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A Novel Synthesis of 2,5-Dihydropyrrole Derivatives as Enantiomerically Enriched Building Blocks

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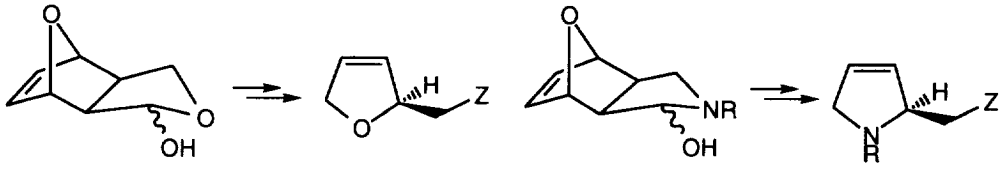
Abstract : A general synthesis of optically active 2,5-dihydropyrroles (3-pyrrolines) substituted at the 2-position by a functionalized chain is described. A highly stereoselective intramolecular Michael reaction afforded the five-membered nitrogen rings with an excellent enantiomeric purity. The unsaturation was generated by a retro Diels-Alder reaction.

Introduction

Alkaloids containing five membered nitrogen heterocycles such as pyrrolidines [1], pyrrolizidines [2] or indolizidines [3] are found in numerous sources and have recently attracted much attention due to their interesting biological activities. In particular polyhydroxylated alkaloids of this type can act as powerful and selective inhibitors of glycosidases and exhibit bactericidal, antidiabetic and antiviral activities. Consequently, the development of general and selective methods for the synthesis of such compounds either in racemic or in optically active form is an active field of research.[4] Most of the synthetic approaches reported so far are based on functional group manipulations of products coming from the chiral pool such as sugars. It appeared to us that chiral 2-substituted 2,5-dihydropyrroles [5] could be useful intermediates for the enantioselective synthesis of these alkaloids since the double bond would allow the stereoselective introduction of one or two hydroxyl groups and the 2-functionalized chain would help to create the second five or six membered ring.

We have recently described the synthesis of optically active 2-substituted-2,5 dihydrofurans **2** starting from the lactol **1**.[8] We wish to report in this paper the use of an analogous strategy for the synthesis of enantiomerically enriched 3-pyrrolines, **4**, from the hydroxy amides or carbamates **3**. This method involves a highly stereoselective tandem Wittig-Horner/intramolecular Michael reaction followed by a retro Diels-Alder cleavage.



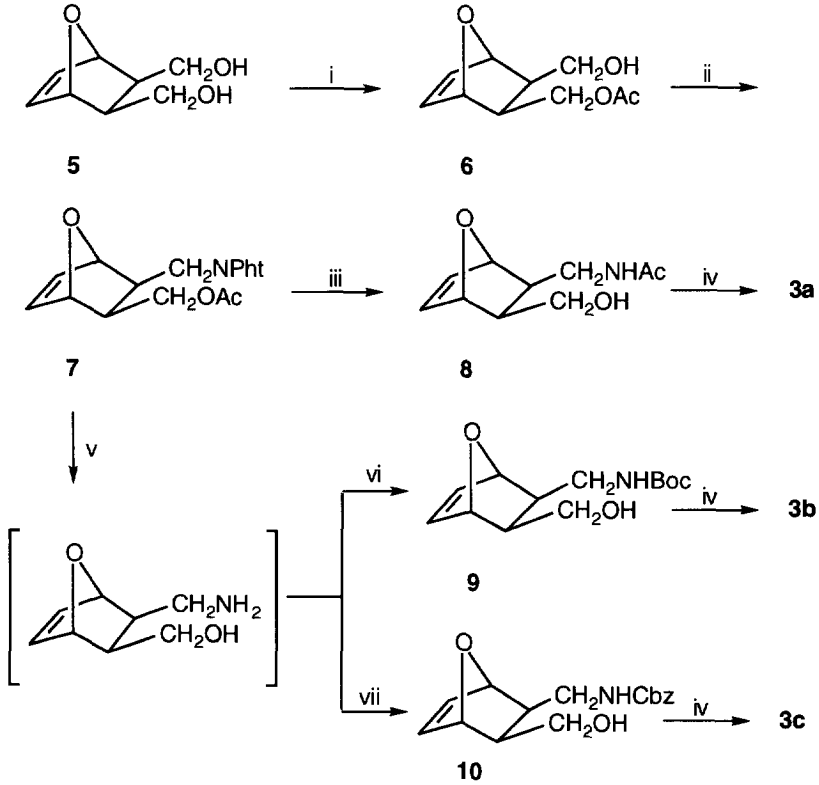
1 **2** **3a** R = $COCH_3$ **b** R = COOtBu **c** R = $COOCH_2Ph$ **4**

