17</u>. To a stirred solution of the cycloadduct **9** (148 mg, 0.44 mmol) in THF-H_2O (0.5 mL) was added trifluoroacetic acid (0.077 mL). The mixture was heated at 100°C for 3 h. The crude product obtained after evaporation of the solvents was diluted with CH_2Cl_2 before addition of an aqueous solution of Na_2CO_3. After evaporation to dryness, the product was purified by preparative TLC (eluent : CH_2Cl_2-MeOH 9 : 1) to afford **17** as white crystals (107.9 mg, 99%). Mp : 113-5°C, $[\alpha]_D^{25}$ = +36 (c = 0.9). Analysis for $C_{13}H_{16}N_2O_3$: calcd % : C = 62.89, H = 6.50, N = 11.28 ; found % : C = 62.65, H = 6.43, N = 11.23. MS(SI) : 249 [M + H]$^+$, 232, 165, 149, 147, 136. IR : 3425, 3243, 1700. ^{1}H NMR (250 MHz) : 7.32 (m, 5H ArH), 4.55 (m, 1H, C-8-H), 4.07 (m, 1H, exch.), 3.93 (C<u>H</u>$_2$Ph), 3.8-3.5 (OCH_2), 3.66 (NCH), 3.37 (dd, 1H, J ~ 6.5, C-4-H + m, C-3-Ha), 2.80 (m, 1H, C-3-Hb), 2.57 (m, 1H exch.). ^{13}C NMR (75 MHz) : 178.17 (CO), 136.61 (C*, Ar), 128.94, 128.54 and 127.69 (CH, Ar), 78.91 (NOCH), 63.46 (OCH_2), 62.88 (weak, NCH), 61.67 (N<u>C</u>H$_2$Ph), 57.94 (NCH_2), 51.02 (NCH_2<u>C</u>H).

(4*R*, 7*R*, 8*S*)-2-Benzyl-7-hydroxymethyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one <u>17</u> from <u>15</u>. To a solution of the primary alcohol **15** (80.2 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (0.20 mL) were successively added pyridine (52 μL) and Me_3SiI (90 μL) and the mixture was stirred at 30°C for 3 days. After evaporation to dryness *in vacuo,* the separation of the products by preparative TLC (eluent : CH_2Cl_2-MeOH 9 : 1) gave the pyrrolidone **17** (6.2 mg, 10%) and a compound with the same Rf as the starting compound **15** (38.5 mg, 48%).

(*S*)-5-Hydroxymethyl-1-methoxycarbonyl-3-pyrrolin-2-one <u>18</u>. To a solution of **6** (185.4mg, 0.76 mmol) in THF (2.5 mL) was added HCl 0.01N (1.25 mL) and the mixture was stirred at room temperature for 16 h. before extraction with CH_2Cl_2. Usual workup gave the compound **17** as white crystals (99.4 mg, 76%). Mp : 86-8°C, $[\alpha]_D^{29}$ = - 113 (c = 0.39). Analysis for $C_7H_9NO_4$: calcd % : C = 49.12, H = 5.30, N = 8.18 ; found % : C = 49.22, H = 5.33, N = 8.21. MS (CI) : 172 (M+H)$^+$, 142, 96. IR : 3620, 3466, 1785, 1743, 1720 (sh), 1441, 1335. ^{1}H NMR (300 MHz) : 7.30 (dd, 1H, J = 6, J' ~1.5, C-4-H), 6.17 (bd, 1H, J = 6, C-3-H), 4.76, (m, 1H, C-5-H), 4.10 and 3.96 (2m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.50 (m, 1H, exch., OH). ^{13}C NMR (75 MHz) : 169.62 (NCO), 151.73 (NCO_2), 150.25 and 126.94 (CH=CH), 64.69 (NCH), 61.01 (OCH_2), 53.47 (OCH_3).

Reaction between the lactam <u>18</u> and *N*-benzylnitrone <u>8</u> : (4*R*, 7*R*, 8*S*)-2-Benzyl-7-hydroxymethyl-6-methoxycarbonyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one <u>15</u>. To a solution of the alcohol **18** (55.5 mg, 0.32 mmol) in anhydrous toluene (1.6 mL) was added a solution *N*-benzylnitrone **8** (38.0 mg, 0.28 mmol) in toluene (0.4mL). The mixture was heated at 110°C for 4 h. Preparative TLC of the residue obtained after evaporation of the solvent under reduced pressure (eluent : Et_2O) afforded the cycloadduct **15** (31.2 mg, 31%).

