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Asymmetric Synthesis of α-Amino Acids via Cationic Aza-Cope Rearrangements

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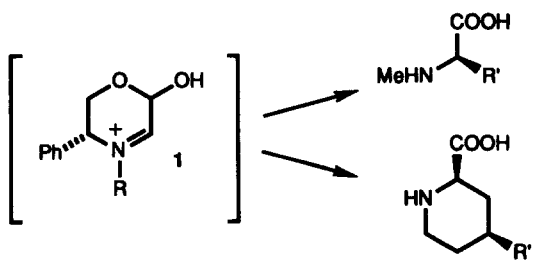
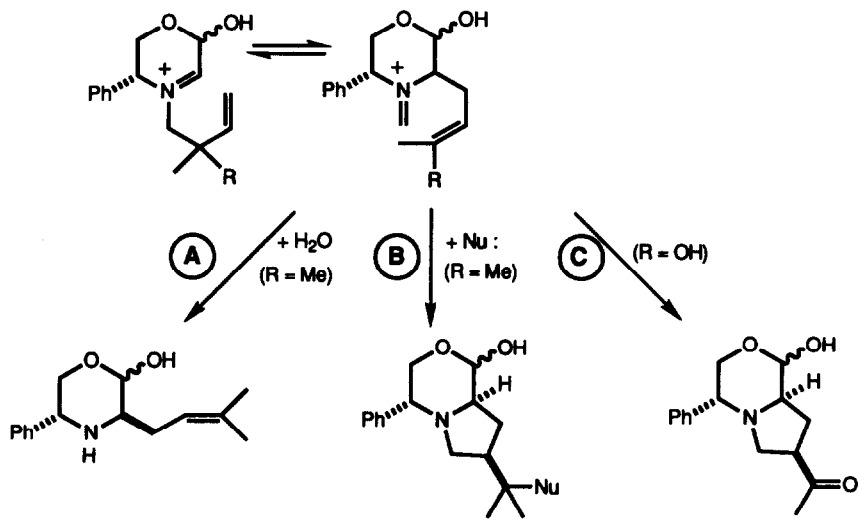
***Abstract** : Ene-iminium intermediates resulting from reaction between glyoxal and β-amino alcohols rearrange by an aza-Cope process. Three different tandem reactions are thus carried out; their first component is this cationic rearrangement, the second step being either an iminium hydrolysis, a nucleophile-induced ene-iminium cyclization or a Mannich reaction. The last two sequences lead to homochiral proline derivatives.*

In order to be of synthetic value, cationic aza-Cope rearrangements must be associated with a subsequent reaction which drives this equilibrated sigmatropic process towards a given product;[1] this is an essential feature in iminium and N-acyliminium chemistry.[2] In this paper, we present three such tandem reactions involving the iminium moiety of type 1 intermediates which result from reaction between (*R*)-β-amino alcohols and glyoxal. The high electrophilicity of these substrates was already exemplified: they react intermolecularly with organozinc reagents[3] and intramolecularly with a N-tethered ethylenic double bond[4,5] leading eventually to acyclic α-amino acids and to pipecolic acid derivatives respectively (Scheme 1). In both cases, attack on the iminium group arose in a totally stereoselective way, thus allowing the asymmetric synthesis of homochiral products.



Scheme 1

When the nitrogen atom of tetrahydrooxazine 1 is linked to a homoallyl chain having a *gem*-disubstituted center adjacent to the ethylenic double bond, a cationic aza-Cope rearrangement occurs. As summarized on Scheme 2, this reaction constitutes the first step of three different tandem reactions whose other components are: (i) iminium ion hydrolysis (path A), (ii) nucleophile-induced ene-iminium cyclization (path B), (iii) Mannich reaction (path C). Whereas the first alternative is relatively poorly documented,[6] the other two processes have been key-steps for achieving many syntheses of complex natural products;[7,8] when applied to the synthesis of homochiral compounds, these works make use of the building block strategy starting from the chiral pool.[9]

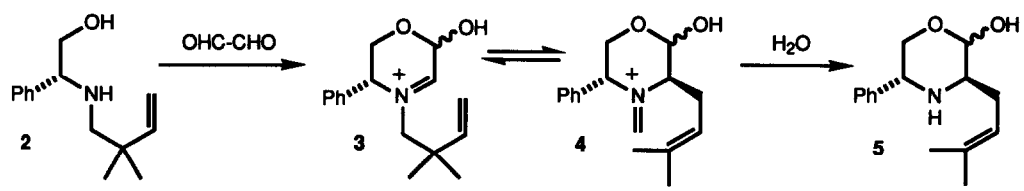


Scheme 2

In the present case, the above three transformations proceed with complete stereoselectivity and, owing to chiral induction, afford valuable homochiral products.[10] In addition, a noteworthy mechanistic problem is addressed: what stereoelectronic control is responsible for the observed stereoselectivity in the ene-iminium and Mannich cyclizations ?

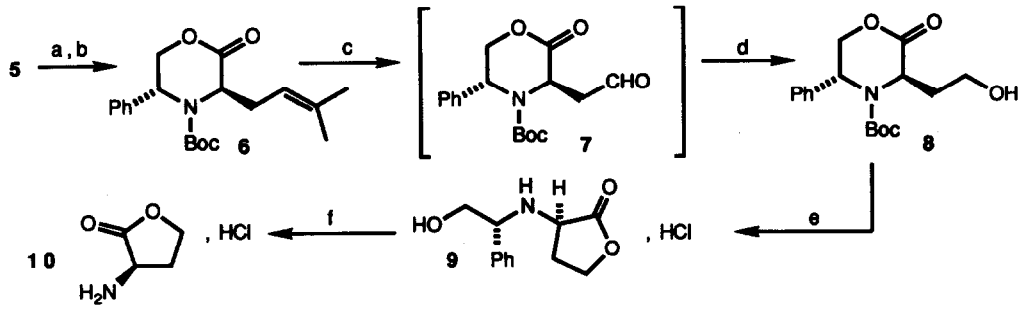
A. AZA-COPE/IMINIUM ION HYDROLYSIS TANDEM REACTION

Reaction of amino alcohol **2** with glyoxal follows two different courses according to the medium. When carried out in water solution, this condensation afforded tetrahydrooxazine **5** showing an ethylenic appendage. This result means that the primary ene iminium system **3**, resulting from the condensation of glyoxal with **2**, rearranges via a cationic aza-Cope process to product **4** which presents another ene iminium framework (Scheme 3). However the methyleneiminium moiety in compound **4** is more prone to react with water[11] than the more substituted iminium group one in **3**, thus leading to the observed product **5** (yield: 54%).



Scheme 3

Absolute configuration of the created stereogenic center in compound **5** was deduced from its transformation into (*R*)-homoserine lactone as shown in Scheme 4. Swern oxidation of the N-Boc derivative yielded lactone **6** which was subjected to reductive ozonolysis. The produced aldehyde **7** was immediately reduced to the corresponding alcohol **8**. N-Deprotection and transesterification of compound **8** resulted from acidic hydrolysis, thus yielding product **9** which was transformed by hydrogenolysis into enantiomerically pure (*R*)-homoserine lactone **10**. The enantiomeric excess and the absolute configuration of this α-amino acid lactone were determined by (^{19}F) NMR analysis of the Mosher amides of **10**, *ent*-**10** and (±)-**10**, the last two reference compounds being synthesized from the commercially available α-amino acids.



