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Asymmetric Synthesis of Pipecolic Acid Derivatives

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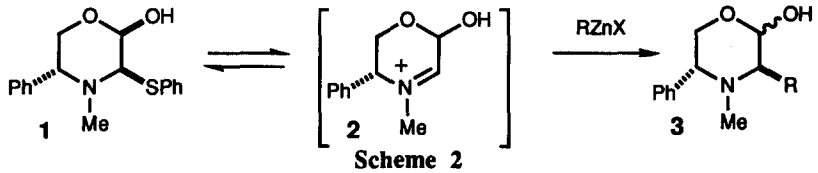
***Abstract** : Condensation of chiral N-homoallyl β-amino alcohols with glyoxal produces iminium ions which are cyclized with complete stereoselectivity. These substrates, whose reactivity is closely dependent on the substitution pattern of the ethylenic moiety, undergo ene-iminium cyclizations that ultimately lead to homochiral pipecolic acid derivatives.*

(*S*)-Pipecolic acid is a nonproteinogenic amino acid widely distributed in plants.[1] Because they often display biological activity,[2] substituted pipecolic acids have been the subject of intensive synthetic efforts in recent years. In addition to several preparations of such compounds in racemic form,[3] asymmetric syntheses based upon the building block strategy starting from the chiral pool have been published.[4,5] We present here a new enantioselective procedure in which the configurations of the stereogenic centers are governed by complete asymmetric induction from a versatile chiral auxiliary during a totally stereoselective ene-iminium cyclization.[6] The usefulness of this methodology in heterocyclic chemistry was highlighted in particular by recent total syntheses of alkaloids.[7]

The ene-iminium cyclization, as depicted in Scheme 1, was first reported by Cope *et al.*[8] ; it requires the participation of an external nucleophile (often arising from the solvent). Actually most syntheses make use of either vinylsilanes as the ene component [9] or an acyliminium moiety instead of the less reactive iminium ion. [10]

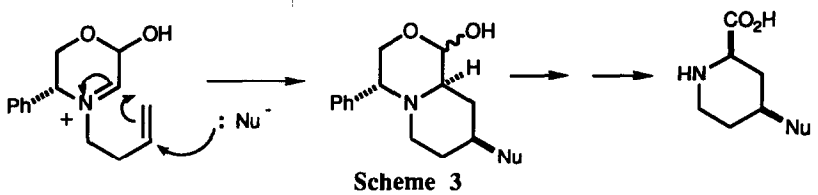
Scheme 1

We recently reported that iminium ions **2** are produced via a condensation between glyoxal and chiral β-amino alcohols.[11] As shown in Scheme 2, these ions can be trapped with thiophenol and lead reversibly to an amino thioether moiety **1**; the reverse reaction, *i.e.* generation of iminium ion **2** from the amino thioether precursor **1** is promoted by Lewis acids.The reaction with organozinc reagents afforded alkylated products **3** with complete retention of configuration at the reactive site.[12]



Scheme 2

The present work reports an intramolecular version of this reaction: now the iminium ion reacts with an ethylenic double bond linked to the nitrogen atom, as schematized below. The cyclization products are conveniently transformed into pipecolic acid derivatives.



Scheme 3

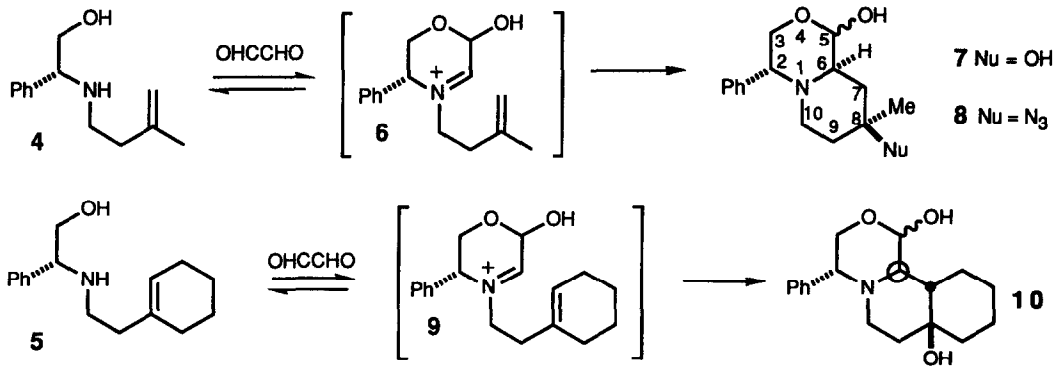
These ene-iminium cyclizations are totally stereoselective thus allowing an efficient control of stereochemistry at the two created stereogenic centers (see Scheme 3).

RESULTS AND DISCUSSION

The reactivity of ene-iminium substrates is highly dependent on the substitution pattern of the ethylenic double bond. In the more favorable case, cyclization occurs spontaneously in aqueous solution. On the other hand, when the double bond in the N-homoallyl chain is unsubstituted, the iminium moiety must be generated from an amino thioether precursor in anhydrous medium.

Spontaneous cyclizations in aqueous medium

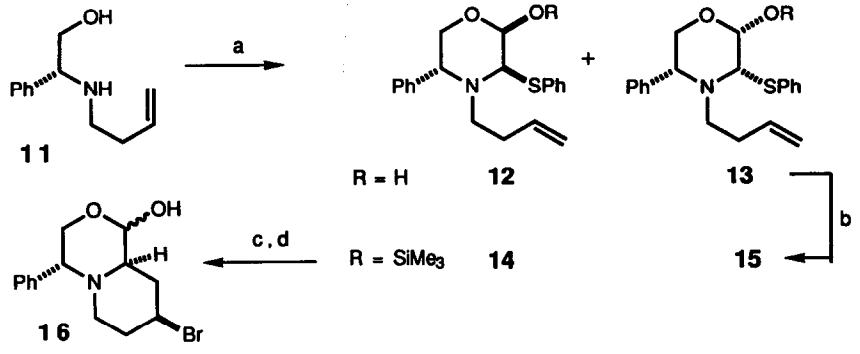
β-Amino alcohols **4** and **5** react with glyoxal (1.2 equiv) in a water-tetrahydrofuran solution to afford bicyclic compounds **7** and **10** (respective yields : 72 and 55%). When an excess of sodium azide was present in the reaction medium, substrate **4** yielded a mixture of products **7** and **8** in a 1/5 respective ratio (Scheme 4). The stereochemical outcome of these cyclizations will be discussed below; the resulting hemiacetals exist as epimeric mixtures at the hemiacetal center (C-5) owing to ring-chain tautomerism.



Scheme 4

Cyclizations from an iminium ion precursor

No cyclized product was isolated when amino alcohol **11** was treated with glyoxal under the above conditions. The iminium ion precursor, *i.e.* the diastereomeric mixture of amino thioethers **12** and **13**, was prepared from the one-pot condensation of compound **11**, glyoxal and thiophenol in aqueous solution; this mixture was then transformed into the trimethylsilyl derivatives **14** and **15** which were treated with zinc bromide and *n*-Bu_4NBr. Desilylation was then effected with *n*-Bu_4NF leading to the cyclized hemiacetal **16** (Scheme 5).

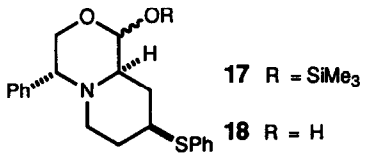


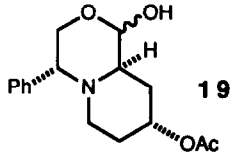
(a) aq.OHCCHO (1 equiv) / PhSH (1 equiv), 70%; (b) Me_3SiCl, NEt_3, 95%; (c) $ZnBr_2$ (1.5 equiv) / *n*-Bu_4NBr (2 equiv) ; (d)*n*-Bu_4NF, 78%.