Reaction between the lactam 2 and *N*-methylnitrone 19.

To *N*-methylnitrone **19** (195.4 mg, 3.31 mmol) was added a solution of the unsaturated lactam **2** (454.4 mg, 2.26 mmol) in anhydrous toluene (11.3 mL) at room temperature and the mixture was heated at 110°C for 3.3 h. Flash chromatography of the residue obtained after removal of the solvent (eluent : heptane-ether-methanol 8 : 2 : 0.8) afforded the compounds **20** (329 mg, 56%), **21** (29 mg, 5%) and **22** (198 mg, 35%) (another isomer was detected but in too small amounts to be characterized).

(3a*S*, 3b*R*, 6*R*, 7a*R*)-2-Methyl-6-phenyl-hexahydro-3,5-dioxa-2,6a-diazacyclopenta[*a*]pentalene-7-one 20. White crystals. Mp : 125-7°C (Et_2O). $[\alpha]_D^{23}$ = + 224 (c = 1.74). Analysis for $C_{14}H_{16}N_2O_3$: calcd.% : C = 64.60, H = 6.20, N = 10.76 ; found % : C = 64.69, H = 6.39, N = 10.76. HRMS : calcd for $C_{14}H_{16}N_2O_3$: 260.1161, found : 260.1170. MS : 260 ($M^{+\cdot}$, 100%), 184, 171, 156, 154, 143, 105, 84, 77. IR : 2997, 2852, 1708. ^{1}H NMR (300 MHz) : 7.38 (m, 5H, ArH), 6.33 (s, 1H, OCHN), 4.64 (d, 1H, $J_{3a,7a}$ = 8, C-3a-H), 4.33 (dd, 1H, $J_{4a,4b}$ ~ 8, $J_{3b,4a}$~ 7, C-4-Ha), 4.10 (dd, 1H, $J_{3b,4a}$ ~ 7, $J_{3b,4b}$ ~ 9, C-3b-H), 3.60 (C-7a-H), 3.52 (C-1-Ha), 3.47 (dd, $J_{4a,4b}$ ~ 8, $J_{3b,4b}$ ~ 9, C-4-Hb), 2.72 (s, 3H, NCH_3), 2.66 (masked m, 1H, C-1-Hb). ^{13}C NMR (75 MHz) : 177.62 (CO), 138.48 (C*, Ar), 128.70, 128.63, 128.48 and 125.99 (CH, Ar), 87.86 (OCHN), 77.56 (NOCH), 68.84 (OCH_2), 66.25 (NCH), 60.98 (NCH_2), 54.82 (NCH_2<u>C</u>H), 44.35 (NCH_3).

Cycloadduct 21 : (3a*R*, 3b*S*, 6*R*, 7a*R*)-2-Methyl-6-phenyl-hexahydro-1,5-dioxa-2,6a-diazacyclopenta[*a*]pentalene-7-one. Colorless oil. $[\alpha]_D^{24}$ = + 137 (c = 0.60). HRMS : calcd for $C_{14}H_{16}N_2O_3$: 260.1161, found : 260.1172. MS : 260 ($M^{+\cdot}$, 100%), 171, 105, 77. IR : 3044, 1716. ^{1}H NMR (300 MHz) : 7.47-7.35 (2m, 5H, ArH), 6.27 (OCHN), 4.70 (d, 1H, J = 8, NOCH), 4.34 (dd, 1H, J = 8, J' = 6.5) and 3.39 (dd, 1H, J = 9.5, J' ~ 8) : OCH_2, 3.90 (m, 1H, J = 9.5, J' = 6.5 and J'' ~ 1.5, NCH), 3.20 (m, 1H, MeN-C<u>H</u>a), 3.14 (m, 1H, NCH_2C<u>H</u>), 2.74 (s, 3H, NCH_3), 2.60 (m, 1H, MeN-C<u>H</u>b). ^{13}C NMR (75 MHz) : 174.55 (CO), 138.40 (C*, Ar), 128.78, 128.48 and 126.01 (CH, Ar), 87.59 (OCHN), 81.93 (NOCH), 71.06 (OCH_2), 63.83 (NCH_2), 63.57 (NCH), 44.49 (NCH_3), 43.31 (NCH_2<u>C</u>H).