Z = CO_2CH_3, CN, $COCH_3$

Synthesis of the optically active hydroxy amide 3a and hydroxy carbamates 3b and 3c

Preparation of the key compounds **3a**, **3b** and **3c** started with the diol **5** arising from the lithium aluminium hydride reduction of the commercially available adduct of furan with maleic anhydride. Transesterification of vinyl acetate with diol **5** in the presence of the lipase of *Pseudomonas cepacia* (Amano) afforded with high yield (75%) the enantiomerically pure monoacetate **6**.[9] Transformation of **6** into the desired compounds **3** was effected by the sequence of reactions depicted in scheme 1. Introduction of the amino functionality was accomplished by the well known Mitsunobu reaction.[10] Aminolysis of the resulting phtalimide **7** gave directly the N-acetyl amino alcohol **8** by a spontaneous transfer of the acetyl group from the oxygen to the nitrogen atom of the intermediate formed. The N-Boc and the N-Cbz amino alcohols **9** and **10** were obtained from compound **7** by acid hydrolysis of the acetate, followed by aminolysis of the phtalimide group and final protection of the free amine by reaction with di-tert-butyldicarbonate or benzylchloroformate respectively. Swern oxidation [11] of the primary alcohol moiety of **8**, **9** or **10** gave mixtures of the diastereomeric hemiaminals **3a**, **3b** or **3c**.[12]

Scheme 1[a)]

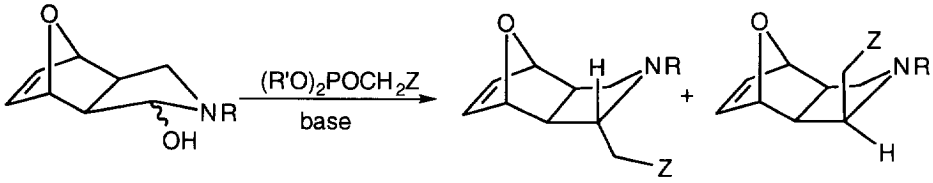


a) Reagents and conditions : i] CH_2=CH-OAc, lipase PS, RT, 1.7 hours (75%) ; ii] Phtalimide, PPh_3, DEAD, THF, RT, 2h (87%) ; iii] CH_3NH_2 aq., CH_3OH, 50°C, 12 h (95%) ; iv] DMSO, $COCl_2$, NEt_3, -78°C, (> 90%) ; v] 1) MeOH, HCl ; 2) CH_3NH_2 aq., MeOH ; vi) Boc_2O, KOH, H_2O, t-BuOH (80% overall from **7**) ; vii] $ClCO_2CH_2Ph$, K_2CO_3, CH_2Cl_2/H_2O (80% from **7**).

Tandem Wittig-Horner/intramolecular Michael reactions

Intramolecular Michael reactions are interesting synthetic tools which can be used for the formation of five or six membered heterocycles.[13] For instance it has already been reported in the literature [14] that, starting from α-hydroxypyrrolidines, tandem Wittig (or Wittig-Horner) olefination / intramolecular Michael cyclizations gave rise to α-substituted pyrrolidines. The yields were in general good but when chiral substrates were used, the diastereoselectivity of the cyclization step was dependent on the nature of the substrate : high 1,2-asymmetric induction was observed only by ring-closure of Z α,β-unsaturated esters [14c] and high 1,4-asymmetric induction was achieved only with very bulky substituents.[14a]

Reaction of the hemiaminals **3a**, **3b** or **3c** with the anion of various stabilized phosphonates in THF under reflux gave rise to the tricyclic pyrrolidines **11** to **15** with good to excellent yields and a high level of diastereoselectivity (~ 16/1) independent of the nature of the phosphonate, of the base and of the N-protecting groups as shown in Table I.