(a) $(Boc)_2O$, 69%; (b) 1. $(COCl)_2$, DMSO, 2. Et_3N, 81%; (c) 1.O_3, 2. Me_2S; (d) $NaBH_4$, EtOH, 75%; (e) 6N HCl, 98%; (f) H_2, Pd/C, 1N HCl, 98%.

Scheme 4

This stereochemical outcome corresponds to an axial attack of the ene onto the iminium double bond during the [3.3]-sigmatropic rearrangement (see Fig.1) in agreement with previous results reporting the electrophilic reactivity of such endocyclic iminium ions.[3,4]

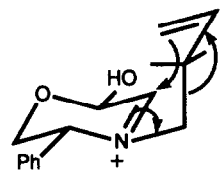
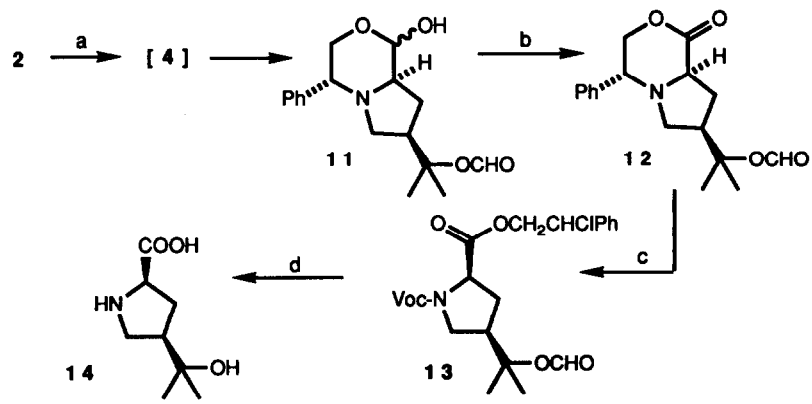


Figure 1. Axial attack onto the $C=N^+$ double bond of intermediate **3** during the cationic aza-Cope rearrangement

B. AZA-COPE/ENE-IMINIUM ION CYCLIZATION TANDEM REACTION

When the usual aqueous solution of glyoxal is diluted with formic acid instead of water, the condensation with amino alcohol **2** gives bicyclic compound **11** resulting from an ene-iminium cyclization of intermediate **4** induced by formic acid. This hemiacetal was transformed into the proline derivative **14** by the three-step procedure depicted in Scheme 5.



(a) OHCCHO, HCO_2H, 76%; (b) 1.$(COCl)_2$, DMSO, 2. Et_3N, 53%; (c) CH_2=CH–OCOCl, 68%; (d) 1. 6N HCl, 2. IRA 68, 96%.

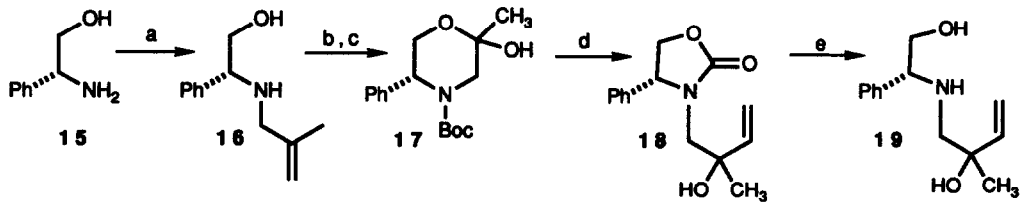
Scheme 5

This result contrasts with what was observed in water solution and is consistent with the known reluctance of methyleneiminium ions to react with formic acid.[12] This is not the case of the more reactive acyl iminium ions which react with formic acid, in similar conditions, and give aminoformate esters.[13]

Intermediate **11** was obtained as a diastereomeric mixture because of easy epimerization of the C-2 center; compounds **12, 13** and **14** were diastereomerically pure as evidenced by their NMR spectra. The absolute configuration of the carboxyl-bearing carbon in **14** corresponds to the stereoselectivity of the aza-Cope rearrangement described above and also of the one which will be presented in section C (*vide infra*). The relative configuration of the two stereogenic centers in this molecule is the result of a stereochemical course which was well documented in similar cases;[13,14] this particular point will be discussed thereafter.

C. AZA-COPE/MANNICH CYCLIZATION TANDEM REACTION

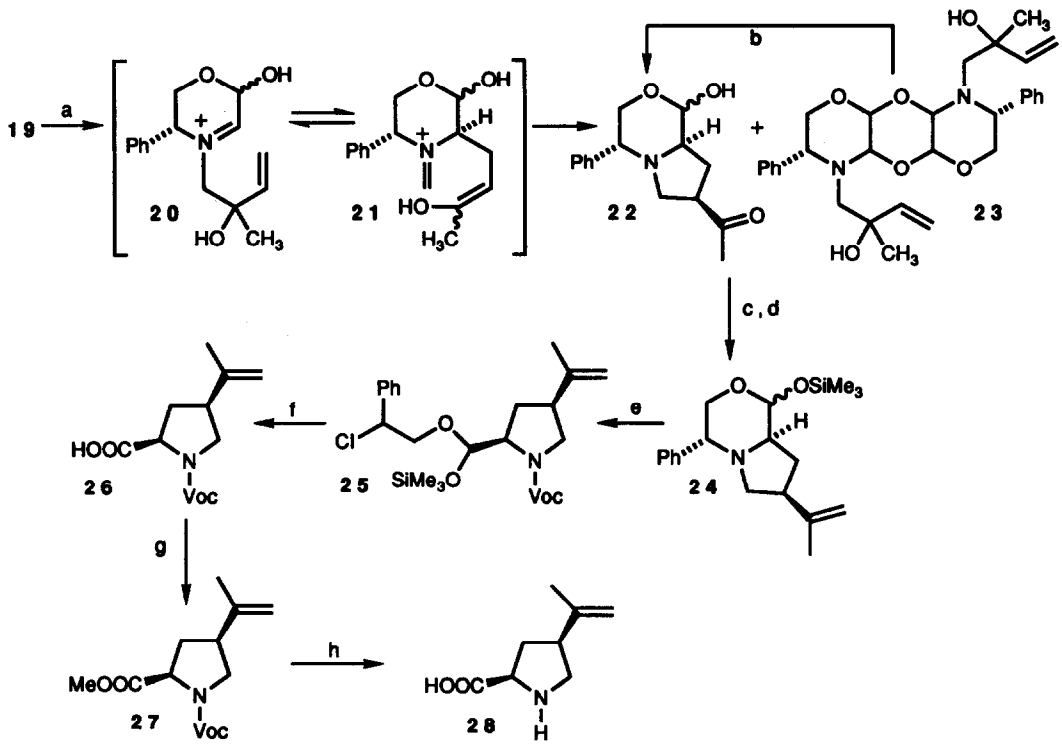
This third sequential reaction starts from another amino alcohol, *i.e.* compound **19** which was synthesized as shown on Scheme 6. This preparation includes: (i) N-alkylation of the usual chiral auxiliary, (*R*)-phenyl glycinol; (ii) ozonolysis of the ethylenic double bond of compound **16**, the amino group being previously protected by transformation into its N-*tert*-butoxycabonyl derivative, and this oxidation was followed by an intramolecular reaction between the produced keto group and the primary hydroxyl which gives rise to an hemiacetal function (two epimers at C-2); (iii) compound **17** was treated with an excess of vinyl Grignard reagent: during this step, a side reaction occurring between the N-Boc and hydroxyde moieties afforded an oxazolidinone ring; (iv) finally, basic hydrolysis of the heterocyclic part of **18** led to the required β-amino alcohol **19**. It is worth mentioning that it was impossible to achieve a substitution reaction between amino alcohol **15** and 2-methyl-2-vinyloxirane (isoprene monoxide) which would have provided a very easy access to compound **19**.