(2*R*, 5*S*, 6*S*)-6-(*N*-Hydroxy *N*-methyl)amino-2-phenyl-3-oxa-1-azabicyclo [3.3.0]-octane-8-one 22. Colorless oil. $[\alpha]_D^{21}$ = + 179 (c = 1.41). Analysis for $C_{13}H_{16}N_2O_3$: calcd.% : C = 62.89, H = 6.50, N = 11.28 ; found % : C = 62.77, H = 6.48, N = 11.41. MS : 248 ($M^{+\cdot}$), 172, 148 (100%), 142, 105, 100, 97, 96, 91, 84, 77, 73, 57. IR : 3580, 3394, 3006, 2875, 1706, 1390, 1360. ^{1}H NMR (300 MHz) : 7.39 - 7.33 (2m, 5H, ArH), 6.55 (bs, 1H exch, OH), 6.32 (s, 1H, OCHN), 4.20 (dd, 1H, J ~ 8, J' ~ 6.5, C-4-Ha), 4.16 (m, 1H, C-5-H), 3.71 (dd, 1H, J = 8, J' = 6.5, C-4-Hb), 3.28 (m, 1H, $J_{6,7b}$ = 8.4, $J_{5,6}$ ~ 5, C-6-H), 2.85 (m, 1H, C-7-Ha), 2.59 (m, 1H, $J_{7a,7b}$ = 16, $J_{6,7b}$ = 8.4, C-7-Hb), 2.58 (s, 3H, NCH_3). ^{13}C NMR (75 MHz) : 174.91 (CO), 138.15 (C*, Ar), 128.78, 128.57 and 126.05 (CH, Ar), 87.02 (OCHN), 71.13 (OCH_2), 69.69 (NCH), 62.76 (NCH), 46.78 (NCH_3), 38.23 (weak and broad signal, CH_2).

Reaction between the lactam 2 and *N*-methyl-hydroxylamine : (2*R*, 5*S*, 6*S*)-6-(*N*-hydroxy *N*-methyl) amino-2-phenyl-3-oxa-1-azabicyclo[3.3.0]-octane-8-one 22. To a stirred solution of α,β-unsaturated lactam **2** (63.0 mg, 0.31 mmol) in toluene (1.6 mL) at room temperature was added *N*-methylhydroxylamine hydrochloride (56.7 mg, 0.68 mmol) and anhydrous K_2CO_3 (129 mg, 0.93 mmol); The mixture was heated at

110°C for 3 h. After being cooled at room temperature and diluted with toluene, the mixture was filtered before removal of the solvent under reduced pressure. Preparative TLC of the crude product (eluent : CH_2Cl_2-MeOH 96 : 4) gave the starting compound **2** [13.5 mg, 21%, $[\alpha]_D^{30}$ = + 222 (c = 0.38)[6]] and the compound **22** (18.6 mg, 24%).

Reaction between the lactam 6 and *N*-methylnitrone 19.

This cycloaddition was performed with **6** (794.6 mg, 3.27 mmol) and *N*-methylnitrone **19** (222.4 mg, 3.77 mmol) following the same protocol as above with heating for 3.5 h. Flash chromatography of the residue obtained after removal of the solvent (eluent : CH_2Cl_2-MeOH 96 : 4 and Et_2O) gave the cycloadducts **24** (552 mg, 56%), **25** (74 mg, 7%), and the compound **26** (238 mg, 25%).

(4*R*, 7*R*, 8*S*)-7-(1-Ethoxy)ethoxymethyl-6-methoxycarbonyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-5-one 24. Colorless oil. HRMS calcd for $C_{13}H_{22}N_2O_6$: 302.1478, found : 302.1467. MS : 302 ($M^{+\cdot}$), 258, 213, 154, 104, 84, 73 (100%). IR : 3010, 2984, 2878, 1789, 1729, 1443, 1370, 1310. ^1H NMR (300 MHz) : 4.67-4.62 (2m 1H, OCHO), 4.60 (m, 1H, C-8-H), 4.35 (m, 1H, C-7-H), 3.88 (s, CO_2CH_3), 3.95, 3.87 and 3.76 (OCH_2), 3.57-3.41 (2m, OCH_2), 3.55 (masked m, C-4-H), 2.68 (s + m, 4H, NCH_3, C-3-Hb), 1.25 (2d, 3H, *J* = 5.5, $CHC\underline{H}_3$), 1.17 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 174.03 (NCO), 151.45 (NCO_2), 99.83-99.40 (OCHO), 75.89 (NOCH), 63.93 (NCH), 63.64-63.33 (OCH_2), 61.62-61.03 (NCH_2, OCH_2), 53.63 (OCH_3), 53.12 ($NCH_2\underline{C}H$), 44.83 (NCH_3), 19.65-19.37 ($CH\underline{C}H_3$), 15.18 ($CH_2\underline{C}H_3$).