3a R = $COCH_3$
b R = COOtBu
c R = $COOCH_2Ph$

11-15 **11'-15'**

Table I. Stereoselectivity and yields of the tandem Wittig Horner-Michael reactions

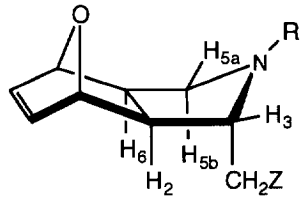
Substrate	Reagent	Base	Products	Yield %	de[a)]
3a	$(CH_3O)_2POCH_2CO_2CH_3$	HNa	**11+11'**[b)]	72[c)]	88
3a	$(C_2H_5O)_2POCH_2CN$	Cs_2CO_3	**12+12'**	90[c)]	90
3a	$(CH_3O)_2POCH_2COCH_3$	Cs_2CO_3	**13+13'**	62[c)]	86
3b	$(CH_3O)_2POCH_2CO_2CH_3$	HNa	**14+14'**	85	88
3c	$(C_2H_5O)_2POCH_2CON(CH_3)OCH_3$	HNa	**15+15'**	81	82

a) de were determined by careful examination of the ^1H NMR spectra of crude compounds.

b) In this case the two diastereomers could not be separated.

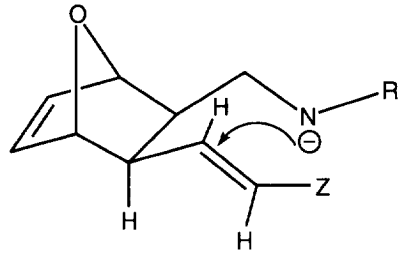
c) Overall yields from **8**.

The exo position of the substituents CH_2Z in the major diastereomers **11-15** is suggested by the small coupling constants J_{H2H3} (2 to 3 Hz) and J_{H5aH6} (3 to 4 Hz) observed in their ^1H NMR spectra. Effectively, simple molecular mechanics calculations (MMX program, PCM4 version) show that in the most stable conformations of **11-15** as well as of **11'-15'**, these substituents adopt a pseudo axial position in order to minimize their steric interaction with the N-protecting groups.



In such conformations, the small values of the coupling constants J_{H2H3} and J_{H5aH6} are only compatible with exo positions of the -CH_2Z chains. Furthermore the stereochemistry of **11** and **12** have been confirmed by their chemical transformations into the known Geissman lactone.[15]

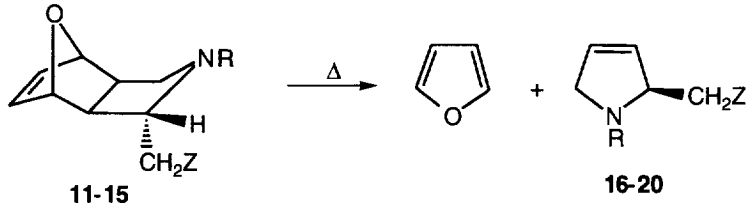
The high diastereoselectivity observed in all cases could result either from a kinetic or a thermodynamic control. However, pure diastereomers **12** or **12'** could not be equilibrated under the reaction conditions used for their preparation. These experiments indicate that the intramolecular Michael reactions are probably kinetically controlled.[16] The stereoselectivity in favor of the "exo" compounds **11-15** can be rationalized by considering the geometry of the transition state. Due to steric interactions, the preferred conformation is assumed to be best represented by **A**, with the hydrogen in allylic position eclipsing the double bond.[17] The attack of the nitrogen nucleophile would then take place preferentially from the Si-face of the double bond to afford the diastereomers **11-15**.



A

Retro Diels-Alder reactions

Heating of the pure compounds **12-15** as well as the mixture (**11+11'**) in flash thermolysis conditions (500°C, contact time 50 ms) afforded 2-substituted protected 3-pyrrolines of high enantiomeric purities in excellent yields (Table 2).



11-15 **16-20**

Table 2. Synthesis of optically active pyrrolines

Substrate	Product	Yield %[a]	$[\alpha]_D^{20}$	ee%[b]
11+11'	**16**	88	-211 ($CHCl_3$, C = 1)	88
12	**17**	91	-354 ($CHCl_3$, C = 0.9)	≥ 98
13	**18**	82	-266 ($CHCl_3$, C = 0.7)	≥ 98
14	**19**	71	-189 ($CHCl_3$, C = 1)	≥ 98
15	**20**	60	-169 ($CHCl_3$, C = 0.8)	not determined

a) Yields are given for pure isolated compounds.

b) Enantiomeric excesses were determined by capillary GC with chiral Cidex B column.

In summary we described here an efficient synthesis of enantiomerically enriched 3-pyrrolines which are useful building blocks for the synthesis of polyhydroxylated alkaloids.

EXPERIMENTAL SECTION

General : IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silicagel 60F-254 precoated on glass.