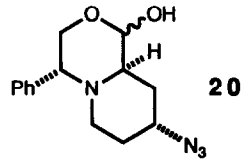
Scheme 5

The respective ratio of amino thioethers **12/13** (as well as the silyl derivatives **14/15**) is 80/20. The *cis* relationship between OH and SPh was deduced from two ^1H NMR observations : (i) a small coupling constant (1.8 Hz) between hydrogens at C-5 and C-6, (ii) a coupling (13.7 Hz) between the hydroxylic and the C-5 hydrogens pointing to an intramolecular hydrogen bond between OH and SPh. Structure of the major isomer **12** was assigned by comparison with the ^1H NMR spectrum of its N-methyl analogue whose stereochemistry was provided unambiguously by X-ray crystallography.[13]

Similarly the phenylthio substituted cyclized compound **18** resulted from the reaction of zinc chloride (0.1 equiv) and thiophenol (1 equiv) with the silylated amino thioethers **14** and **15** followed by deprotection by *n*-Bu_4NF. Substitution of bromine in compound **16** by an acetoxy or an azido group was realized by treating **16** either by cesium acetate in DMF or by sodium azide in DMSO, affording respectively the cyclized products **19** and **20**.



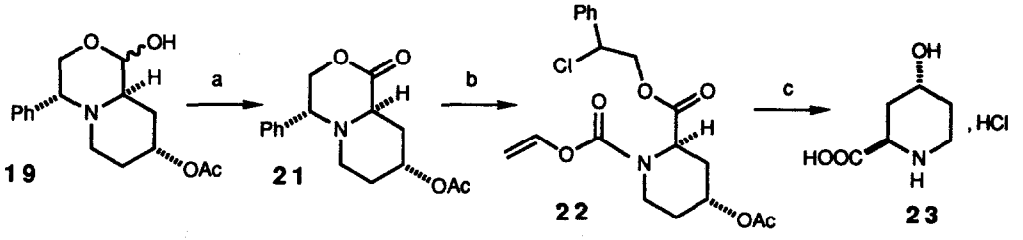




Substrates **4** and **5** showing a *gem*-disubstituted ene double bond are more reactive than **11** in which the *N*-homoallyl chain is unsubstituted. Actually the transient positive charge which appears at the cyclic transition state (cf. Scheme 1) is stabilized when localized on a tertiary carbon atom and this explains why the substituted *N*-homoallyl chain is more prone to react with the iminium moiety. The presence of water is detrimental to the reactivity of compound **11** since this solvent can react with the iminium double bond yielding a carbinolamine moiety thus emphasizing the sluggishness of the substrate. In fact the iminium moiety must be generated in anhydrous medium and this explains the rather tortuous way followed for cyclizing **11** (Scheme 5).

Pipecolic acid derivatives

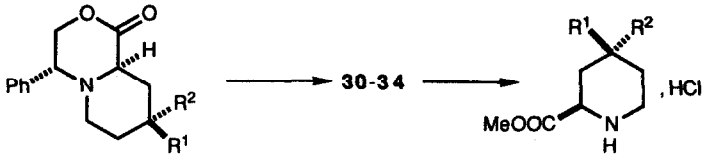
The transformation of the above cyclized products into the corresponding pipecolic acid derivatives was realized in three steps : (i) Swern oxidation of the hemiacetal moiety, (ii) cleavage of the benzylic carbon-nitrogen bond by vinyl chloroformate, (iii) acidic hydrolysis or methanolysis. This process is exemplified below (Scheme 6) with the synthesis of enantiomerically pure (2*R*,4*R*)-(-)-4-hydroxypipecolic acid **23** which is the enantiomer of the naturally occurring amino acid found in *Acacia* species.[14]



(a) $(COCl)_2$, DMSO, NEt_3, 64%; (b) CH_2=CHOCOCl, 73%; (c) 6N HCl, 72%.

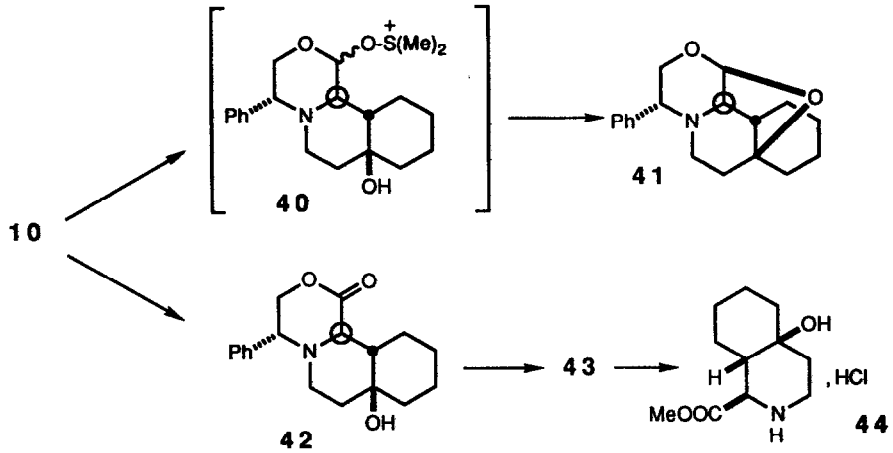
Scheme 6

Likewise hemiacetals **7**, **8**, **16**, **18** and **20** were converted respectively into the substituted pipecolic acid methyl esters **35-39** via the corresponding lactones **25-29** and urethanes **30-34** (prior to the debenzylation step, hydroxylactone **24** was acetylated and the resulting ester **25** was treated with vinyl chloroformate in order to yield urethane **30**).



24	R^1 = OH	R^2 = Me		
25	R^1 = OAc	R^2 = Me	**35**	R^1 = OH (cf.ref[15])
26	R^1 = N_3	R^2 = Me	**36**	
27	R^1 = Br	R^2 = H	**37**	
28	R^1 = SPh	R^2 = H	**38**	
29	R^1 = H	R^2 = N_3	**39**	

Swern oxidation of the cyclized compound **10** afforded the expected lactone **42** provided that an excess amount (3 equiv) of the oxidizing reagents was used. Otherwise compound **41** was produced, presumably from an intramolecular nucleophilic substitution of the oxosulfonium moiety by the tertiary hydroxylic group in intermediate **40** (Scheme 7). Side-reactions are known in such DMSO-mediated oxidations[16] but, to our knowledge, only one similar example of intramolecular etherification was reported.[17]



Scheme 7

Compound **41** is a crystalline material which was analyzed by X-ray crystallography (Figure 1).[18] Its structure is in agreement with the stereochemistry of the ene-iminium cyclization products, showing in particular the *trans* relationship between the external nucleophile (here OH) and the phenyl group of the chiral auxiliary.

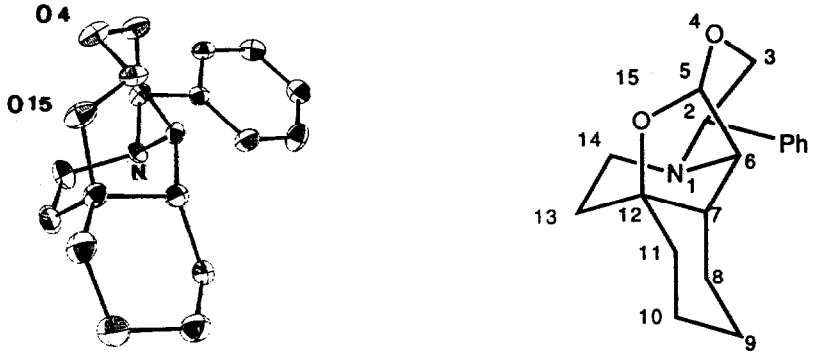
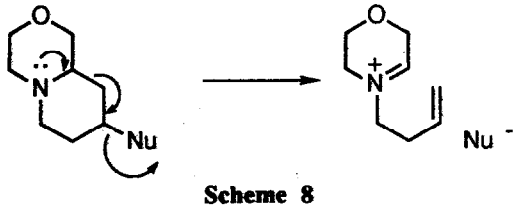
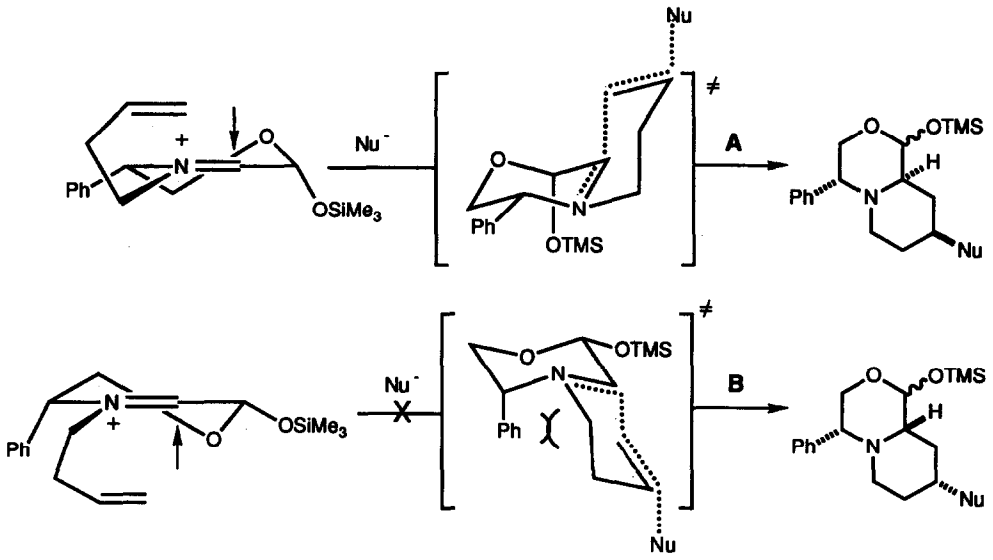