Cycloadduct 25 : (4*R*, 5*S*, 8*R*)-5-(1-Ethoxy)ethoxymethyl-6-methoxycarbonyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-7-one. Colorless oil. HRMS calcd for $C_{13}H_{22}N_2O_6$: 302.1478, found : 302.1471. MS : 302 ($M^{+\cdot}$), 257, 229, 213, 154, 144, 140, 127, 73 (100%). IR : 2980, 1792, 1757, 1722, 1441, 1378, 1300. ^1H NMR (300 MHz) : 4.70-4.64 (2m, 1H, OCHO), 4.72 (d, 1H, *J* = 8 *J'* ~ 1, NOCH), 4.28 (m, 1H, NCH), 3.89 (s, CO_2CH_3), 3.9-3.5 and 3.78-3.66 (OCH_2), 3.6-3.4 (OCH_2), 3.22 (m, 1H, $MeNC\underline{H}a$), 3.13 (m, 1H, N-CH_2-$C\underline{H}$), 2.71 (s + m, 4H, NCH_3, $MeNC\underline{H}b$). ^{13}C NMR (75 MHz) : 99.92-99.48 (OCHO), 80.02 (NOCH), 64.70-64.44-64.09 (OCH_2, NCH_2), 61.71- 61.08 (OCH_2), 61.51 (NCH), 53.86 (OCH_3), 44.84 (NCH_3), 43.05 ($NCH_2\underline{C}H$), 19.80-19.50 ($CH\underline{C}H_3$), 15.28 ($CH_2\underline{C}H_3$).

(4*S*, 5*S*)-5-(1-ethoxy)ethoxymethyl-4-(*N*-hydroxy*N*-methyl)amino-1-methoxycarbonyl pyrrolidin-2-one 26. Colorless oil. MS(CI) : 291 $(M + H)^+$, 275, 245, 229, 203, 172 (100%), 73, 57. IR : 3575, 3027, 1789, 1755, 1722, 1443, 1377, 1310. ^1H NMR (300 MHz) : 5.28 (bs, 1H exch., OH), 4.71-4.65 (2m, 1H, OCHO), 4.48 (m, 1H, C-5-H), 3.89 (s, 3H, CO_2CH_3), 3.93-3.58 and 3.85-3.74 (OCH_2), 3.6-3.4 (OCH_2), 3.27 (m, 1H, C-4-H), 2.88 (m, 1H, C-3-Ha), 2.65 (s, 3H, NCH_3), 2.58 (m, 1H, C-3-Hb), 1.27 (2d, 3H, $CHC\underline{H}_3$), 1.18 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 173.44-173.29 (CO), 152.07 (NCO_2), 99.93-99.57 (OCHO), 64.64-64.36 (OCH_2), 63.12 (NCH), 61.61-61.01 (OCH_2), 53.55 (OCH_3), 44.95 (NCH_3), 19.72-19.52 ($CH\underline{C}H_3$), 15.21 ($CH_2\underline{C}H_3$).

Reaction between the lactam 7 and *N*-methylnitrone 19.

This cycloaddition was performed with **7** (3.01 g, 10.6 mmol) and *N*-methylnitrone **19** (0.655 g, 11.1 mmol) following the same protocol as above with heating for 3 h. Flash chromatography of the residue obtained after removal of the solvent (eluent : CH_2Cl_2-MeOH 97 : 3 and Et_2O) gave the cycloadducts **27** (1.95 g, 54%), **28** (0.195 g, 5%), and the compound **29** (0.52 g, 15%).