(+)-(1S,2S,3R,4R)-2-Acetoxymethyl-3-phtalimidomethyl-7-oxabicyclo[2.2.1]hept-5-ene (7). To a stirred solution of alcohol **6** [9] (2.01 g, 10.15 mmol), triphenylphosphine (2.92 g, 11.15 mmol) and phtalimide (1.64 g, 11.15 mmol) in dry tetrahydrofuran (50 mL) was added dropwise diethyl azodicarboxylate (1.76 mL, 11.15 mmol). The resulting mixture was stirred for 2 h and tetrahydrofuran was evaporated in vacuo. The residue was triturated with ether (100 mL) and the solid formed was washed with ether (2x100 mL). Crystallization from ethanol afforded 2.88 g (87%) of **7** as a colorless solid : mp 170°C; $[\alpha]_D^{20}$ = +64 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1750, 1730, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.0 - 2.2 (m, 2H), 2.1 (s, 3H), 3.79 (d, J = 7 Hz, 2H), 4.18 (dd, J = 11 Hz, J' = 5 Hz, 1H), 4.36 (dd, J = 11 Hz, J' = 7 Hz, 1H), 4.7 (bs, 1H), 4.84 (bs, 1H), 6.26 - 6.37 (m, 2H), 7.81 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.0, 37.9, 39.5, 39.6, 64.0, 80.4, 80.9, 123.4, 132.0, 134.1, 135.3, 135.7, 168.5, 170.8; CIMS (NH_3) m/z (relative intensity) : 345 (MNH_4^+, 100). Anal. calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found : C, 65.84; H, 5.22; N, 4.28.

(+)-(1S,2S,3R,4R)-3-Acetamidomethyl-2-hydroxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (8). To a solution of compound **7** (1.62 g, 4.95 mmol) in ethanol (60 mL) was added a 33% aqueous solution of methylamine (2.1 mL, 19.8 mmol). The solution was stirred for 12 h at 50°C. After addition of silicagel (5 g), solvents were evaporated. The residue was purified by chromatography on silicagel (CH_2Cl_2/EtOH 85/15) to give 922 mg (94.5%) of amide **8** as a colorless solid : mp 143.5°C; $[\alpha]_D^{20}$ = +34 (c 1, $CHCl_3$); IR ($CHCl_3$) 3470, 1680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.9 (m, 2H), 2.0 (s, 3H), 2.25 (m, 1H), 3.45 (m, 2H), 3.85 (m, 2H), 4.70 (s, 1H), 4.80 (s, 1H), 6.45 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.3, 39.2, 39.8, 42.2, 62.1, 80.9, 81.7, 135.4, 135.8, 170.6; CIMS (NH_3) m/z (relative intensity) : 215

(MNH_4^+, 30), 198 (MH^+, 100). Anal. calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.11. Found : C, 60.83; H, 7.46; N, 7.20.

(+)-(1S,2S,3R,4R)-3-Tertiobutoxycarbonylaminomethyl-2-hydroxymethyl-7-oxabicyclo [2.2.1]hept-5-ene (9). A suspension of phtalimide **7** (0.986 g, 2.93 mmol) in methanol (15 mL) containing a small amount (0.2 mL) of concentrated aqueous HCl was heated under reflux for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in methanol (18 mL) containing a 33% aqueous solution of methylamine (1.5 mL, 17.6 mmol). The solution was heated under reflux for 2.5 h and the solvents were removed *in vacuo*. The solid obtained was dissolved in a mixture of water (4 mL) and tert-butanol (2 mL) and to this solution was successively added potassium hydroxide (0.41 g, 7.32 mmol) and di-tert-butylcarbonate (1.7 mL, 7.32 mmol). The mixture was stirred for 15 h at room temperature and extracted with dichloromethane (4x10 mL). The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure and the residue was purified by chromatography on silicagel (CH_2Cl_2/EtOH 95/5) to give 600 mg of alcohol **9** as a colorless solid : mp 128°C; $[\alpha]_D^{20}$ = +15 (c 0.7, $CHCl_3$); IR ($CHCl_3$) 3400, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.85 (m, 3H), 3.10 - 3.45 (m, 2H), 3.65 - 3.9 (m, 2H), 4.73 (bs, 1H), 4.85 (bs, 1H), 5.05 (m, 1H), 6.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3, 40.2, 42.0, 62.0, 79.4, 80.7, 81.3, 135.4, 135.6, 156.1; CIMS (NH_3) m/z (relative intensity) : 217 (100), 200 (41), 156 (91). Anal. calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found : C, 60.99; H, 7.91; N, 5.55.