Figure 1

It should be noticed that such ene-iminium cyclizations can be viewed as reverse Grob fragmentations (Scheme 8); actually it is known that such eliminations require rather drastic experimental conditions in the case of γ-halo amines[19] and are inoperative for γ-hydroxy amines.[20] Furthermore an acetic acid solution of compound **16** refluxed in the presence of sodium acetate does not show any exchange between Br and AcO.



Scheme 8



Scheme 9

All these reactions are totally stereoselective and this can be ascribed to two features. Firstly the nucleophile-assisted ene-iminium cyclization is a stereospecific process[10] whose mechanism implies that the ene double bond undergoes an *anti* addition of the external nucleophile and of the electrophilic iminium ion. On the other hand, stereoselectivity governs the direction of the ene fixation onto the $C=N^+$ site. This point is depicted on Scheme 9 which shows that the axial attack leading to a pre-chair transition state may follow two directions for cyclizing the iminium ion derived from **13**. Path B is unfavored because of the steric hindrance between the phenyl group and the incipient cycle on the lower side of the molecule, *i.e. syn* to the phenyl substituent. It should be noted that this stereochemical outcome corresponds exactly to what we already observed[12] (cf. Scheme 2) with similar substrates reacting in an *intermolecular* fashion with organozinc reagents.

EXPERIMENTAL SECTION

General comments

^1H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were respectively carried out on a Bruker AC 200 spectrometer at 200 and 50 MHz; chemical shifts are reported in ppm downfield from TMS, unless otherwise stated. Optical rotations were determined with a Perkin-Elmer 141 instrument. Melting points were obtained with a Reichert apparatus (hot stage provided with a microscope). Mass spectra were performed on a Kratos MS 30 apparatus. Infrared spectra were recorded on a Perkin Elmer 1420 spectrometer. Microanalyses were obtained by the Laboratory of Microanalysis of the Université P. et M. Curie.

All reactions were carried out under nitrogen except those performed in aqueous solution. Column chromatography was performed on silica gel, 230-400 mesh. Mention of "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification.

3-Methyl-3-butenyl-p-toluenesulfonate

p-Toluenesulfonyl chloride (12g, 63 mmol) was added portionwise at room temperature to a solution of 3-methylbut-3-enol (5.85 ml, 60 mmol) and pyridine (10 ml, 120 mmol) in chloroform (40 ml). The solution was stirred for 15h at room temperature and was then diluted with ether (150 ml). To the resulting suspension was added a solution of 1N HCl (100ml), the organic layer was separated and washed successively with 1N HCl (2 x 100 ml), a saturated solution of $NaHCO_3$ (2 x 100 ml), and brine. Drying over $MgSO_4$ and solvent evaporation under reduced pressure yielded the tosylate as an oil (13.5g, 94 %), which was used without further purification. ^1H NMR : 1.75 (s, 3H, $CH_3C=C$), 2.44 (s, 3H, CH_3Ar), 2.47 (t, J = 6.8 Hz, 2H, $CH_2C=C$),

4.12 (t, J = 6.8 Hz, 2H, CH_2O), 4.77 (b s, 1H, C=CH), 4.85 (b s, 1H, C=CH), 7.34 (d, J = 8Hz, 2H, Ar), 7.78 (d, J = 8Hz, 2H, Ar).

N-(3-Methyl-3-butenyl)-(R)-phenylglycinol 4

A solution of (*R*)-phenylglycinol (1g, 7.35 mmol), 3-methyl-3-butenyl-*p*-toluenesulfonate (1.94 g, 8.1 mmol) and diisopropylethylamine (1.4 ml, 8.1 mmol) in acetonitrile (30 ml) was refluxed for 24 h. Addition of water (30 ml) and usual workup yielded, after flash chromatography (ether and then 3 % MeOH/ether), amino alcohol **4** as a colorless oil (789 mg, 53%) : $[\alpha]_D^{20}$ -55° (*c* 0.55, $CHCl_3$); ^1H NMR : 1.56 (s, 3H, CH_3), 2.10 (t, J = 7.2 Hz, 2H, CH_2C=C), 2.4-2.6 (m, 2H, CH_2N), 3.16 (b s, 2H, OH and NH), 3.5-3.7 (m, 3H, PhCHN and CH_2O), 4.62 (b s, 1H, C=CH), 4.67 (b s, 1H, C=CH), 7.1-7.25 (m, 5H, Ph); ^{13}C NMR : 22.1, 37.9, 44.7, 64.7, 111.6, 127.2, 127.4, 128.5, 140.5, 143.2. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.23; N, 6.82. Found : C, 76.38; H, 9.23; N, 6.74.

N-[2(1-Cyclohexen-yl)ethyl]-(R)-phenylglycinol 5

A solution of (*R*)-phenylglycinol (5g, 36 mmol), 1-(2-*p*-toluenesulfonylethyl)cyclohexene[21] (10 g, 36 mmol) and diisopropylethylamine (6.4 ml, 39 mmol) in acetonitrile (80 ml) was refluxed for 24 h. Addition of water (50 ml) and usual workup yielded, after flash chromatography (ether and then 10 % MeOH/ether), amino alcohol **5** as a white solid (5.5 g, 62%): mp 73°C; $[\alpha]_D^{20}$ -50.5° (*c* 0.5, $CHCl_3$). ^1H NMR : 1.4-1.6 (m, 4H), 1.7-1.8 (m, 2H), 1.9-2.0 (m, 2H), 2.05 (t, J = 6.5 Hz, 2H, CH_2N), 2.36 (b s, 2H, OH and NH), 2.45-2.65 (m, 2H), 3.45-3.75 (m, 3H), 5.43 (b s, 1H, CH=C), 7.2-7.5 (m, 5H, Ar); ^{13}C NMR : 22.4, 22.9, 25.2, 28.0, 38.3, 44.8, 64.5, 66.4, 123.0, 127.1, 127.5, 128.6, 140.6. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found : C, 78,06; H, 9.32; N, 5.83.

(2R,6R,8S)-5,8-Dihydroxy-8-methyl-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane 7

To an emulsion of amino alcohol **4** (540mg, 2.65 mmol) in THF (3 ml) and water (3 ml) was added dropwise an aqueous solution of glyoxal (40 % wt, 0.35 ml, 3.15 mmol). After stirring at room temperature for 5h, the emulsion was extracted with ether (4 x 10 ml). Drying over $MgSO_4$ and solvent evaporation under reduced pressure gave a residue which was purified by flash chromatography over a short column of silica gel (5% MeOH/ether): Rf = 0.25. Compound **7** was obtained as an oil (65/35 epimeric mixture at C-5, 502 mg, 72%). ^1H NMR : 1.1 (s, 1.95H, CH_3), 1.18 (s, 1.05H, CH_3), 1.2-2.4 (m, 5H), 2.6-3.1 (m, 2H), 3.6-4.15 (m, 5H), 4.80 (d, J = 5.4 Hz, 0.65H, H-5), 5.11 (b s, 0.35H, H-5), 7.2-7.6 (m, 5H, Ph); ^{13}C NMR (major epimer) : 25.5, 35.0, 36.6, 48.3, 56.6, 59.1, 66.8, 69.5, 96.4, 127.9, 128.3, 128.8, 137.9.