(a) Br-$CH_2C(CH_3)$=CH_2, DBU, 92%; (b) $(Boc)_2O$, 97%; (c) O_3, Me_2S, 90%; (d) CH_2=CH-MgCl(2.5 equiv), 87%; (e) KOH, MeOH, 69%.

Scheme 6

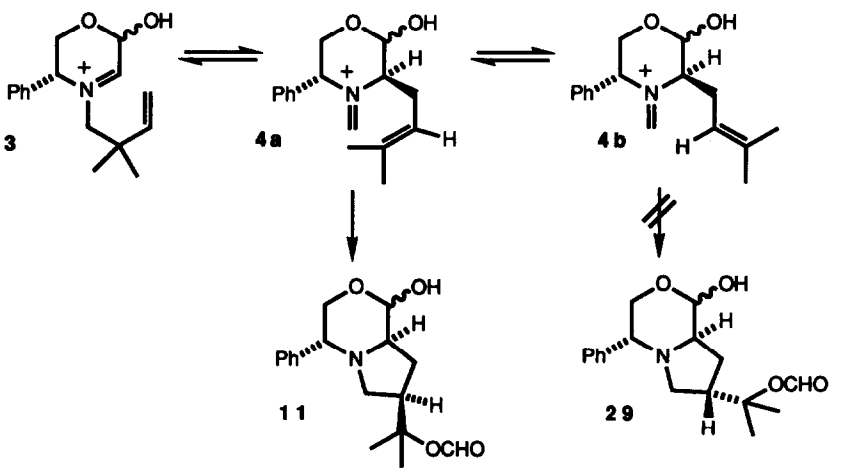
Reaction of amino alcohol **19** with glyoxal proceeded smoothly and yielded a 1:1 mixture of compounds **22** and **23** (Scheme 7). It appears that intermediate **20** was transformed by two pathways into: (i) bicyclic product **22** via aza-Cope/Mannich tandem reaction and (ii) tricyclic product **23** via a head-to-tail self-condensation (similar examples of such reactions have already been reported[15]). However compound **23** was transformed into the required compound **22** by a subsequent acid treatment. The end of the synthesis is straightforward: (i) the hydroxy group in **22** was transformed into the TMS derivative prior to the Wittig methylenation, (ii) N-debenzylation was effected by reaction with vinyl chloroformate, (iii) the N-Voc derivative was oxidized by Jones reagent and the resulting carboxylic acid **26** was esterified (this step allowed an efficient purification by flash chromatography), (iv) saponification and treatment with a basic anion exchange resin afforded proline derivative **27** whose optical purity was ascertained by comparison of its optical rotation with a literature value.[16]



(a) OHC-CHO (1.5 equiv), H_2O-THF, r.t., 95%; (b) p-TsOH, H_2O-THF, r.t., 55%.(c) Me_3SiCl, DMAP, Et_3N, r.t., 73%; (d) $Ph_3P{=}CH_2$, THF, 0°C, 76%; (e) $CH_2{=}CH{-}OCOCl$, CH_2Cl_2, reflux; (f) CrO_3-H_2SO_4, acetone, r.t.; (g) K_2CO_3, MeI, DMF, r.t. (40 % overall yield from **24**); (h) 10N NaOH, reflux, 95%.

Scheme 7

The high level of stereoselectivity displayed by both the ene-iminium and Mannich cyclizations deserves special comment. The *cis* C_6-H and C_8-H relative configuration in products **11** and **22** is governed by steric requirements during the five-membered ring closure and this point was scrutinized by Speckamp and Hiemstra[2] on the basis of a "favorable chair-like transition state of a bridged intermediate". However another parameter might be instrumental to stereoselectivity given that substrate **4** presents two conformations as regards the relative geometry of the double bonds, *i.e.* **4a** and **4b** (Scheme 8). The first one corresponds to the structure of the primary product which results directly from aza-Cope rearrangement whereas conformer **4b** derives from the former by a single bond rotation. Yet diastereoisomer **29** was not produced and the selectively obtained bicyclic compound **11** corresponds exclusively to cyclization of conformer **4a** (similar considerations apply to the Mannich reaction leading to **22**). Since it would hardly be conceivable that the equilibrium between conformations **4a** and **4b** is slower than the cyclization that leads to product **11**, clearly some stereoelectronic factor comes into play in order to control the stereochemical course.



Scheme 8

Actually this result means that the synclinal geometry of the interacting double bonds affording **11** is the more reactive and this is in complete agreement with Seebach and Golinsky[17] general topological rule for the reaction of such trigonal centers. This statement was originally put forward in order to explain the stereochemical course of enamine addition to nucleophilic ethylenic double bonds but had soon gained wide generality.[18]

The above aza-Cope/ene-iminium cyclization as well as the aza-Cope/Mannich tandem reaction define a new entry into the synthesis of proline derivatives. Two peculiar characteristics of these compounds are currently being intensively investigated : they often display biological activity[19] and dramatic conformational changes result from their incorporation into peptides[20]. These properties justify that so many syntheses are devoted to this series.

EXPERIMENTAL SECTION

General comments

^{1}H, ^{13}C, ^{19}F NMR spectra ($CDCl_3$ solution unless otherwise stated) were respectively carried out on a Bruker AC 200 spectrometer at 200, 50 and 188 MHz; chemical shifts are reported in ppm from TMS (13C and 1H NMR) or from α,α,α-trifluorotoluene (^{19}F NMR). 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. 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.