(4*R*, 7*R*, 8*S*)-6-*tert*-Butoxycarbonyl-7-(1-ethoxy)ethoxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-5-one 27. Colorless oil. Analysis : $C_{16}H_{28}N_2O_6$: calcd % : C = 55.80, H = 8.20, N = 8.13 ; found % : C = 55.66, H = 7.95, N = 8.05. MS : 344 ($M^{+\cdot}$), 244, 199, 153, 140, 73 (100%), 60, 57. IR : 3030, 1781, 1738, 1719. ^{1}H NMR (300 MHz) : 4.70-4.63 (2m, 1H, OCHO), 4.56 (m, 1H, C-8-H), 4.26 (m, 1H, C-7-H), 3.90-3.55 and 3.80-3.72 (2dd, OCH_2), 3.55-3.40 (2m, $OC\underline{H}_2CH_3$), 3.5 (masked, C-4-H), 2.70 (s + m, NCH_3 + C-3-Hb), 1.55 (s, 9H, *t*-Bu), 1.25 (2d, 3H, $CHC\underline{H}_3$), 1.17 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 99.79-99.34 (OCHO), 83.32 (C*, *t*-Bu), 75.76 (NOCH), 63.56 (CH_2 + NCH), 60.94 (CH_2), 53.03 ($NCH_2\underline{C}H$), 44.97 (NCH_3), 28.02 (CH_3, *t*-Bu), 19.59-19.36 ($CH\underline{C}H_3$), 15.22 ($CH_2\underline{C}H_3$). Deprotection of primary alcohol was performed by acid hydrolysis : HCl 0.5N (5.3 mL) was added to a solution of **27** (984 mg, 2.86 mmol) in THF (10 mL). The mixture was stirred at room temperature under argon for 16 h. before addition of saturated aqueous solution of Na_2CO_3 (2 mL) and extraction with CH_2Cl_2. Usual workup afforded (4*R*, 7*R* , 8*S*)-6-*tert*-butoxycarbonyl-7-hydroxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-5-one as white crystals (726 mg, 93%). Mp : 117-9°C (Et_2O), $[\alpha]_D^{21}$ = - 92 (c = 1.65). Analysis : $C_{12}H_{20}N_2O_5$: calcd % : C = 52.93, H = 7.40, N = 10.29 ; found % : C = 52.91, H = 7.19, N = 10.16. HRMS calcd for $C_{12}H_{20}N_2O_5$: 272.1372, found : 272.1359.. MS : 272 ($M^{+\cdot}$), 199, 172 (100%), 86, 84, 60, 57. IR : 3469, 2994, 1780, 1744, 1719. ^{1}H NMR (300 MHz) : 4.64 (bd, 1H, C-8-H), 4.20 (m, 1H, C-7-H), 3.97 (dd, 1H, $J_{9a,9b}$ = 11, $J_{7,9a}$ = 2, C-9-Ha), 3.82 (dd, 1H, $J_{9a,9b}$ = 11, $J_{7,9b}$ = 1, C-9-Hb), 3.60 (m, 1H, $NCH_2C\underline{H}$), 3.53 (m, 1H, C-3-Ha), 2.78 (m, 1H, C-3-Hb), 2.68 (bs, 3H, NCH_3), 1.53 (s, , 9H, *t*-Bu). ^{13}C NMR (75 MHz) : 175.02 (NCO), 149.33 (NCO_2), 83.59 (C*, *t*-Bu), 75.55 (NOCH), 65.19 (NCH), 62.05 (OCH_2), 60.66 (NCH_2), 52.99 ($NCH_2\underline{C}H$), 44.97 (NCH_3), 28.02 (CH_3, *t*-Bu).

Cycloadduct 28 : (4*R*, 5*S*, 8*R*)-6-*tert*-Butoxycarbonyl-5-(1-ethoxy)ethoxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0] octane-7-one. Colorless oil. Analysis : $C_{16}H_{28}N_2O_6$: calcd % : C = 55.80, H = 8.20, N = 8.13 ; found % : C = 56.02, H = 8.01, N = 8.01. MS : 344 ($M^{+\cdot}$, 100%), 244, 216, 199, 140, 128, 111, 96, 85, 73, 57. IR : 2988, 2935, 2882, 1791, 1762, 1709, 1460, 1370. ^{1}H NMR (300 MHz) : 4.72-4.65 (2m, OCHO), 4.68 (d, 1H, *J* = 8, NOCH), 4.20 (m, 1H, NCH), 3.87 (dd, *J* = 10, *J'* ~ 2.5) - 3.46 and 3.75 (dd, *J* = 10, *J'* ~2.5) - 3.64 (OCH_2), 3.58-3.41 (OCH_2), 3.21 (m, 1H, MeNC$\underline{H}$a), 3.08 (m, 1H, $MeNCH_2C\underline{H}$), 2.70 (s + m, 4H, NCH_3, MeNC$\underline{H}$b), 1.54 (s, 9H, *t*-Bu), 1.26 (dd, 3H, $CHC\underline{H}_3$), 1.17 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 99.84-99.36 (OCHO), 83.49 (C*, *t*-Bu), 80.01 (NOCH), 64.51 (OCH_2), 64.01 (NCH_2), 61.73-60.93 (OCH_2), 61.21 (NCH), 44.88 (NCH_3), 42.69 ($NCH_2\underline{C}H$), 28.08 (CH_3, *t*-Bu), 19.69-19.42 ($CH\underline{C}H_3$), 15.29 ($CH_2\underline{C}H_3$).