(+)-(1S,2S,3R,4R)-3-Benzyloxycarbonylaminomethyl-2-hydroxymethyl-7-oxabicyclo [2.2.1]hept-5-ene (10). Phtalimide **7** (950 mg, 3.3 mmol) was successively treated by MeOH/HCl then $MeNH_2$/MeOH as described for the preparation of **9**. The residue was dissolved in a mixture of water (15 mL) and dichloromethane (15 mL) and after addition of potassium carbonate (920 mg, 6.7 mmol) and benzyl chloroformate (0.95 mL, 6.7 mmol), the solution was stirred for 2 h at rt. After decantation, the aqueous phase was extracted with dichloromethane (4x20 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated *in vacuo* and the residue was purified by chromatography on silicagel to give 770 mg (80%) of compound **10** as a colorless solid : mp 102°C; $[\alpha]_D^{20}$ = +16 (c 0.8, $CHCl_3$); IR ($CHCl_3$) 3460, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.79 (m, 1H), 1.89 (m, 2H), 3.4 (m, 2H), 3.80 (m, 2H), 4.72 (bs, 1H), 4.83 (bs, 1H), 5.11 (s, 2H), 5.4 (m, 1H), 6.38 (m, 2H), 7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.3, 40.8, 42.0, 62.2, 66.7, 80.9, 81.4, 128.1, 128.5, 135.5, 135.6, 136.4, 156.5; CIMS (NH_3) m/z (relative intensity) : 307 (MNH_4^+, 46), 290 (MH^+, 100). Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found : C, 66.63; H, 6.32; N, 4.82.

(1S,2S,6R,7R)-4-Aza-4-acetyl-10-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-ol (3a). To a solution of oxalyl chloride (1.11 mL, 12.7 mmol) in dry dichloromethane (25 mL) cooled to -78°C was added dropwise a solution of dimethylsulfoxide (1.81 mL, 25.5 mmol) at such a rate that the temperature remained below -65°C. After 2 min a solution of alcohol **8** (2.28 g, 11.5 mmol) in chloroform (45 mL) was added dropwise at -70°C and the reaction mixture was stirred at this temperature for 1 h. Triethylamine (8.05 mL, 57.8 mmol) was then added and after 30 min the solution was allowed to warm to room temperature and was vigorously stirred with a saturated aqueous solution of potassium carbonate (90 mL). After decantation, the aqueous phase was extracted with dichloromethane (5x90 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silicagel (CH_2Cl_2/EtOH/NEt_3 89.5/10/0.5) gave a yellow oil containing

3a [as two diastereomers (ratio ~ 90/10)] and dimethylsulfoxide. A small fraction of the pure major diastereomer could be obtained as a yellow oil : IR (film) 3700, 3400, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.38 (dd, J = 8.4 Hz, J' = 2.2 Hz, 1H), 2.63 (ddd, J = 8.4 Hz, J' = 8.4 Hz, J" = 3.4 Hz, 1H), 3.42 (dd, J = 11.2 Hz, J' = 3.4 Hz, 1H), 3.92 (dd, J = 11.2 Hz, J' = 8.4 Hz, 1H), 4.45 (bs, 1H), 4.75 (bs, 1H), 4.95 (bs, 1H), 5.55 (bs, 1H), 6.35 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (Two rotamers are present) δ 22.5 and 21.8, 42.6 and 41.1, 50.6 and 48.3, 51.6 and 54.4, 81.7 and 81.5, 83.8 and 84.2, 84.5 and 85.7, 136.0 and 136.2, 136.7, 171.3; CIMS (NH_3) m/z (relative intensity) : 213 (MNH_4^+, 19), 196 (MH^+, 100), 195 (M^+, 30), 178 (31), 110 (31). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71. Found : C, 61.43; H, 6.77.

(1S,2S,6R,7R)-4-Aza-4-tertiobutoxycarbonyl-10-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-ol (3b). According to the procedure used for **8** (dichloromethane replacing chloroform), the alcohol **9** (1.0 g, 3.93 mmol) was oxidized to the hemiaminal **3b** (1.0 g, 99%) as a mixture of two diastereomers (~ 95/5). A pure fraction of the major diastereomer gave the following spectral data : IR (film) 3420, 1680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 60°C) δ 1.49 (s, 9H), 3.34 (dd, J = 7.7 Hz, J' = 1.4 Hz, 1H), 2.47 (ddd, J = 7.7 Hz, J' = 8.8 Hz, J" = 3.3 Hz, 1H), 3.39 (dd, J = 11.2 Hz, J' = 3.3 Hz, 1H), 3.73 (dd, J = 11.2 Hz, J' = 8.8 Hz, 1H), 4.71 (bs, 1H), 4.95 (bs, 1H), 6.38 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$, 60°C) δ 28.5, 42.1, 49.3, 52.6, 80.3, 81.5, 83.7, 89.2, 136.4, 136.5, 154.8. Anal. calcd for $C_{13}H_{19}NO_4$: C, 61.66; H, 7.51. Found : C, 61.73; H, 7.63.