N-(3,3-Dimethylbut-1-en-4-yl)-(R)-phenylglycinol 2

A solution of (*R*)-phenylglycinol (3g, 2.19 mmol) in dichloromethane (30 ml) was added to an ether solution (400 ml) of crude 2,2-dimethylbut-3-enal, prepared according to Julia's procedure[21] from *N,N*-dimethyl-1-phenylthiomethaneamine (4g), in the presence of molecular sieves 4Å (10g). After 2h, the mixture was filtered over $MgSO_4$, the solvent was evaporated and the residue dissolved in ethanol (30 ml). To this solution was added at 0°C sodium borohydride (1g, 26.5 mmol) in ethanol solution (50 ml). The resulting

mixture was stirred for 2h at r.t. and treated by a saturated solution of ammonium chloride (30 ml). After usual workup and flash chromatography (ether/pentane: 50/50), amino alcohol **2** was obtained as white crystals (3g, 63%): mp. 53°C; $[\alpha]_D^{20}$ -59.4° (*c* 0.6, $CHCl_3$); ^1H NMR: 1.02 (s, 3H), 1.04 (s, 3H), 2.30 and 2.41 (AB, J = 11 Hz, 2H), 2.5 (bs, 2H), 3.4-3.5 (m, 1H), 3.65-3.75 (m, 2H), 4.95-5.05 (m, 2H), 5.70-5.85 (m, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR: 24.9, 25.4, 37.8, 58, 65.1, 66.7, 112.2, 127.1, 127.5, 128.6, 141, 146.7. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found : C, 76.46; H, 9.63; N, 6.46.

(3R,5R)-2-Hydroxy-3-(2-methylbut-2-en-3-yl)-5-phenylmorpholine **5**

To an emulsion of amino alcohol **2** (0.5g, 2.3 mmol) in THF (4 ml) and water (4 ml) was added dropwise an aqueous solution of glyoxal (40% wt, 0.29 ml, 2.53 mmol). After stirring at r.t. for 3.5h, 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 (ether/pentane : 85/15). Compound **5** was obtained as a gummy oil (67/33 epimeric mixture at C-2, 304 mg, 54%): ^1H NMR: 1.67 (s, 6H), 2.2-2.6 (m, 2H), 2.9-3.0 (m, 1H), 3.6-4.2 (m, 5H), 4.85 (d, J = 1.7Hz, 0.67H), 5.05 (d, J = 2.3Hz, 0.33H), 4.9-5.1 (m, 1H), 7.25-7.45 (m, 5H); ^{13}C NMR (major isomer): 18, 25.8, 28.6, 52.8, 54.4, 64.9, 92.2, 120, 127.2, 127.5, 128.6, 135.1, 140.1.

N-Boc derivative: A solution of morpholine **5** (0.2g, 0.81 mmol) and *tert*-butyl dicarbonate (353 mg, 1.62 mmol) in ethyl acetate (20 ml) was refluxed during 12h. After cooling, water (20 ml) was added. Usual workup and flash chromatography (ether/pentane: 50/50) afforded *(3R,5R)-N-tert-butoxycarbonyl-2-hydroxy-3-(2-methylbut-2-en-3-yl)-5-phenylmorpholine* as an amorphous solid (193 mg, 69%): ^1H NMR:[22] 1.1 (s, 9H), 1.6-1.7 (m, 6H), 2.15-2.35 (m, 1H), 2.45-2.7 (m, 1H), 3.55 (dd, J = 5 and 12 Hz, 1H), 3.9-4 (m, 2H), 4.25 (bs, 1H), 4.4-4.5 (m, 1H), 5.1-5.2 (m 2H), 7.2-7.3 (m, 5H); ^{13}C NMR (major isomer): 17.8, 25.8, 27.8, 28.3, 55.4, 56.8, 63.6, 80.3, 91.6, 120, 126.3, 128.2, 134.8, 141.7, 156.8. Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found : C, 69.12; H, 8.39; N, 3.99.

(3R,5R)-2,3,4,6-Tetrahydro-3-(2-methylbut-2-en-3-yl)-5-phenyl-N-(t-butoxycarbonyl)-4H-1,4-oxazin-2-one **6**

Dimethyl sulfoxide (241 mg, 3 mmol) was added dropwise to a solution of oxalyl chloride (212 mg, 1.17mmol) in CH_2Cl_2 (5 ml) at -50°C. After stirring 5 min at -50°C, the above *N*-Boc derivative (485 mg, 1.4 mmol) in CH_2Cl_2 (4ml) was introduced. After 1 h at -50°C, triethylamine (691 mg, 7 mmol) was added, and the mixture was allowed to warm to r.t. during 1h 30. Addition of water (15 ml) followed by usual workup yielded a residue which was purified by flash chromatography (ether/pentane: 50/50). Lactone **6** was obtained as an oil which crystallized on standing (391 mg, 81%): mp 88°C; $[\alpha]_D^{20}$ -165,6° (*c* 0.4, $CHCl_3$); ^1H NMR: 1.19 (bs, 6H), 1.47 (bs, 3H), 1.66 (s, 3H), 1.96 (s, 3H), 2.6-2.9 (m, 2H), 4.3-4.5 (m, 1H), 4.81 (dd, J = 2.9 and 11.6 Hz, 1H), 4.8-5.3 (m, 3H), 7.1-7.4 (m, 5H); ^{13}C NMR: 17.8, 25.9, 28.1, 32.6, 54, 57.1, 69.9, 81.3, 118, 125.5, 127.7, 128.8, 136.7, 153.6, 169.3. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found : C, 69.42; H, 7.86; N, 4.02.

(3R,5R)-2,3,4,6-Tetrahydro-3-hydroxyethyl-5-phenyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazin-2-one **8**

An ozone stream was passed through solution of lactone **6** (1.3g, 3.75 mmol) in dichloromethane (250 ml) at - 50°C during 45 min. After elimination of ozone in excess by a nitrogen stream, dimethyl sulfide (2 ml, 27.2 mmol) was introduced. A new addition of dimethyl sulfide (2 ml) was effected at r.t. The resulting solution was stirred at r.t. and the solvent was evaporated. Sodium borohydride (50 mg, 27.2 mmol) was added to an ethanol solution (20 ml) of the residue and, after stirring for 1h, a saturated solution of NH_4Cl (20 ml) was added to the mixture. After usual workup, flash chromatography (ether) yielded alcohol **8** as an oil which crystallizes on standing (0.9g, 74%): mp 96°C; $[\alpha]_D^{20}$ -7.9° (*c* 0.4, $CHCl_3$); ^1H NMR: 1.55 (bs, 9H), 1.9-2.1 (m, 1H), 2.45-2.7 (m, 1H), 3.67-3.90 (m, 1H), 4.2-4.6 (m, 5H), 5.39-5.57 (m, 1H), 7.27-7.43 (m, 5H); ^{13}C NMR: 25.6, 27.4, 27.8, 52.4, 58.8, 61.1, 65.9, 81.5, 127, 127.6, 128.5, 137.3, 154.2, 178.2. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found : C, 63.40; H, 7.27; N, 4.30.

(R)-Homoserine lactone chlorhydrate ***10***

A 6N HCl aqueous solution (10 ml) was added to a THF solution (10 ml) of alcohol **8** (150 mg, 4.67 mmol) and the resulting solution was refluxed during 1h. The solvent was evaporated and the residue dried at 60°C under vacuum. Chlorhydrate **9** was obtained as a gummy oil (125 mg, 98%): ^{1}H NMR: 2.3-2.6 (m, 2H), 3.75-3.95 (m, 2H), 4-4.15 (m, 2H), 4.35-4.5 (m, 2H), 7.3-7.5 (m, 5H); ^{13}C NMR: 25.5, 52.8, 61.6, 63, 67.1, 128.3, 129.7, 130.4, 173.3.