(4*S*,5*S*)-1-*tert*-butoxycarbonyl-5-(1-ethoxy)ethoxymethyl-4-(*N*-hydroxy*N*-methyl)amino-pyrrolidin-2-one 29. Colorless oil. Analysis : $C_{15}H_{28}N_2O_6$: calcd % : C = 54.20, H = 8.49, N = 8.43 ; found % : C = 54.47, H = 8.59, N = 8.18. MS (CI) : 333 $(M+H)^+$, 233, 158, 140, 114, 74 (100%). MS : 231 ($M^{+\cdot}$ -BOC), 204, 186, 140, 127, 100, 73 (100%), 57. IR : 3588, 3420, 2988, 2938, 2880, 1787, 1737, 1706, 1375, 1306. ^{1}H NMR (300 MHz) : 6.28 (bs, 1H exch., OH), 4.71-4.65 (2m,1H, OCHO), 4.39 (m, 1H, C-5-H), 3.91-3.55 and 3.79-3.71 (OCH_2), 3.6-3.4 (OCH_2), 3.23 (m, 1H, C-4-H), 2.81 (m, 1H, C-3-Ha), 2.64 (s, 3H, NCH_3), 2.55 (m, 1H, C-3-Hb), 1.53 (s, 9H, *t*-Bu), 1.27 (2d, 3H, $CHC\underline{H}_3$), 1.19 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) :173.4 (NCO), 149.90 (NCO_2) 99.93-99.55 (OCHO), 83.10 (C*, *t*-Bu), 64.67-64.52 (OCH_2), 63.15 (NCH), 61.67-60.95 (OCH_2), 60.3 (broad and weak, NCH), 45.03 (NCH_3), 28.16 (CH_3, *t*-Bu), 19.73-19.56 ($CH\underline{C}H_3$), 15.32 ($CH_2\underline{C}H_3$).

(4*R*, 7*R*, 8*S*)-7-hydroxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one 30. A solution of the cycloadduct **20** (68.8 mg, 0.26 mmol) in THF-H_2O (1 : 1) was treated by CF_3CO_2H as described for **9**. The crude primary alcohol **30** was purified by preparative TLC (eluent : CH_2Cl_2-MeOH-NH_4OH 8 : 2 : 0.5). Colorless oil (32.0 mg, 70%). $[\alpha]_D^{30} = +5$ (c = 2.37, CH_3OH). MS (CI) : 173 (M + H)+, 73. IR : 3688, 3602, 3429, 1702, 1603. ^1H NMR (300 MHz, CD_3OD) : 4.68 (d, 1H, *J* = 7, C-8-H), 3.6 (m, OCH_2), 3.44 (masked m, C-4-H), 3.37 (C-3-Ha), 2.72 (m, C-3-Hb), 2.67 (s, NCH_3). ^{13}C NMR (75 MHz, CD_3OD) : 179.11 (CO), 80.26 (NOCH), 63.91 (OCH_2), 60.90 (NCH_2), 60.51 (NCH), 52.39 ($NCH_2\underline{C}H$), 44.80 (NCH_3).