(1S,2S,6R,7R)-4-Aza-4-benzyloxycarbonyl-10-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-ol (3c). According to the procedure used for **8**, the alcohol **10** (608 mg, 2.1 mmol) was oxidized to the hemiaminal **3c** (576 mg, 95%) as a mixture of two diastereomers (~ 95/5). The major diastereomer gave the following spectral data: ^1H NMR (200 MHz, $CDCl_3$) δ 2.36 (d, J = 8.7 Hz, 1H), 2.53 (ddd, J = 8.7 Hz, J' = 8.7 Hz, J" = 2.9 Hz, 1H), 3.26 (dd, J = 11.2 Hz, J' = 2.9 Hz, 1H), 3.8 (dd, J = 11.2 Hz, J' = 8.7 Hz, 1H), 3.87 (s, 1H), 4.74 (bs, 1H), 4.98 (bs, 1H), 5.45 (bs, 1H), 6.40 (m, 2H), 7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.4, 49.0, 51.9, 66.9, 81.5, 83.7, 85.3, 127.8, 128.0, 128.4, 136.2, 136.5, 153.6; CIMS (NH_3) m/z (relative intensity) : 287 (M^+, 28), 271 (18), 270 (100), 202 (30).

General procedures for the Wittig Horner-Michael reactions

Method A : To a stirred solution of hemiaminal **3** (2 mmol) in dry tetrahydrofuran (15 mL) was added the Wittig-Horner reagent (2.2 mmol) and cesium carbonate (2.2 mmol) and the resulting mixture was refluxed until no more starting material was present (CCM). After coolingto room temperature, 1 g of silicagel was added and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silicagel.

Method B : To a stirred suspension of sodium hydride (2.2 mmol) in dry tetrahydrofuran (25 mL) was added dropwise the Wittig-Horner reagent (2.2 mmol). After addition, the mixture was stirred for an additional 30 min and a solution of hemiaminal **3** (2 mmol) in dry THF (5 mL) was then added. The reaction mixture was heated under reflux until no more starting material was present (CCM). After cooling at room temperature, water (10 mL) was added and the solution was extracted with dichloromethane (4x10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silicagel.

(1S,2S,3RS,6R,7R)-3-Methoxycarbonylmethyl-4-acetyl-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$] dec-8-enes (11 and 11'). Prepared from **3a** following method B (5 h reflux) to give a mixture (94/6) of diastereomers **11** and **11'** (72% overall yield from **8**) which could not be separated : IR (film) 1735, 1640 cm^{-1}; CIMS (NH_3) m/z (relative intensity) : 252 (MH^+, 100), 183 (10.7). NMR data for **11** (two distinct conformers) follows : ^1H NMR (200 MHz, $CDCl_3$) δ 2.02 (s, 2.3H), 2.09 (s, 0.7H), 2.2 (dd, J = 7.6 Hz, J' = 2.3 Hz, 1H), 2.45 - 2.7 (m, 2H), 2.85 (dd, J = 16.7 Hz, J' = 3.9 Hz, 1H), 3.3 - 3.5 (m, 1H), 3.6 - 3.8 (m with two s, 4H), 4.2 (m, 0.75H), 4.35 (m, 0.25H), 4.8 (m, 2H), 6.35 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.6 and 21.6, 37.1 and 39.6, 43.2 and 41.7, 49.6 and 47.5, 51.1 and 50.5, 51.2 and 51.4, 57.2 and 59.0, 83.5 and 78.8, 83.9 and 84.1, 135.7 and 135.9, 136.2 and 136.6, 168.2 and 167.9, 171.7 and 170.7.