A 1N HCl aqueous solution (10 ml) of the above lactone **9** (125 mg, 0.48 mmol) was stirred under hydrogen pressure (1 atm) during 72h with palladium on carbon. After filtration through a C-18 reversed phase cartridge, concentration and drying, lactone **10** was obtained as an hygroscopic solid (64 mg, 98%): ^{1}H NMR: 2.17-2.4 (m, 1H), 2.58-2.71 (m, 1H), 4.2-4.4 (m, 2H), 4.45 (t, J = 9 Hz); ^{13}C NMR: 30.2, 52.0, 70.9, 178.0. Moscher amide derivative was prepared by action of (+)-MTPACl (0.2 M in THF, 1.65 ml) on lactone chlorhydrate **10** (45.3 mg, 0.33mmol) in THF (5 ml) in the presence of diisopropylethylamine (0.12 ml). After stirring at r.t. during 16h, water was added to the resulting mixture and usual workup afforded, after flash chromatography, the Moscher amide as an oil (100 mg, 96%) whose spectroscopic features correspond to the Mosher derivative of (*R*)-homoserine lactone chlorhydrate described thereafter.

*(S)-Homoserine lactone chlorhydrate ent-***10** *and(±)-homoserine lactone chlorhydrate (±)-***10**

(*S*)-Homoserine (45 mg, 0.378 mmol) was refluxed during 1h in a 1N HCl aqueous solution (5ml). After evaporation, the lactone chlorhydrate was crystallized in methanol-ether (30 mg). Same treatment was applied to racemic homoserine. The CF_3 signals in the (^{19}F) NMR spectra of the corresponding Mosher amides, prepared as above, were at -6.39 and -6.31 ppm respectively for the (*S*) and the (*R*)-homoserine derivatives.

(2R,6R,8R)-5-Hydroxy-8-(1-formyloxy-1-methylethyl)-2-phenyl-4-oxa-1-azabicyclo [3 .3 .0 .] nonane ***11***

To a solution of amino alcohol **2** (1g, 4.56 mmol) in formic acid (20 ml) was added dropwise an aqueous solution of glyoxal (40 % wt, 0.78 ml, 6.84 mmol). After stirring for 1h, the solution was concentrated under reduced pressure and the residue was subjected to flash chromatography (ether then methanol/ether: 5/95). Hemiacetal **11** was obtained as a thick oil (77/23 epimeric mixture at C-2, 1.06g, 76 %): ^{1}H NMR: 1.22 (s, 3H) 1.24 (s, 3H), 1.95-2.10 (m, 2H), 2.4-2.9 (m, 3H), 3.50-3.71 (m, 4H), 4.02-4.15 (m, 1H), 4.91 (d, J = 4 Hz, 0.77H), 5.21 (d, J = 2.5 Hz, 0.23H), 7.15-7.30 (m, 5H), 7.69 (s, 0.77H), 8.01 (s, 0.23 H); ^{13}C NMR (major epimer): 24.0, 24.3, 26.9, 44.4, 52.0, 60.0, 60.1, 62.2, 83.3, 91.9, 128.4, 128.8, 137.6, 160.4.

(2R,6R,8R)-5-oxo-8-(1-formyloxy-1-methylethyl)-2-phenyl-4-oxa-1-azabicyclo [3 .3 .0 .] nonane ***12***

Swern oxidation of hemiacetal **11** (1.2g, 3.9 mmol) was conducted as described above for the oxidation of the N-Boc derivative of compound **5** and yielded after flash chromatography (ether/pentane: 40/60) lactone **12** as an oil which crystallized on standing (573mg, 53 %): mp 107°C; $[\alpha]_D^{20}$ -1.4° (*c* 4.3, $CHCl_3$); ^{1}H NMR: 1.40 (s, 3H), 1.43 (s, 3H), 1.90-2.20 (m, 2H), 2.45-2.55 (m, 2H), 2.9-3.0 (m, 1H), 3.75 (dd, J = 7.5 and 11 Hz, 1H), 4.05 (dd, J = 4.6 and 11 Hz, 1H), 4.15-4.25 (m, 2H), 7.10-7.45 (m, 5H), 7.86 (s, 1H); ^{13}C NMR : 23.9, 24.1, 28.2, 45.9, 54.9, 59.2, 65.5, 71.5, 83.4, 127.1, 128.2, 128.6, 138.1, 160, 172.2. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 68.28; H, 6.98; N, 4.62. Found : C, 68.00; H, 6.98; N, 4.30.

Urethane derivative ***13***

The above lactone **12** (300mg, 1 mmol) was treated with vinyl chloroformate (2ml) in dichloromethane (4 ml) and the solution was refluxed for 5 days. Concentration under reduced pressure and flash chromatography (ether/pentane: 40/60) yielded urethane **13** as an oil (270 mg, 68 %) : $[\alpha]_D^{20}$ +64.4° (*c* 1.8, $CHCl_3$); ^{1}H NMR: 1.48 (s, 3H), 1.51 (s, 3H), 1.65-2.10 (m, 2H), 2.10-2.50 (m, 2H), 3.30-3.51 (m, 1H), 3.55-3.75 (m, 1H), 4.4-4.9 (m, 5H), 5.10 (t, J = 6.6 Hz, 1H), 7.00-7.25 (m, 5H), 7.97 (s, 1H). Anal. Calcd for $C_{20}H_{24}ClNO_6$: C, 58.60; H, 5.90; N, 3.42. Found : C, 58.15; H, 5.65; N, 3.31.

(2R,4R)-4-(1-Hydroxy-1-methylethyl)-2-carboxypyrrolidine ***14***

To a solution of urethane **13** (96mg, 0.234 mmol) in THF (3ml) was added an aqueous solution of 6N HCl, and the solution was refluxed for 3h. After cooling at r.t., concentration under reduced pressure gave a residue which was dissolved in water (5ml) and the resulting solution was washed with ether.To this aqueous layer was then added IRA 68 (750 mg), and the suspension was stirred for 2h. Filtration over a C-18 reversed phase cartridge, concentration and drying yielded amino acid **14** as a white solid (47 mg, 96 %): mp 145°C (dec); $[\alpha]_D^{20}$ +57° (*c* 2, H_2O); ^1H NMR (D_2O): 1.04 (s, 3H), 1.05 (s, 3H), 1.9-2.1 (m, 2H), 2.1-2.3 (m, 1H), 2.97 (t, J = 11.6 Hz, 1H), 3.78 (dd, J = 7.8 and 11.6 Hz, 1H), 3.99 (dd, J = 5.2 and 7.8 Hz, 1H); ^{13}C NMR (D_2O): 23.8, 24.3, 27.3, 43.7, 44.5, 58.7, 67.7, 171.9; m/z 173 (M^+), 158, 128, 110, 68, 58, 41, 30.