(2R,6R,8S)-8-Azido-5-hydroxy-8-methyl-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane 8

To an emulsion of amino alcohol **4** (412mg, 2.02 mmol) and sodium azide (523 mg, 8.08 mmol) in THF (2.5 ml) and water (2.5 ml) was added dropwise an aqueous solution of glyoxal (40 % wt , 0.275 ml, 2.42 mmol). After stirring at room temperature for 3h, the emulsion was extracted with ether (4 x 10 ml). Drying over $MgSO_4$ and solvent evaporation under reduced pressure gave a residue which was purified by flash chromatography (90% ether/petroleum ether): Rf = 0.5. Compound **8** was obtained as an oil (75/25 epimeric mixture at C-5, 319 mg, 55%). ^1H NMR : 1.19 (s, 2.25H, CH_3), 1.24 (s, 0.75H, CH_3), 1.5-2.5 (m, 4H), 2.6-3.15 (m, 2H), 3.5-4.2 (m, 4H), 4.7 (b s, 1H, OH), 4.76 (d, J = 4.5 Hz, 0.75H, H-5), 5.11 (d, J = 2.6 Hz, 0.25H, H-5), 7.2-7.5 (m, 5H, Ph); ^{13}C NMR (major epimer) : 22.0, 32.7, 35.4, 46.9, 55.9, 58.8, 60.0, 66.6, 95.9, 127.9, 128.5, 129.1, 137.8.

(2R,6R,7S,12S)-5,12-Dihydroxy-2-phenyl-4-oxa-1-azatricyclo[8.4.0.0^{7,12}]tetradecane 10

To an emulsion of amino alcohol **5** (4.1 g, 16.4 mmol) in THF (75 ml) and water (75 ml) was added dropwise an aqueous solution of glyoxal (40 % wt, 2.4 ml, 16.6 mmol). After stirring at room temperature for 48 h, the emulsion was extracted with ether (4 x 50 ml). Drying over $MgSO_4$ and solvent evaporation under reduced pressure gave a residue which was purified by flash chromatography over a short column of silica gel (10% MeOH/ether): Rf = 0.25. Compound **10** was obtained as an oil (60/40 epimeric mixture at C-5, 4.6g, 91%). ^1H NMR : 1.0-2.0 (m, 10H), 2.05-2.3 (m, 1.2H), 2.4-2.6 (m, 0.8H), 2.75-3.1 (m, 2H), 3.6-4.65 (m, 5H), 5.21 (b s, 0.4H, H-5), 5.29 (d, J = 3.1 Hz, 0.6H, H-5), 7.15-7.6 (m, 5H, Ar); ^{13}C NMR (major epimer): 21.3, 21.7, 22.0, 23.1, 33.4, 42.3, 46.5, 57.6, 59.9, 64.3, 71.0, 91.1, 127.5, 127.8, 128.3, 129.6, 138.6.

N-(3-Butenyl)-(R)-phenylglycinol 11

4-Bromo-1-butene (5g, 36.5 mmol) was added to a solution of (*R*)-phenylglycinol (5g, 36.5 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (5.54 g, 36.5 mmol) in toluene (100ml). The solution was heated at 80°C for 12h and water (50 ml) was then added. The organic layer was washed with water (50 ml), brine (50 ml), and the aqueous layer was extracted with dichloromethane (2 x 50 ml). Drying of the combined organic extracts over MgSO4 and solvent evaporation under reduced pressure yielded a residue which was flash chromatographied (ether and then 5 % MeOH/ether). Amino alcohol **11**was obtained as an oil which crystallised on standing (3.65 g, 56 %) : mp 46°C; $[\alpha]_D^{20}$ -64.9° (*c* 0.5, $CHCl_3$); ^1H NMR : 2.22 (q, J = 6.7 Hz, 2H, CH_2-CH=CH_2), 2.5-2.6 (m, 2H, CH_2N), 2.63 (bs, 2H, OH; NH), 3.53 (dd, J = 8.8 and 10.5 Hz, 1H, PhCHN), 3.7-3.8 (m, 2H, CH_2O), 5-5.1 (m, 2H, CH=CH_2), 5.7-5.8 (m, 1H, CH=CH_2), 7.2-7.4 (m, 5H, Ph);

^{13}C NMR: 34.4, 46.4, 64.6, 66.7, 116.4, 127.2, 127.6, 128.6, 136.4, 140.9. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.94; N, 7.32. Found : C, 75.16; H, 8.85; N, 7.42.

(2R, 3R, 5R) and (2S, 3S, 5R)-N-(3-Butenyl)-2-hydroxy-5-phenyl-3-phenylthiomorpholines12 and 13

Amino alcohol **11** (3g, 17 mmol) was added portionwise into an aqueous solution of glyoxal (1M solution, 16.8 ml). The resulting suspension was vigourously stirred for 12h at room temperature. Addition of water (20 ml) and thiophenol (1.83g, 17 mmol) followed by a 4h additional stirring gave a suspension which was extracted with dichloromethane (3 x 30 ml). Drying over $MgSO_4$ and solvent evaporation under reduced pressure yielded a residue which was purified by flash chromatography (40% ether/petroleum ether, Rf : 0.8).Title compounds were obtained as a thick oil (mixture of diastereoisomers : **12/13** : 75/25, 4.1g, 72%). ^1H NMR : 1.65 (m, 1.5H, CH_2C=C), 1.85 (m, 0.5H, CH_2C=C), 2.3-2.5 (m, 1H, NCH_2), 2.6-2.8 (m, 1H, NCH_2), 3.4-4.2 (m, 3H), 4.5-5.1 (m, 4H), 5.3-5.6 (m, 1H), 7.15-7.6 (m, 10H, Ph). In the multiplet between 4.5 and 5.1 ppm the following resonances are caracteristic of the major diastereoisomer **12** : 4.54 (d, J = 13.7 Hz, OH), 4.81 (d, J = 1.3 Hz, H-3), 5.04 (dd, J = 13.7 and 1.3 Hz, H-5); ^{13}C NMR (major diastereoisomer) : 30.1, 48.9, 61.0, 71.5, 84.2, 93.3, 115.8, 127.4, 129.3, 133.2, 135.6, 137.7. Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 4.10; N, 6.79. Found : C, 70.06; H, 3.97; N, 6.76.

(2R, 3R, 5R) and (2S, 3S, 5R)-N-(3-Butenyl-5-phenyl-3-phenylthio-2-trimethylsilyloxymorpholines 14 and 15

Trimethylsilyl chloride (0.524g, 4.83 mmol) was added dropwise at 0°C to a solution of oxazines **12** and **13** (1.1g, 3.22 mmol) and triethylamine (0.49g, 9.66 mmol) in THF (20 ml). The resulting suspension was stirred for 15 min at room temperature. Addition of water (20 ml) and ether (20 ml), followed by usual workup, yielded a residue which was purified by flash chromatography (10% ether/petroleum ether, Rf : 0.85). Compounds **14** and **15** were obtained as a 80/20 mixture (oil, 1.22g, 92%).^1H NMR : 0.22 and 0.33 (two singlets, 9H, $SiMe_3$), 1.8-2.1 (m, 2H, CH_2C=C), 2.4-2.6 (m, 1H, NCH_2), 2.7-3.05 (m, 1H, NCH_2), 3.45-5.2 (m, 7H), 5.5-5.7 (m, 1H, CH_2C=C), 7.1-7.75 (m, 1H, Ph). In the multiplet between 4.5 and 5.1 ppm, the following resonances are caracteristic of the major diastereoisomer **14** : 4.61 (s, H-3), 5.21 (s, H-5); ^{13}C NMR : (major diastereoisomer) : 0.3, 30.5, 48.4, 61.3, 71.4, 80.2, 96.4, 115.5, 126.5, 138.2. Anal. Calcd for $C_{23}H_{31}NO_2SiS$: C, 66.78; H, 7.56; N, 3.39. Found : C, 66.89; H, 7.72; N, 3.54.