(-)-(1S,2S,3R,6R,7R)-3-Cyanomethyl-4-acetyl-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene (12). Prepared from **3a** following method A (3 h reflux) to give **12** (80% yield from **8**) as a colourless oil : $[\alpha]_D^{20}$ = -135 (c 1, $CHCl_3$); IR (film) 2240, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.35 (dd, J = 7.7 Hz, J' = 5.5 Hz, 1H), 2.62 (dd, J = 16.7 Hz, J' = 3.1 Hz, 1H), 2.72 (m, 1H), 3.08 (dd, J = 16.7 Hz, J' = 5.5 Hz, 1H), 3.51 (dd, J = 11 Hz, J' = 3 Hz, 1H), 3.96 (dd, J = 11 Hz, J' = 9 Hz, 1H), 4.3 (m, 1H), 4.84 (s, 1H), 4.89 (s, 1H), 6.44 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.7, 43.6, 51.6, 57.3, 59.0, 83.2, 84.1, 118.0, 136.2, 136.5, 196.1; CIMS (NH_3) m/z (relative intensity) : 236 (MNH_4^+, 100), 219 (MH^+, 51). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.83. Found : C, 65.85; H, 6.41; N, 12.63.

(-)-(1S,2S,3R,6R,7R)-4-Acetyl-4-aza-3-propanoyl-10-oxabicyclo[5.2.1.$0^{2,6}$]dec-8-ene (13). Prepared from **3a** following method A (30 h reflux) to give **13** (62% yield from **8**) as a yellow oil : $[\alpha]_D^{20}$ = -83 (c 0.9, $CHCl_3$); IR ($CHCl_3$) 1720, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.07 (s, 3H), 2 - 2.15 (m, 1H), 2.4 (m, 1H), 2.66 (dd, J = 17.5 Hz, J' = 8.1 Hz, 1H), 3.03 (dd, J = 17.5 Hz, J' = 3.1 Hz, 1H), 3.39 (dd, J = 10.8 Hz, J' = 2.7 Hz, 1H), 3.68 (dd, J = 10.8 Hz, J' = 8.8 Hz, 1H), 4.62 (m, 1H), 4.7 (s, 1H), 4.88 (s, 1H), 6.31 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.8, 30.2, 43.4, 46.8, 50.1, 51.3, 57.1, 83.7, 83.9, 135.7, 136.9, 168.6, 207.2; CIMS (NH_3) m/z (relative intensity) : 236 (MH^+, 100), 235 (M^+, 48).

(-)-(1S,2S,3R,6R,7R)-4-Aza-4-tertiobutoxycarbonyl-3-methoxycarbonylmethyl-10-oxatricyclo [5.2.1.$0^{2,6}$]dec-8-ene (14). Prepared from **3b** following method B (15 h reflux) to give **14** (80% yield) as a colorless oil : $[\alpha]_D^{20}$ = -72 (c 1.6, $CHCl_3$); IR ($CHCl_3$) 1735, 1680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 60°C) δ 1.46 (s, 3H), 2.19 (dd , J = 7.3 Hz, J' = 2.4 Hz, 1H), 2.35 (dt, J = 7.3 Hz, J' = 4.4 Hz, 1H), 2.52 (dd, J = 15.5 Hz, J' = 9 Hz, 1H), 2.85 (dd, J = 15.5 Hz, J' = 3.9 Hz, 1H), 3.52 (m, 2H), 4.12 (ddd, J = 9 Hz, J' = 3.9 Hz, J" = 2.4 Hz, 1H), 4.73 (s, 1H), 4.89 (s, 1H), 6.37 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$, 60°C) δ 28.5, 39.1, 43.0, 49.8, 50.9, 51.3, 58.3, 79.5, 83.7, 84.0, 136.3, 136.5, 153.5, 171.9; CIMS (NH_3) m/z (relative intensity) : 310 (MH^+, 46), 254 (100). Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49. Found : C, 62.16; H, 7.25.

(-)-(1S,2S,3R,6R,7R)-4-Aza-4-benzyloxycarbonyl-3-N-methoxy-N-methylcarbamoylmethyl-10-oxatricyclo [5.2.1.$0^{2,6}$]dec-8-ene (15). Prepared from **3c** following method B (5 h reflux) to give **15** (81% yield) as a colorless oil : $[\alpha]_D^{20}$ = -76 (c 0.4, $CHCl_3$); IR (film) 1725, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.3 (dd, J = 7.4 Hz, J' = 2.9 Hz, 1H), 2.39 (m, 1H), 2.62 (dd, J = 15.8 Hz, J' = 9.4

Hz, 1H), 3.0 (dd, J = 15.8 Hz, J' = 2.9 Hz, 1H), 3.16 (s, 3H), 3.57 - 3.68 (m, 5H), 4.26 (dt, J = 9.4 Hz, J' = 2.9 Hz, 1H) ; 4.74 (bs, 1H), 4.96 (bs, 1H), 5.13 (d, J = 12.5 Hz, 1H), 5.17 (d, J = 12.5 Hz, 1H), 6.37 (m, 2H); CIMS (NH_3) m/z (relative intensity) : 373 (MH^+, 100).