(R)-N-(2-Methylprop-1-en-3yl)-phenylglycinol ***16***

3-Bromo-2-methylpropene (7.88g, 0.058 mol) was added dropwise at r.t. to a toluene solution (80 ml) of (*R*)-phenylglycinol (8g, 0.058 mol) and 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU)(8.88g, 0.058 mol). This solution was heated at 80°C for 2h, the stirred at r.t. for 12h. After addition of water, the usual workup gave amino alcohol **16** as an oil (10g, 92%): $[\alpha]_D^{20}$ -216° (*c* 0.6, $CHCl_3$); ^1H NMR: 1.73 (s, 3H), 2.60 (bs, 2H), 2.97 and 3.1(AB, J = 14.2 Hz, 2H), 3.53 (dd, J = 8.6 and 10.5 Hz, 1H), 3.6-3.8(m, 2H), 4.84 (bs, 2H), 7.1-7.3 (m, 5H); ^{13}C NMR: 20.8, 53.0, 63.7, 66.7, 111.1, 127.3, 127.5, 128.6, 140.8, 143.8.

N-Boc derivative: A solution of amino alcohol **16** (20.5g, 0.11 mol) and *tert*-butyl dicarbonate (25 ml, 0.11mol) in ethyl acetate (200 ml) was refluxed during 12h. After cooling, water (100 ml) was added. Usual workup and flash chromatography (ether/pentane: 30/70) afforded *(3R,5R)-N-tert-butoxycarbonyl-N-(2-methylprop-1-en-3-yl)-2-hydroxy-3-(2-methylbut-2-en-3-yl)-phenylglycinol* as an oil (30.3g, 97%): $[\alpha]_D^{20}$ -61.6° (*c* 1.7, $CHCl_3$); ^1H NMR: 1.45 (s, 9H), 1.63 (s, 3H), 3.63-3.70 (m, 2H), 4.04-4.07 (m, 2H), 4.77 (bs, 1H), 4.79-4.83 (m, 2H), 4.98 (bt, J = 7 Hz, 1H), 7.21-7.42 (m, 5H); ^{13}C NMR: 20, 28.3, 49.8, 62.2, 63.5, 80.1, 110.2, 127.5, 127.7, 128.5, 138.1, 142.6, 156.7. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.00; H, 8.65; N, 4.81. Found : C, 69.71; H, 8.31; N, 4.79.

(5R)-N-t-butoxycarbonyl-2-hydroxy-2-methyl-5-phenyl morpholine ***17***

An ozone stream was passed through solution of the above N-Boc derivative (4.5g, 16 mmol) in dichloromethane (100 ml) at - 50°C during 5h. After elimination of ozone in excess by a nitrogen stream, dimethyl sulfide (2.9g, 47 mmol) was added. The resulting solution was stirred at r.t. for 3h and the solvent was evaporated. Flash chromatography (ether/pentane: 50/50) yielded compound **17** as an oil (4.1g, 90%): ^1H NMR: 1.2-1.7 (m, 12H), 2.05-2.15 (m, 1H), 2.74-4.4 (m, 4H), 4.8-5.2 (m, 1H), 7.1-7.4 (m, 5H). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found : C, 64.87; H, 7.86; N, 4.48.

(R)-N-(3-Hydroxy-3-methylbut-1-en-4-yl)-4-phenyloxazolidinone ***18***

A THF solution of vinylmagnesium chloride (15% wt, 20.8 ml, 35 mmol) was added dropwise to a THF solution (60 ml) of hemiacetal **17** (4.1g, 14 mmol). After being refluxed for 12h, the mixture was cooled to r.t. and hydrolyzed by a saturated solution of NH_4Cl (20 ml). Usual workup gave oxazolidinone **18** (57/43 epimeric mixture, 3g, 87%): ^1H NMR: 1.42 and 1.46 (2s, 3H), 3.17-3.44 (m, 2H), 4.01-4.21 (m, 3H), 4.91-4.94 (m, 1H), 5.18-5.39 (m, 2H), 5.94-5.98 (m, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR: 25.1, 25.3, 53.1, 53.5, 59.2, 59.6, 61.9, 62.0, 77.4, 79.2, 114.6, 114.9, 127.3, 127.5, 128.1, 128.2, 128.8, 128.9, 133.2, 139, 158, 158.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found : C, 67.59; H, 7.28; N, 5.21.

(R)-N-(3-Hydroxy-3-methylbut-1-en-4-yl)-phenylglycinol ***19***

Oxazolidinone **19** (3.1g, 12.6 mmol) was dissolved in a 5N EtOH solution of KOH (100ml). After refluxing for 2h, the solution was diluted with water (100 ml) and extracted with ether. Usual workup yielded a residue which was flash chromatographied (ether then ether/methanol: 95/5) to yield amino alcohol **19** as an oil (57/43 epimeric mixture, 1.9g, 69%): ^1H NMR: 1.28 and 1.30 (2s, 3H), 2.45-2.65 (m, 2H), 2.6 (bs, 3H), 3.6-

3.9 (m, 3H), 5.1-5.2 (m, 1H), 5.3-5.45 (m, 1H), 5.75-6.0 (m, 1H), 7.3-7.4 (m, 5H). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found : C, 70.18; H,8.65; N, 6.02.

(2R,6R,8R)-5-hydroxy-8-(1-oxo-1-methylethyl)-2-phenyl-4-oxa-1-azabicyclo [3 .3 .0 .] nonane **22** *and (3R, 7R)-Perhydro-4,8-(1-Hydroxy-1-methylethyl)-3,7-diphenyl-4,8-diaza-1,5,9,10-tetraoxaanthracene* **23**

Glyoxal (40% wt aqueous solution, 1.7ml, 11.5 mmol) was added dropwise to a solution of amino alcohol **19** (1.7g, 7.69 mmol) and p-TsOH (100mg, 0.58 mmol) in THF (50ml) and water (50ml). This solution was stirred for 40h and neutralized by addition of an aqueous saturated solution of $NaHCO_3$ (5ml). Extraction with ether and usual workup, followed by flash chromatography of the residue (ether then ether/methanol: 95/5) yielded two products:

(i) Tricyclic compound **23** (0.9g, 45%) as an amorphous solid (mixture of diastereoisomers):^{1}H NMR (major diastereoisomer): 1.52 (s, 3H), 2.28 and 3.02 (AB, J = 10.5 Hz, 2H), 3.52 (dd, J = 10.5 and 6.1 Hz, 1H), 4.0-4.2 (m, 3H), 4.48 (s, 1H), 4.98 (dd, J = 10.7 and 2.1 Hz, 1H), 5.17 (dd, J = 15.8 and 2.1 Hz, 1H), 5.50 (s, 1H), 5.82 (dd, J = 15.8 and 10.7 Hz, 1H), 7.3-7.5 (m, 5H); ^{13}C NMR: 27.6, 60.4, 62.3, 64.3, 78.4, 88.9, 89.8, 111.6, 127.9, 128.2, 128.6, 138.6, 142.5; m/z (DCI-ammonia): 549, 524, 306, 262; Anal. Calcd for $C_{30}H_{38}N_2O_6$: C, 68.94; H, 7.33; N, 5.36. Found : C, 68.57; H, 7.49; N, 5.20.