(2R,6R,8S)-8-Bromo-5-hydroxy-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane 16

To a suspension of *n*-Bu_4NBr (3.8g, 11.6 mmol) and compounds **14** and **15** (2.4g, 5.8 mmol) in dry ether (100ml) was added dropwise at -50°C a solution of zinc bromide in ether (1M solution, 8.7 ml). The suspension was allowed to reach room temperature within 2h under vigourous stirring. A solution of *n*-Bu_4NF in THF was then added (1.1M solution, 7.9 ml) and stirring was maintained during 12h at room temperature.After addition of water (150 ml) the organic phase was separated and the aqueous suspension was extracted with dichloromethane (3 x 50 ml). Organic layers were washed with water, brine, and dried over $MgSO_4$. Concentration in vacuo gave a residue which was purified by flash chromatography (75% ether/petroleum ether, Rf = 0.7). Hemiacetal **16** was obtained as an oil (50/50 epimeric mixture at C-5, 1.4g, 78 %): ^1H NMR : 1.7-2.4 (m, 5H), 2.6-2.8 (m, 1.5H, H-10), 2.9-3.1 (m, 0.5H, H-10), 3.55-4.1 (m, 4H), 4.72 (d, J = 4.2 Hz, 0.5H, H-5), 5.03 (d, J = 2.5 Hz, 0.5H, H-5), 5.2 (b s, 1H, OH), 7.0-7.5 (m, 5H, Ph); ^{13}C NMR : 31.6, 33.0, 33.7, 48.1, 49.1, 50.8, 50.7, 58.7, 57.6, 59.3, 59.9, 66.4, 68.6, 93.8, 95.2, 128.0, 137.7.

(2R,5S,6R,8S)-5-Trimethylsilyloxy-2-phenyl-8-phenylthio-4-oxa-1-azabicyclo[4.4.0]decane 17

To a solution of compounds **14** and **15** (600 mg, 1.45 mmol) and thiophenol (160 mg, 1.45 mmol) in dichloromethane (15 ml), was added zinc chloride (1M ether solution, 0.145 ml). The solution was refluxed for 24h. Addition of water and usual work up gave a residue which was flash chromatographied (15% ether/petroleum ether). The following products were eluted successively: (i) thiophenol and starting compounds (284mg, Rf = 0.9), (ii) silylated bicyclic hemiacetal **17** (115 mg, 26%, Rf = 0.5).Compound **17** was obtained as an oil : $[\alpha]_D^{20}$ -46.8° (*c* 0.9, $CHCl_3$); ^1H NMR : 0.17 (s, 9H, $SiMe_3$), 1.5-2.0 (m, 4H), 2.1-2.35 (b t, J = 9 Hz, 1H, H-8), 2.7-3.15 (m, 3H), 3.58 (dd, J = 6.7 and 11.1 Hz, 1H), 3.85 (dd, J = 6.7 and 3.5 Hz, 1H), 4.15 (dd, J = 11.1 and 3.5 Hz, 1H), 5.01 (d, J = 2.1 Hz, 1H, H-5), 7.15-7.5 (m, 10H, Ph); ^{13}C NMR : 0.1, 28.9, 45.9, 50.7, 58.2, 59.7, 68.4, 94.6, 127.2, 127.9, 128.5, 128.9, 129.0, 133.0, 139.8. Anal. Calcd for $C_{23}H_{31}NO_2SiS$: C, 66.78; H, 7.56; N, 3.39. Found : C, 66.46; H, 7.71; N, 3.60.

(2R,6R,8S)-5-Hydroxy-2-phenyl-8-phenylthio4-oxa-1-azabicyclo[4.4.0]decane 18

A solution of *n*-Bu_4NF in THF (1.1M solution, 0.896 ml, 0.996 mmol) was added dropwise to a solution of compound **17** (370 mg, 0.9 mmol) in THF (10 ml). The solution was stirred for 15 min at r.t., then water (10 ml) and ether (10 ml) were added. Usual workup and flash chromatography (ether, Rf = 0.8) afforded **18** as an oil (60/40 epimeric mixture at C-5, 250 mg, 83 %). ^1H NMR: 1.5-2.3 (m, 5H), 2.7-2.8 (m, 1.2H, H-10), 2.9-3.1 (m, 0.8H, H-10), 3.6-4.2 (m, 4H), 4.74 (d, J = 4.6 Hz, 0.6H, H-5), 5.1 (d, J = 2 Hz, 0.4H, H-5), 5.15 (b s, 1H, OH), 7.1-7.55 (m, 10H, Ph); ^{13}C NMR (major epimer): 15.1, 28.7, 31.8, 44.3, 50.4, 58.2, 65.7, 93.6, 127.1, 128.4, 137.2, 137.7.

(2R,6R,8R)-8-Acetoxy-5-hydroxy-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***19***
A suspension of hemiacetal **16** (1.3g, 4.2 mmol) and cesium acetate (8g, 41.6 mmol) in DMF (20 ml) was heated at 80°C for 5 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (50 ml) and ether (50 ml). Usual workup followed by flash chromatography (50% ether/petroleum ether, then ether) gave by order of elution: (i) starting compound **16** (300 mg, 23%), (ii) hemiacetal **19** (660 mg, 54%) as an oil, 70/30 epimeric mixture at C-2 (Rf = 0.3 and 0.2, ether) : ^{1}H NMR : 1.25-2.1 (m, 7H), 2.5-2.65 (m, 2H), 3.1-4.1 (m, 5H), 4.77 (d, J = 3.6 Hz, 0.7H, H-5), 5.07 (d, J = 2.8 Hz, 0.3H, H-5), 5.1-5.2 (m, 1H, H-8), 7.2-7.5 (m, 5H, Ph); ^{13}C NMR (major epimer) : 22.0, 25.2, 28.0, 44.5, 54.0, 58.0, 66.5, 68.0, 95.3, 127.9, 128.5, 128.9, 139.8, 170.1.

(2R,6R,8R)-8-Azido-5-hydroxy-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***20***
A solution of **16** (1.3 g, 4.2 mmol) and sodium azide (1.36 g, 21 mmol) in DMSO (30 ml) was heated at 100°C for 12 h. The solution was cooled and water (50 ml) was then added. Usual workup and flash chromatography (ether) yielded by order of elution: (ii) starting compound **16** (400 mg, 29 %), (ii) hemiacetal **20** (326 mg, 29%) as an oil, 75/25 epimeric mixture at C-2 (Rf = 0.35). ^{1}H NMR : 1.4-1.55 (m, 1H), 1.6-2.1(m, 3H), 2.4-2.6 (m, 2H), 3-3.4 (m, 1H), 3.6-4.2 (m, 4H), 4.76 (d, J = 4.4 Hz, 0.75H, H-5), 5.0 (b s, 1H, OH), 5.09 (d, J = 2.4 Hz, 0.25H, H-5), 7.2-7.5 (m, 5H, Ph); ^{13}C NMR (major epimer) : 25.5, 28.4, 44.5, 53.9, 56.1, 57.9, 66.4, 95.6, 127.9, 128.4, 129.9, 137.8.

(2R,6R,8R)-8-Azido-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***21*** *(general procedure)*
Dimethyl sulfoxide (314 mg, 4 mmol) was added dropwise to a solution of oxalyl chloride (276 mg, 2.18 mmol) in CH_2Cl_2 (5 ml) at -50°C. After stirring 5 min at -50°C, hemiacetal **20** (529 mg, 1.82 mmol) in CH_2Cl_2 (5 ml) was introduced. After 1 h at -50°C, triethylamine (899 mg, 9.1 mmol) was added, and the mixture was allowed to warm to r.t. during 1h 30. Addition of water (20 ml) followed by usual workup yielded a residue which was purified by flash chromatography (75% ether/petroleum ether, Rf = 0.45). Lactone **21** was obtained as an oil which crystallized on standing (336 mg, 64%): mp 80°C; $[\alpha]_D^{20}$ -7.6° (*c* 0.3, $CHCl_3$); ^{1}H NMR: 1.5-1.7 (m, 1H), 1.75-1.9 (m, 1H), 1.97 (s, 3H, CH_3CO), 2.1-2.9 (m, 2H), 2.6-2.7 (m, 2H, H-10), 3.73 (t, J = 6.2 Hz, 1H, H-2), 4.03 (b t,J = 5.4 Hz, 1H, H-6), 4.41 (dd, J = 6.2 and 11.2 Hz, 1H, H-3), 4.64 (dd, J = 6.2 and 11.2 Hz, 1H, H-3), 5.1 (b q, J = 4.1 Hz, 1H, H-8), 7.3-7.4 (m, 5H, Ph); ^{13}C NMR : 20.9, 28.1, 30.6, 46.5, 53.9, 67.2, 72.0, 127.9, 128.6, 135.5, 169.7, 170.2. IR ($CHCl_3$) : 1740 cm^{-1}; m/z 289 (M^+), 185, 171, 104. This procedure was followed for the preparation of the lactones described hereafter.