(4*R*, 7 *R* , 8*S*)-7-(1-ethoxy)ethoxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one 31. Magnesium chloride (15.5 mg, 0.16 mmol) was added under inert atmosphere to a stirred solution of the compound **24** (138.3 mg, 0.46 mmol) in acetonitrile (1.2 mL) at room temperature. The mixture was heated at 50°C for 4 days. After elimination of the solvent under reduced pressure, the lactam **27** was separated from unreacted **24** (5%) by preparative TLC (eluent CH_2Cl_2-MeOH 95 : 5). Colorless oil (33.5 mg, 30%). $[\alpha]_D^{20} = +23$ (c = 1.74). HRMS calcd for $C_{11}H_{20}N_2O_4$: 244.1423, found : 244.1420. MS : 244 ($M^{+\bullet}$), 199, 172, 155, 143, 140, 108, 96, 84, 73, 60. IR : 3429, 1702. ^1H NMR (200 MHz) : 6.54 (bs, 1H, NH), 4.70 (m, 1H, *J* = 6, OCHO), 4.51 (m, 1H, C-8-H), 3.78 (m, 1H, C-7-H), 3.72-3.28 (m, 6H, 2 OCH_2, C-3-Ha, C-4-H), 2.70 (s, 3H, NCH_3), 2.62 (m, 1H, C-3- Hb), 1.29 (d, 3H, *J* = 6, $CH\underline{H}_3$), 1.18 (t, 3H, *J* = 7, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz) : 99.87-99.75 (OCHO), 78.72 (NOCH), 66.06 (OCH_2), 61.26 (OCH_2), 61.05 (NCH), 60.43 (NCH_2), 51.07-50.98 ($NCH_2\underline{C}H$), 44.58 (NCH_3), 19.65-19.56 ($CH\underline{C}H_3$), 15.28 ($CH_2\underline{C}H_3$).

Alcohol 30 by O-deprotection of 31. To a solution of the compound **31** (24.3mg, 0.10 mmol) in THF (0.6 mL) was added HCl 0.01N (0.23 mL) and the mixture was stirred at room temperature for 5 days. Preparative TLC of the residue obtained by evaporation of the solvents under reduced pressure (eluent : CH_2Cl_2-MeOH-NH_4OH 8 : 2 : 0.5) gave the alcohol **30** (8.8 mg, 51%).

Alcohol 30 by deprotection of 27. A solution of the cycloadduct **27** (70.0 mg, 0.20 mmol) in CH_2Cl_2-CF_3CO_2H 1 : 1 (1.0 mL) was stirred at room temperature for 45 min. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2 before the addition of a saturated aqueous solution of Na_2CO_3. After evaporation to dryness, the residue was purified by preparative TLC (eluent : CH_2Cl_2-MeOH-NH_4OH 8 : 2 : 0.5) to give the alcohol **30** (26.2 mg, 75 %).

REFERENCES AND NOTES

1. Preliminary communication : Langlois, N.; Griffart-Brunet, D.; Van Bac, N.; Chiaroni, A.; Riche, C. *C.R. Acad. Sci.* **1995**, *320* Série II b, 155-158.
2. [a]Tufariello, J.J. "1,3-Dipolar Cycloaddition Chemistry", 2, Chap. 9, 83-168 Ed. Padwa, A., Wiley, J. and Sons Inc., NY, 1984. [b]Carruthers, W. "Cycloaddition Reactions in Organic Synthesis", Chap. 6, p. 298-313, Pergamon Press, 1990.
3. (*S*)-pyroglutaminol is commercially available but rather expensive ; we obtained it from (*S*)-pyroglutamic acid as described[4] (except the purification : filtration on silica gel instead of distillation) in 98% yield (20.0 g scale).
4. Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449-1458.
5. Phenylselenide intermediates were oxidized by hydrogen peroxide instead of ozone (71%).

6. Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635-8652.
7. Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett.* **1988**, *29*, 3259-3262.
8. Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77-82.
9. The protection of primary alcohol functions of (S)-pyroglutaminol derivatives as ethoxyethoxymethyl acetals and their deprotection are very easy and have been often used in our laboratory during the last decade [7-9,11-13] Generally, the newly created asymmetric center do not complicate the interpretation of the NMR spectra. When double sets of resonance were observed, they were mentioned in the experimental section ; in some cases, the primary alcohol function has been deprotected and acylated in order to clarify the analysis by NMR.
10. Andriamialisoa, R.Z.; Langlois, N. *Tetrahedron Lett.* **1986**, *27*, 1149-1152.
11. Langlois, N.; Favre, F. *Tetrahedron Lett.* **1991**, *32*, 2233-2236.
12. Langlois, N.; Favre, F.; Rojas, A.*Tetrahedron Lett.* **1993**, *34*, 4635-4638.
13. Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119-122.
14. The yields previously obtained[1] were slightly improved by using longer reaction time on a larger scale.
15. [a]Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S. *Tetrahedron Lett.* **1992**, *33*, 667-670. [b]Banerji, A.; Basu, S. *Tetrahedron* **1992**, *48*, 3335-3344. [c]Alonso-Perarnau, D.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron*, **1993**, *49*, 4267-4274. [d]Rispens, M.T.; Keller, E.; de Lange, B.; Zijlstra, R.W.J.; Feringa, B.L. *Tetrahedron, Asymmetry* **1994**, *5*, 607-624.
16. Wazeer, M.; Asrof, A.S. *Magn. Reson. Chem.* **1993**, *31*, 12-16.
17. [a]Chiacchio, U.; Buemi, G.; Casuscelli, F.; Procopio, A.; Rescifina, A.; Romeo, R. *Tetrahedron* **1994**, *50*, 5503-5514. [b]Hermitage, S.A.; Moloney, M.G. *Tetrahedron Asymmetry*, **1994**, *5*, 1463-1464. [c]Gothelf, K.V.; Jorgensen, K.A. *J. Org. Chem.* **1994**, *59*, 5687-5691.
18. Weidner-Wells, M.A.; Fraga, S.A.; Demers, J.P. *Tetrahedron Lett.* **1994**, *35*, 6473-6476.
19. Chiaroni, A.; Riche, C.; Griffart-Brunet, D.; Langlois, N. Acta Cryst. C **1994**, to be published.
20. For clarity, the numbering of the regioisomers are not cited in the theoretical part.
21 [a]Stafford, J.A.; Brackeen, M.F.; Karanewsky, D.S.; Valvano, N.L. *Tetrahedron Lett.* **1993**, *34*, 7873-7876. [b]Wei Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* **1994**, *35*, 847-848.
22. It was verified during another study using the racemic compound (±) **13** which was converted to (±)**17** in 55% yield through the *N*-deprotected derivative : MS : 320 ($M^{+\cdot}$, 100%), 275, 231, 219, 160, 136, 120, 106, 96, 91, 73. IR : 3433, 3000, 1705. ^{1}H NMR (300 MHz) : 7.34 (5H, ArH), 6.36 (1H, NH), 4.70 (m, 1H, OCHO), 4.51 (m, 1H, NOCH), 3.96 (2H, C$\underline{H_2}$Ph), 3.79 (m, 1H, NCH), 3.7-3.2 (2 OCH_2), 3.36 ($NCH_2C\underline{H}$), 1.27 (d, 3H, *J* ~ 6, $CHC\underline{H_3}$), 1.18 (t, 3H, *J* = 7, $CH_2C\underline{H_3}$). ^{13}C NMR (75 MHz) : 136.78 (C*, Ar), 129.01, 128.76, 128.45, 127.55 (CH, Ar), 99.84-99.76 (OCHO), 78.76 (NOCH), 66.04 (OCH_2), 61.57 (NCH_2), 61.23 (OCH_2), 60.9 (NCH), 58.07 (NCH_2), 50.48-50.39 ($NCH_2\underline{C}H$), 19.66-19.54 ($CH\underline{C}H_3$), 15.29 ($CH_2\underline{C}H_3$).
23. Menard, M.; Rivest, P.; Morris, L.; Meunier, J.; Perron, Y.G. *Canad. J. Chem.* **1974**, *52*, 2316-2326.
24. [a]Fornefeld, E.J.; Pike, A.J. *J. Org. Chem.* **1979**, *44*, 835-839. [b]Huang, S.-P.; Koyama, Y.; Ikeda, D.; Kondo, S.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1939-1948.
25 [a]Bailey, J.T.; Berger, I.; Friary, R.; Puar, M.S. *J. Org. Chem.* **1982**, *47*, 857-863. [b]Green, M.J.; Tiberi, R.L.; Friary, R.; Lutsky, B.N.; Berkenkoph, J.; Fernandez, X.; Monahan, M. *J. Med. Chem.* **1982**, *25*, 1492-1495.
26. Koot, W-J.; Hiemstra, H.; Speckamp, W; N. *Tetrahedron Asymmetry* **1993**, *4,* 1941-1948.
27. Ali, S.A.; Perzanowski, P. H. *J. Chem. Research* (S) **1992**, 146-147.

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