(ii) Bicyclic compound **22** as an oil (53/47 epimeric mixture at C-2, 1g, 50%): ^{1}H NMR: 1.9-2.1 (m, 2H), 2.21 and 2.25 (two s, 3H), 2.5-2.72 (m, 1H), 3.0-3.2 (m, 3H), 3.6-3.75 (m, 2H), 4.0-4.25(m, 1H), 4.6 (bs, 1H), 5.0 (d, J = 4 Hz, 0.53H), 5.25 (d, J = 2.5 Hz, 0.47H), 7.25-7.5 (m, 5H); ^{13}C NMR: 26.3, 28.1, 28.9, 29.1, 49.0, 52.1, 52.5, 58.9, 59.3, 59.8, 60.6, 66.0, 66.8, 93.2, 94.7, 127.7, 127.8, 128.3, 128.9, 129.0, 137.7, 137.9, 208.9, 209.4. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found : C, 68.04; H, 7.81; N, 4.96.

Formation of hemiacetal **22** *from tricyclic compound* **23**

A solution of tricyclic compound **23** (1g, 3.84 mmol) and p-TsOH (50mg, 0.29 mmol) in THF (50ml) and water (50ml) was stirred at r.t. for 48h and then neutralized by addition of an aqueous saturated solution of $NaHCO_3$ (5ml). Extraction with ether and usual workup, followed by flash chromatography of the residue (ether then ether/methanol: 95/5) gave hemiacetal **22** as an oil (0.55g, 55%).

O-Timethylsilyloxy derivative of **22**

Trimethylsilyl chloride (20.7ml, 16.46 mmol) was added dropwise to a solution of hemiacetal **22** (2.15g, 8.23 mmol), triethylamine (2.27ml, 16.46 mmol) and dimethylaminopyridine (130mg, 0.82 mmol) in THF (100ml) . The resulting suspension was stirred for 12h at r.t.. After addition of water (100ml) and ether (100ml), usual workup followed by flash chromatography (ether/pentane : 80/20) gave O-TMS **22** as an oil (66/33 epimeric mixture at C-2, 1.97g, 73 %): ^{1}H NMR: 0.13 and 0.15 (two s, 9H), 1.9-2.1 (m, 2H), 2.03 and 2.07 (two s, 3H), 2.52-2.75 (m, 1H), 2.95-3.2 (m, 3H), 3.65-3.75 (m, 2H), 4.05-4.20 (m, 1H), 5.0 (d, J = 4 Hz, 0.33H), 5.25 (d, J = 2.5 Hz, 0.66H), 7.2-7.55 (m, 5H). Anal. Calcd for $C_{18}H_{27}NO_3Si$: C, 64.82; H, 8.16; N, 4.20. Found : C, 64.58; H, 8.37; N, 4.07.

(2R,6R,8R)-5-trimethylsilyloxy-8-(2-methylethenyl)-2-phenyl-4-oxa-1-azabicyclo [3 .3 .0 .] nonane **24**

To a suspension of triphenylphosphonium bromide (8g, 22.4 mmol) in THF (150ml), was added at 0°C a solution of butyllithium in hexane (1.6N, 15ml, 21.7 mmol). The mixture was stirred at 0°C for 10mn, then a solution of the above O-trimethylsilylated derivative of **22** (2.5g, 7.5 mmol) in THF (40ml) was added dropwise and stirring at 0°C was maintained for 15mn, after which a saturated aqueous solution of NH_4Cl (25ml) was added. Dilution with water (100ml) and ether (150ml) gave, after usual workup and flash chromatography (pentane/ether : 90/10) compound **24** as a clear oil (66/33 epimeric mixture at C-2, 2.05g, 76%): ^{1}H NMR: 0.29 and 0.31 (two s, 9H), 1.6-1.8 (m, 1H), 1.85 (s, 3H), 1.92-2.23 (m, 1H), 2.6-3.15 (m, 3H), 3.5-3.75 (m, 1H), 3.8-4.0 (m, 2H), 4.1-4.2 (m, 1H), 4.78 (s, 1H), 4.82 (s, 1H), 4.95 (d, J = 5.8 Hz, 0.66H), 5.29 (d, J = 1.9 Hz, 0.33H), 7.2-7.55 (m, 5H); ^{13}C NMR: 0.2, 0.3, 20.8, 21.0, 30.5, 32.7, 43.2, 44.4, 54.9, 54.6, 60.2,

60.6, 61.3, 61.6, 95.1, 97.6, 109.1, 109.5, 127.3, 127.9, 128.0, 128.2, 128.6, 128.8, 133.5, 133.9, 138.2, 140.4, 146.4, 147.2. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82; N, 4.22. Found : C, 68.78; H, 8.99; N, 4.10.

Urethane derivative 25

The above compound **24** (390mg, 1.17 mmol) was treated with vinyl chloroformate (2ml) in dichloromethane (4 ml) and the solution was refluxed for 45mn. Concentration under reduced pressure yielded crude urethane **24** as an oil (476 mg) which was immediately subjected to Jones oxidation (*vide infra*). An analytical sample was purified by flash chromatography (ether/pentane : 10/90) and showed the following data: ^{1}H NMR: 0.09 and 0.21 (two s, 9H), 1.9-2.2 (m, 2H), 2.4-2.6 (m, 1H), 2.9-3.1 (m, 1H), 3.65-4.1 (m, 4H), 4.4-4.9 (m, 1H), 4.7-5.1(m, 4H), 5.32 (bs, 0.33H), 5.43 (d, J = 2.3 Hz, 0.66H), 7.1-7.45 (m, 6H); Anal. Calcd for $C_{22}H_{32}ClNO_4Si$: C, 60.32; H, 7.36; N, 3.20. Found : C, 60.44; H, 7.47; N, 3.07.

(2R,4R)-2-carboxy-4-(2-methylethenyl)-N-vinyloxicarbonylpyrrolidine 26

Jones reagent (2.67N, 4.4ml, 11.7 mmol) was added dropwise to a solution of the above crude urethane **25** in acetone (20ml) at 0°C. After being stirred at 0°C for 5 mn, the mixture was allowed to warm to r.t. and water (1ml) was added. After 1h at r.t., 2-propanol (1ml) was added dropwise and the suspension was stirred for 15 mn. Addition of water (25ml) and ether (50ml) was followed by usual workup; this gave a clear oil which was partitioned between ether (20ml) and a 0.5N aqueous solution of NaOH (5ml). The aqueous layer was then acidified to pH 2 by careful addition of an aqueous solution of 1N HCl and extracted with ether. Drying (MgSO4) and concentration of the ether layer gave crude acid **26** as a clear oil (187 mg): ^{1}H NMR: 1.79 (s, 3H), 1.8-2.1 (m, 1H), 2.5-2.6 (m, 1H), 2.7-2.95 (m, 1H), 3.25-3.4 (m, 1H), 3.95 (dd, J = 7.5 and 10.4 Hz, 1H), 4.4-4.6 (m, 2H), 4.73 (bs, 1H), 4.83 (bs, 1H), 7.1-7.3 (m, 1H), 8.88 (bs, 1H).