(2R,6R,8S)-8-Hydroxy-8-methyl-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***24*** : From hemiacetal **7** with 2.4 equiv. of reagents; oil, 63%; $[\alpha]_D^{20}$ +40.1° (*c* 0.52, $CHCl_3$); ^{1}H NMR: 1.22 (s, 3H, CH_3), 1.4-1.5 (m, 1H, H-7 or H-9), 1.6-1.7 (m, 1H, H-7 or H-9), 1.98 (ddd, J = 1.1, 3.7 and 8.8 Hz, 1H, H-7 or H-9), 2.1-2.2 (m, 1H, H-7 or H-9), 2.5-2.6 (m, 1H, H-10), 2.9 (b s, 1H OH), 3.66 (dd, J = 5 and 7 Hz, 1H, H-3), 4.02 (dd, J = 5 and 8 Hz, H-5), 4.37 (dd, J = 8 and 11.6 Hz, 1H, H-6), 4.58 (dd, J = 5 and 11.6 Hz, 1H, H-6), 7.3-7.4 (m, 5H, Ar); ^{13}C NMR: 31.6, 40.5, 41.3, 51.2, 58.4, 64.1, 70.9, 74.8, 131.2, 140.0, 170.0. IR ($CHCl_3$): 3400, 1740, 1400 and 1450 cm^{-1}; m/z 261 (M^+), 217, 104.

(2R,6R,8S)-8-Azido-8-methyl-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***26*** : From hemiacetal **8**. Oil, 62%; $[\alpha]_D^{20}$ -42.3° (*c* 0.3, $CHCl_3$); ^{1}H NMR: 1.24 (s, 3H, CH_3), 1.4-1.55 (m, 1H, H-7; H-9), 1.65-1.8 (m, 1H, H-7; H-9), 1.95-2.2 (m, 1H, H-7; H-9), 2.35-2.5 (m, 1H, H-10), 2.9 (td, J = 4.3 and 12.8 Hz, 1H, H-10), 3.45 (dd, J = 4.5 and 9 Hz, 1H, H-3), 3.86 (t, J = 5 Hz, 1H, H-5), 4.49 (dd, J = 5 and 11.2 Hz, 1H, H-6), 4.68 (dd, J = 5 and 11.2 Hz, 1H, H-6), 7.3-7.4 (m, 5H, Ph); ^{13}C NMR: 22.2, 33.8, 36.0, 46.5, 54.9, 59.1, 71.8, 128.2, 128.7, 135.2, 169.4. IR ($CHCl_3$): 2100, 1740, 1450 cm^{-1}; m/z 286 (M^+), 242, 228, 104.

(2R,6R,8S)-8-Bromo-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***27*** : From hemiacetal **16**. Oil, 67%; $[\alpha]_D^{20}$ -57.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR: 1.7-2.1 (m, 4H, H-7; H-9), 2.4-2.5 (m, 1H, H-10), 2.63 (td, J = 3.1 and 12.9 Hz, 1H, H-10), 3.05 (dd, J = 3 and 11.8 Hz, 1H, H-3), 3.55-3.65 (m, 1H, H-8), 3.86 (t, J = 4.5 Hz, 1H, H-5), 4.24 (dd, J = 4.5 and 11 Hz, 1H, H-6), 4.38 (dd, J = 4.5 and 11 Hz, 1H, H-6), 6.9-7.2 (m, 5H, Ph); ^{13}C NMR: 34.2, 37.3, 46.5, 50.1, 57.4, 59.0, 73.0, 128.5, 128.7, 134.0, 167.9. IR ($CHCl_3$): 1740, 650 cm^{-1}; m/z 309 (M^+), 307, 267, 265, 252, 230, 172.

(2R,6R,8S)-5-Oxo--2-phenyl-8-phenylthio-4-oxa-1-azabicyclo[4.4.0]decane ***28*** : From hemiacetal **18**. Oil, 74%; $[\alpha]_D^{20}$ -82.9° (*c* 0.1, $CHCl_3$); ^{1}H NMR: 1.45-2.1 (m, 3H), 2.26 (td, j = 11.9 and 2.5 Hz, 1H, H-8), 2.4-2.55 (m, 1H), 2.8-3.05 (m, 2H), 3.25 (dd, J = 11.6 and 2.8 Hz, 1H, H-6), 4.03 (t, J = 4.3 Hz, 1H, H-2), 4.48 (dd, J = 4.3 and 10.8 Hz, 1H, H-3), 4.64 (dd, J = 4.3 and 10.8 Hz, 1H, H-3), 7.05-7.5 (m, 10H, Ar). ^{13}C NMR: 29.7, 33.6, 44.7, 50.2, 57.9, 58.8, 73.1, 127.5, 128.6, 128.7, 128.9, 133.0, 134.3, 169.0. Anal. Calcd for $C_{20}H_{21}NSO_2$: C, 60.14; H, 5.30; N, 3.51. Found : C, 59.72; H, 5.34; N, 3.35. .

(2R,6R,8R)-8-Azido-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane ***29*** : From hemiacetal **20**. Oil, 85%; $[\alpha]_D^{20}$ +24.1° (*c* 1, $CHCl_3$); ^{1}H NMR: 1.5-1.7 (m, 1H, H-7 or H-9), 1.7-2.15 (m, 2H, H-7 or H-9), 2.15-2.3 (m, 1H, H-7 or H-9), 2.55-2.8 (m, 2H, H-10), 3.7-3.9 (m, 2H, H-3; H-8), 3.94 (dd, J = 5.4 and 7 Hz, 1H,

H-5), 4.34 (dd, J = 7 and 11 Hz, 1H, H-6), 4.62 (dd, J = 5.4 and 11 Hz, 1H, H-6), 7.2-7.5 (m, 5H, Ph); 13C NMR : 29.2, 30.5, 48.2, 53.4, 55.0, 61.0, 71.3, 127.6, 128.3, 136.0, 170.6; IR ($CHCl_3$): 1740,2100 cm^{-1} ; m/z 272 (M^+), 228, 214, 104.

(2R,6R,8S)-8-Acetoxy-8-methyl-5-oxo-2-phenyl-4-oxa-1-azabicyclo[4.4.0]decane **25**

To a solution of lactone **24** (244 mg, 0.934 mmol) and dimethylaminopyridine (183 mg, 1.2 mmol) in dichloromethane (4 ml) was added acetic anhydride (0.125 ml, 1.2 mmol). The mixture was stirred overnight at room temperature, and water (5 ml) was then added. After usual workup and flash chromatography (70 % ether/petroleum ether, Rf = 0.5), acetate **25** was obtained as an oil (141 mg, 50 %): $[\alpha]_D^{20}$ -21.6° (*c* 0.2, $CHCl_3$); ^1H NMR: 1.49 (s, 3H, CH_3), 1.7-1.8 (m, 1H, H-7 or H-9), 1.9-2.2 (m, 2H, H-7 or H-9), 2.06 (s, 3H, $COCH_3$), 2.4-2.6 (m, 2H), 2.8-3.0 (m, 1H, H-10), 3.57 (dd, J = 4.4 and 9.4 Hz, 1H, H-3), 4.1 (dd, J = 4.6 and 6.7 Hz, 1H, H-5), 4.43 (dd, J = 4.6 and 11.3 Hz, 1H, H-6), 4.59 (dd, J = 4.6 and 11.3 Hz, 1H, H-6), 7.3-7.4 (m, 5H, Ph); ^{13}C NMR: 22.3, 23.0, 34.0, 35.0, 46.7, 55.3, 58.7, 71.8, 78.9, 128.1, 128.4, 128.9, 135.6, 169.8, 170.2.

Urethane derivative **22** *(general procedure)*

A solution of lactone **21** (259 mg, 0.9 mmol) in dichloromethane (2 ml) and vinyl chloroformiate (1.5 ml) was refluxed for 24 h. Concentration and flash chromatography of the residue (50% ether/petroleum ether) yielded urethane **22** as an oil (240 mg, 68%): $[\alpha]_D^{20}$ -72.8° (*c* 0.6, $CHCl_3$); ^1H NMR:[22] 1.1-1.8 (m, 4H), 1.96 (s, 3H, $COCH_3$), 2.4-2.5 (m, 1H, H-6), 2.9-3.15 (m, 1H, H-6), 4.05-4.2 (m, 1H), 4.4-4.9 (m, 4H), 5.0-5.2 (m, 1H, CH=C*H*$_2$), 5.1 (t, J = 7 Hz, 1H, H-5), 7.0-7.2 (m, 1H, C*H*=CH_2), 7.15-7.45 (m, 5H, Ph). Anal. Calcd for $C_{19}H_{22}NClO_6$: C, 57.65; H, 5.60; N, 3.54. Found : C, 57.77; H, 5.69; N, 3.69.This procedure was followed for the preparation of the urethanes described hereafter.

Urethane derivative **30** *(from lactone* **25***)* : oil, 71%; $[\alpha]_D^{20}$ +92.7° (*c* 0.2, $CHCl_3$); ^1H NMR: 1.48 and 1.50 (two singlets, 3H, CH_3), 1.5-1.9 (m, 2H, H-3 or H-5), 1.87 and 1.88 (two singlets, 3H, CH_3CO), 2.45-2.65 (m, 2H, H-3 or H-5), 3.05-3.45 (m, 1H, H-6), 3.9-4.1 (m, 1H, H-6), 4.3-4.6 (m, 3H), 4.7-4.9 (m, 2H), 5.0-5.1 (m, 1H), 7.05-7.4 (m, 6H, Ar; C*H*=CH_2). Anal. Calcd for $C_{20}H_{24}NClO_6$: C, 58.61; H, 5.90; N, 3.12. Found : C, 58.31; H, 5.81; N, 3.12.

Urethane derivative **31** *(from lactone* **26***)* : oil, 74%; $[\alpha]_D^{20}$ +62.8° (*c* 0.2, $CHCl_3$); ^1H NMR: 1.32 and 1.33 (two singlets, 3H, CH_3), 1.4-1.9 (m, 2H, H-3 or H-5), 2.45-2.65 (m, 2H, H-3 or H-5), 3.15-3.45 (m, 1H, H-6), 3.95-4.05 (m, 1H, H-6), 4.4-4.9 (m, 4H), 5.05-5.15 (m, 1H), 7.1-7.45 (m, 6H, Ar; C*H*=CH_2). Anal. Calcd for $C_{18}H_{21}N_4ClO_4$: C, 55.03; H, 5.39; N, 14.26. Found : C, 54.88; H, 5.19; N, 14.14.

Urethane derivative **32** *(from lactone* **27***)* : oil, 75%; $[\alpha]_D^{20}$ + 58.4° (*c* 0.5 $CHCl_3$); ^1H NMR: 1.8-2.1 (m, 2H, H-3 or H-5), 2.4-2.4 (m, 1H, H-3 or H-5), 2.5-2.65 (m, 1H, H-3 or H-5), 3.3-3.65 (m, 2H, H-6), 3.85-4.1 (m, 1H), 4.4-5.1 (m, 6H), 7.1-7.5 (m, 11H, Ph; OC*H*=CH_2). Anal. Calcd for $C_{17}H_{19}NBrClO_4$: C, 49.00; H,4.60; N, 3.36. Found : C, 48.82; H, 4.56; N, 3.30.

Urethane derivative **33** *(from lactone* **28***)* : 75%; mp. 68°C; $[\alpha]_D^{20}$ + 38° (*c* 0.3 $CHCl_3$); ^1H NMR: 1.65-2.0 (m, 2H), 2.15-2.25 (m, 1H), 2.5-265 (m, 1H), 3.3-3.65 (m, 2H), 3.85-4.1 (m, 1H), 4.4-5.1 (m, 6H), 7.1-7.5 (m, 11H). Anal. Calcd for $C_{23}H_{24}NClSO_4$: C, 61.94; H, 5.42; N, 3.14. Found : C, 61.93; H, 5.47; N, 3.07.

Urethane derivative **34** *(from lactone* **29***)* : oil, 80%; $[\alpha]_D^{20}$ +72° (*c* 0.6, $CHCl_3$); ^1H NMR: 1.3-1.7 (m, 2H, H-3 or H-5), 1.8-2.0 (m, 1H, H-3 or H-5), 2.3-2.5 (m, 1H, H-3 or H-5), 2.8-3.2 (m, 2H, H-6), 4.05-4.25 (m, 1H), 4.4-4.9 (m, 4H), 4.95-5.15 (m, 2H), 7.05-7.2 (m, 1H, C*H*=CH_2), 7.3-7.5 (m, 5H, Ph). Anal. Calcd for $C_{17}H_{19}N_4ClO_4$: C, 53.76; H, 5.04; N, 14.73. Found : C, 53.70; H, 5.03; N, 14.62.

(2R, 4R)-trans-4-Hydroxy pipecolic acid hydrochloride **23**

An emulsion of urethane **22** (190 mg, 0.48 mmol) in 6N HCl (5 ml) was refluxed for 2 h. The mixture was then cooled and extracted with ether (4 x 5 ml). The aqueous layer was concentrated under reduced pressure, and the residue was dried. Amino acid **23** was obtained as an amorphous solid (80 mg, 92 %): $[\alpha]_D^{20}$ -2.7° (*c* 1, 6N HCl), lit.[15] $[\alpha]_D^{20}$ +2.7 (*c* 1, 6N HCl) for *ent*-**23**; ^1H NMR (D_2O): 1.9-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.33 (td, J = 3.8 and 14.8 Hz, 1H), 3.35-3.5 (m, 2H), 4.2-4.4 (m, 2H). ^{13}C NMR (D_2O, dioxane): 28.5, 32.7, 39.7, 52.9, 67.4, 172.3; m/z 128 (M^+-HCl), 100.

(2R,4S)-4-Methyl-4-hydroxypipecolic acid methyl ester hydrochloride **35** *(General procedure)*

A suspension of urethane **30** (74 mg, 0.18 mmol) in a 6N MeOH solution of HCl (5 ml) was refluxed for 48h, and then concentrated under reduced pressure. The residue was dissolved in MeOH and the solution was concentrated under reduced pressure. This operation was repeated three times to remove the excess of HCl.The residue was then dissolved in water (5 ml), and the resulting solution was extracted with ether (3 x 5 ml). Concentration of the aqueous layer yielded a residue which was dissolved in HCl/MeOH (3 ml, 6N). This solution was again refluxed overnight. Final concentration of this solution and drying of the residue afforded compound **35**: sticky solid (37 mg, 99%): $[\alpha]_D^{20}$ -24.7° (*c* 1.8, MeOH); ^1H NMR (D_2O): 1.41 (s, 3H, CH_3),

1.85-2.05 (m, 2H, H-3 or H-5), 2.29 (dd, J = 15 and 5.2 Hz, 2H, H-3 or H-5), 3.2-3.35 (m, 1H, H-6), 3.55 - 3.7(m, 1H, H-6), 3.91 (s, 3H, OCH_3), 4.34 (b t, J = 5 Hz, 1H, H-2); ^{13}C NMR (D_2O, dioxane): 27.0, 33.7, 36.5, 38.6, 52.3, 53.3, 66.0, 170.0. m/z 155 (M^+- HCl - H_2O), 141. This procedure was followed for the preparation of the pipecolic acid methyl esters described hereafter.