(2R,4R)-2-carbomethoxy-4-(2-methylethenyl)-N-vinyloxicarbonylpyrrolidine 27

Solid K_2CO_3 (344mg, 2.49 mmol) was added into a solution of crude acid **26** (187mg, 0.831 mmol) in DMF (5ml). Iodomethane (0.207ml, 3.32 mmol) was then added dropwise, and the suspension was stirred at r.t. for 1h. Concentration under reduced pressure gave a residue which was partitioned between ether (20ml) and water (20ml). Usual workup and flash chromatography (ether/pentane : 40/60) yielded **27** as an oil (111mg, 40% overall yield from **24**): $[\alpha]_D^{20}$ +79.6° (*c* 2.9, $CHCl_3$); ^{1}H NMR: 1.73 (s, 3H), 1.70-2.9 (m, 1H), 2.38-2.52 (m, 1H), 2.6-2.8 (m, 1H), 3.2-3.5 (m, 1H), 3.73 (s, 3H), 3.88 (dd, J = 7.5 and 10.2 Hz, 1H), 4.3-4.5 (m, 2H), 4.65-4.85 (m, 1H), 4.74 (s, 1H), 4.82 (s, 1H), 7.1-7.25 (m, 1H); ^{13}C NMR: 21.0, 34.3, 35.3, 44.1, 44.8, 50.4, 50.7, 52.2, 59.1, 59.3, 95.1, 111.5, 140.0, 140.2, 140.5, 151.3, 151.8, 172.3, 172.6. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16; N, 5.85. Found : C, 60.33; H, 6.82; N, 5.43.

(2R,4R)-4-(2-methylethenyl)-2-carboxypyrrolidine 28

A 10N aqueous solution of NaOH (2.5 ml) was added into a solution of compound **27** (67.2 mg, 0.283 mmol) in MeOH (1.5 ml). The mixture was refluxed for 14h and cooled to r.t. After dilution with water (5ml), the solution was washed with CH_2Cl_2 (3x3ml), and was passed through a column packed with an ion exchange resin (DOWEX-1, OH^- form)[23]. Elution, effected by water until neutrality and then by a 1N aqueous solution of formic acid, afforded, after concentration and drying, the amino acid **28** as a white solid (41.6 mg, 95 %): mp > 260°C; $[\alpha]_D^{20}$ +28.4° (*c* 0.4, H_2O); lit.[16] $[\alpha]_D^{20}$ +30.5° (*c* 0.4, H_2O); ^{1}H NMR (D_2O): 1.63 (s, 3H), 1.80 (td, J = 10 and 13 Hz, 1H), 2.39-2.56 (m, 1H), 3.11 (t, J = 11 Hz, 1H), 3.40 (dd, J = 3.5 and 7 Hz, 1H), 4.06 (t, J = 8.5 Hz, 1H), 4.72 (bs, 1H), 4.80 (bs, 1H); ^{13}C NMR (D_2O): 19.4, 32.9, 44.1, 48.1, 60.5, 110.9, 142, 170.7.

REFERENCES AND NOTES

1. Ho, T.L. *Tandem Organic Reactions*; Wiley: New York, 1992; p.124.; Carruthers, W. *Some Modern Methods of Organic Synthesis*, Cambridge University Press, 3rd edition, 1992; p. 178.
2. Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. For applications of acyliminium chemistry in the field of proline derivatives, see: Renaud, P.; Seebach, D. *Helv. Chem. Acta* **1986**, *69*, 1704; Thaning, M.; Wistrand, L.G. *Helv. Chem. Acta* **1986**, *69*, 1711.
3. Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343.
4. Agami, C.; Couty, F.; Poursoulis, M.; Vaissermann, J. *Tetrahedron*, **1992**, *48*, 431.
5. A similar reactant possessing a O-tethered (allyloxy hemiacetal) ethylenic appendage also displayed an intramolecular ene-iminium reaction leading to a lactone: Agami, C.; Couty, F.; Lin, J. *Heterocycles*, **1993**, *36*, 25.
6. Castelhano, A.L.; Krantz,A.; *J. Am. Chem. Soc.* **1984**, *106*, 1877; Cook, G.R.; Stille, J.R. *J. Org. Chem.* **1991**, *56*, 5578.
7. For nucleophile-induced ene-iminium cyclizations following aza-Cope rearrangements, see: Meyers, A.I.; Miller, D.B.; White, F.H. *J. Am. Chem. Soc.* **1988**, *110*, 4778; Mooiwer, H.H.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron*, **1991**, *47*, 3451;Hays, S.J.; Malone, T.C.; Johnson, G. *J. Org. Chem.* **1991**, *56*, 4084; Gelas-Mailhe, Y.; Gramain, J.C.; Louvet, A.; Remuson, R. *Terahedron Lett.* **1992**, *33*, 73.
8. For Mannich reactions following aza-Cope rearrangements, see: Overman, L.E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310; Overman, L.E.; Kakimoto, M. J.; Okasaki, M.E.; Meier, G.P. *J. Am. Chem. Soc.* **1983**, *105*, 6622; Overman, L.E.; Robertson, G.M.; Robichaud, A.J. *J. Am. Chem. Soc.* **1991**, *113*, 2598.
9. For an overview of this topic, see: Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385.
10. Preliminary communications: Agami, C.; Couty, F.; Poursoulis, M. *Synlett* **1992**, 847; Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A. *Synlett* **1993**, in press.
11. Böhme, H.; Haake, M. Methyleneiminium salts. In *Iminium Salts in Organic Chemistry*; Böhme, H.; Viehe, H.G. Eds.; Wiley: New York, 1976, part 1; p. 107.
12. Böhme, H.; Backhaus, P. *Liebigs Ann. Chem.* **1975**, 1790; ref. 11, p.162.
13. Ent, H.; de Koning, H.; Speckamp, W.N. *Tetrahedron Lett.* **1983**, *24*, 2109.
14. Hart, D.J.; Yang, T.K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.
15. Agami, C.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C. *Tetrahedron*, **1990**, *46*, 7003.
16. Baldwin, J.E.; Li, C.H. *J. Chem. Soc., Chem. Commun.* **1987**, 166.
17. Seebach, D.; Golinsky, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
18. See *inter alia* : Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* **1984**, *106*, 7970; Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron*, **1985**, *41*, 1693; Danishefsky, S.J.; De Ninno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082; Agami, C. *Bull. Soc. Chim. Fr.*, **1988**, 499; Pearson, A.J.; Blystone, S.L.; Nar, H.; Pinkerton, A.A.; Roden, B.A.; Yoon, H. *J. Am. Chem. Soc.* **1989**, *111*, 134.
19. Johnson, R.; Koerner, J.F. *J. Med. Chem.* **1988**, *31*, 2057.
20. Delaney, N.G.; Madison, V. *J. Am. Chem. Soc.* **1982**, *104*, 6635.
21. Michelot, D.; Lorne, R.; Huynh, C.; Julia, S. *Bull. Soc. Chim. Fr.* **1976**, 1482.
22. Owing to the conformational exchange of the carbamate moiety, which is slow on NMR time scale, the ^{1}H NMR spectra of urethanes showed broadened signals and some of the ^{13}C NMR resonances are split. Similar effects are described in: Williams, R.M.; Sinclair, P.J.; Zhai, D.; Chen. D. *J. Am. Chem. Soc.* **1988**, *110*, 1547.
23. Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.