(2R,4S)-4-Azido-4-methyl-pipecolic acid methyl ester hydrochloride 36 : sticky solid (97%); $[\alpha]_D^{20}$ -60.9° (*c* 4.1, MeOH); ^1H NMR (D_2O): 1.56 (s, 3H, CH_3) 1.95-2.05 (m, 2H, H-3 or H-5), 2.29 (dd, J = 15 and 5.5 Hz, 1H, H-3 or H-5), 2.4-2.5 (m, 1H, H-3 or H-5), 3.4-3.5 (m, 1H, H-6), 3.5 -3.6(m, 1H, H-6), 3.96 (s, 3H, OCH_3), 4.52 (b t, J = 5.4 Hz, 1H, H-2); ^{13}C NMR (D_2O, dioxane): 23.4, 31.9, 34.1, 38.3, 52.1, 53.7, 57.2, 169.3. m/z 198 (M^+- HCl), 156.

(2R,4S)-4-Bromopipecolic acid methyl ester hydrochloride 37 : sticky solid (88%); $[\alpha]_D^{20}$ -4.5° (*c* 1.4, MeOH); ^1H NMR (D_2O): 2.1-2.45 (m, 2H, H-3 or H-5), 2.55-2.7 (m, 1H, H-3 or H-5), 3.0-3.15 (m, 1H, H-3 or H-5), 3.29 (td, J = 13 and 3 Hz, 1H, H-6), 3.6-3.8 (m, 1H, H-6), 3.97 (s, 3H, OCH_3), 4.34 (dd, J = 11.8 and 3.4 Hz, 1H, H-2), 4.4-4 (m, 1H, H-4); ^{13}C NMR (D_2O, dioxane): 32.9, 36.1, 42.2, 43.9, 54.7, 57.1, 169.3.

(2R,4S)-4-Phenylthiopipecolic acid methyl ester hydrochloride 38 : 83 %; mp 155°C; $[\alpha]_D^{20}$ -65° (*c* 0.4, MeOH); ^1H NMR (CD_3OD): 1.9-2.1 (m, 2H, H-3 or H-5), 2.5-2.6 (m, 1H, H-3 or H-5), 2.75-2.95 (m, 1H, H-3 or H-5), 3.46 (td, J = 13 and 2.9 Hz, 1H, H-6), 3.7-3.9 (m, 1H, H-4; H-6), 4.17 (s, 3H, OCH_3), 4.51 (dd, J = 12.4 and 3.1 Hz, 1H, H-2), 7.6-7.9 (m, 5H, Ar); ^{13}C NMR (D_2O, dioxane): 15.7, 16.8, 28.8, 32.7, 41.4, 44.1, 54.6, 57.2, 129.3, 130.3, 134.0, 169.8. m/z 251 (M^+), 192.

(2R,4R)-4-Azidopipecolic acid methyl ester hydrochloride 39 : 98%; mp 138°C; $[\alpha]_D^{20}$ -14.5° (*c* 2.4, MeOH); ^1H NMR (D_2O): 2.1-2.4 (m, 3H, H-3 or H-5), 2.5-2.65 (m, 1H, H-3 or H-5), 3.35-3.6 (m, 2H, H-6), 4.0 (s, 3H, OCH_3), 4.45-4.55 (m, 1H, H-4), 4.48 (dd, J = 3.6 and 12Hz, 1H, H-2); ^{13}C NMR (D_2O, dioxane): 25.3, 29.2, 39.1, 52.2, 52.8, 53.7, 169.5; m/z 184 (M+-HCl), 163, 125; IR : 1740, 2100 cm^{-1}.

(2R,5S,6R,7S,12S)-2-Phenyl-4,5-dioxa-1-azatetracyclo[8.4.1^{5,12}.0^{7,12}]pentadecane 41

Dimethyl sulfoxide (392 mg, 5 mmol) was added dropwise to a solution of oxalyl chloride (455 mg, 3,6 mmol) in CH_2Cl_2 (20 ml) at -50°C. After stirring 5 min at -50°C, hemiacetal **10** (1 g, 3.3 mmol) in CH_2Cl_2 (10 ml) was introduced. After 1 h at -50°C, triethylamine (988 mg, 10 mmol) was added, and the mixture was allowed to warm to r.t. during 1h 30. Addition of water (20 ml) followed by usual workup yielded a residue which was purified by flash chromatography (80% ether/petroleum ether, Rf = 0.7). Compound **41** was obtained as an oil which crystallized on standing (301 mg, 32%): mp 88°C; $[\alpha]_D^{20}$ -25.7° (*c* 0.7, $CHCl_3$). ^1H NMR: 1.3-2.1 (m, 10H), 2.2-2.4 (m, 1H), 3.06 (b t, J = 2.6 Hz, 1H), 3.2-3.35 (m, 1H), 3.4-355 (m, 2H), 4.03 (t, J= 7.5 Hz, 1H, H-3), 4.44 (dd, J = 7.5 and 11.9 Hz, 1H, H-3), 5.32 (d, J= 2.5 Hz, 1H, H-5), 7.2-7.4 (m, 5H, Ar). ^{13}C NMR: 23.4, 23.6, 25.3, 29.5, 36.5, 46.8, 48.8, 54.4, 60.5, 62.8, 82.8, 101.9, 126.2, 126.6, 128.3, 141.0. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found : C, 75.37; H, 8.04; N, 4.56.

(2R,6R,7S,12S)-12-Hydroxy-5-oxo-2-phenyl-4-oxa-1-azatricyclo[8.4.0.0^{7,12}]tetradecane 42

The general procedure described above for preparation of lactone **21** was applied to the oxidation of hemiacetal **10** using an excess of oxalyl chloride (3 equiv). Flash chromatography (ether) afforded lactone **42** as a white solid: 37%; mp 142°C; $[\alpha]_D^{20}$ +117.4° (*c* 0.4, $CHCl_3$); ^1H NMR: 1.2-1.8 (m, 8H), 1.9-2.2 (m, 2H), 2.2-2.4 (m, 1H), 2.7-2.9 (m, 1H), 3.1 (b t, J = 11 Hz, 1H), 3.3 (b s, 1H), 3.5 (b s, 1H), 3.9 (dd, J = 5.9 and 9.7 Hz, 1H, H-2), 4.2 (t, J = 10 Hz, 1H, H-3), 4.6 (dd, J = 5.8 and 12 Hz, 1H, H-3), 7.2-7.5 (m, 5H, Ar). ^{13}C NMR: 23.4, 25.6, 29.8, 30.9, 40.9, 41.2, 48.6, 59.3, 63.3, 68.8, 69.5, 126.9, 128.1, 128.8, 138.5, 175.3. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found : C, 71.61; H, 7.71; N, 4.49.

*Urethane derivative 43*See general procedure above. Oil, 82%; $[\alpha]_D^{20}$ +89.4° (*c* 1.6, $CHCl_3$); ^1H NMR: 1.0-1.7 (m, 10H), 1.9-2.15 (m, 2H), 3.15-3.55 (m, 1H), 3.85-4.0 (m, 1H), 4.2-4.8 (m, 5H), 5.08 (dd, J = 6.2 and 7.9 Hz, 1H, C*H*-COO), 7.0-7.2 (m, 1H), 7.2-7.4 (m, 5H, Ar). Anal. Calcd for $C_{21}H_{26}NClO_5$: C, 61.83; H, 6.43; N, 3.43. Found : C, 61.46; H, 6.43; N, 3.22.

(1S,2R,6S)-6-Hydroxy-2-methoxycarbonyl-3-azabicyclo[4.4.0]decane hydrochloride 44

See general procedure above.Sticky solid, 90%; $[\alpha]_D^{20}$ -16.3° (*c* 0,15 MeOH); ^1H NMR (D_2O): 1.4-2.0 (m, 9H), 2.3-2.6 (m, 2H), 3.3-3.45 (m, 1H, H-10), 3.76 (td, J = 12.9 and 4 Hz, 1H, H-10), 3.95 (s, 3H, COOC*H*$_3$), 4.25 (b s, 1H, H-2). ^{13}C NMR (D_2O-dioxane): 24.8, 26.7, 29.7, 40.4, 40.9, 44.9, 45.1, 55.9, 59.4, 70.7, 172.6.

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