General procedure for thermolysis

Small samples (100 mg to 1 g) of compounds **11-15** were evaporated through an horizontal mullite tube (500°C, 10^{-2} torr) and the products were collected in a trap cooled to liquid nitrogen temperature. After warming to room temperature, the content of the trap was dissolved in ether, the resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography on silicagel.

(-)-(2R)-N-Acetyl-2-methoxycarbonylmethyl-2,5-dihydropyrrole (16). 219 mg of **11+11'** gave 141 mg (88%) of pyrroline **16** as a pale yellow oil : $[\alpha]_D^{20}$ = -211 (c 1, $CHCl_3$); IR (film) 1740, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (major conformer) 2.07 (s, 3H), 2.59 (dd, J = 15.6 Hz, J' = 8.2 Hz, 1H), 3.08 (dd, J = 15.6 Hz, J' = 4.2 Hz, 1H), 3.67 (s, 3H), 5.04 (m, 2H), 4.69 (m, 1H), 5.85 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) (two distinct conformers) δ 22.1 and 21.1, 36.9 and 39.8, 51.0 and 51.4, 54.0 and 52.4, 60.2 and 60.7, 129.6 and 126.2, 124.9 and 128.7, 168.5 and 168.4, 171.0; CIMS (NH_3) m/z (relative intensity) : 184 (MH^+, 100), 140 (24).

(-)-(2R)-N-Acetyl-2-cyanomethyl-2,5-dihydropyrrole (17). 256 mg of adduct **12** gave 161 mg (91.5%) of dihydropyrrole **17** as a colourless oil : $[\alpha]_D^{20}$ = -354 (c 0.9, $CHCl_3$); IR ($CHCl_3$) 2250, 1660, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.7 (dd, J = 16.9 Hz, J' = 2.9 Hz, 1H), 3.25 (dd, J = 16.9 Hz, J' = 5.9 Hz, 1H), 4.3 (m, 2H), 4.45 (m, 1H), 5.95 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 22.2, 54.7, 60.1, 116.8, 127.4, 127.7, 169.5; CIMS (NH_3) m/z (relative intensity) : 168 (MNH_4^+, 100), 151 (MH^+, 45). Anal. calcd for $C_8H_{10}N_2O$: C, 64.00; H, 6.67. Found : C, 64.14; H, 6.62.

(-)-(2R)-N-Acetyl-2-propanoyl-2,5-dihydropyrrole (18). 254 mg of **13** gave 148 mg (82%) of ketone **18** as a yellow oil : $[\alpha]_D^{20}$ = -266 (c 0.7, $CHCl_3$); IR ($CHCl_3$) 1715, 1645, 1625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.15 (s, 3H), 2.50 (dd, J = 17.1 Hz, J' = 8.9 Hz, 1H), 3.4 (dd, J = 17.1Hz, J' = 3.7 Hz, 1H), 4.25 (m, 2H), 5.0 (m, 1H), 5.85 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (two distinct conformers) δ 21.3 and 22.9, 30.1 and 30.4, 46.5 and 48.9, 54.0 and 52.4, 60.1 and 60.2, 124.3 and 125.8, 130.4 and 129.4, 168.8, 206.5; CIMS (NH_3) m/z (relative intensity) : 168 (MH^+, 100).

(-)-(2R)-N-Tertiobutoxycarbonyl-2-methoxycarbonylmethyl-2,5-dihydropyrrole (19). 1.19 g of tricyclic compound **14** gave 661 mg (71%) of **19** as a yellow oil : $[\alpha]_D^{20}$ = -189 (c 1, $CHCl_3$); IR ($CHCl_3$) 1740, 1695, 1630 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.5 (s, 9H), 2.45 (m, 1H), 3.0 (m, 1H), 3.65 (s, 3H), 4.1 (m, 2H), 4.85 (m, 1H), 5.85 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) (two distinct conformers) δ 28.2, 38.3 and 39.2, 51.3 and 51.4, 53.1 and 53.3, 60.5 and 60.7, 79.4 and 79.8, 125.8 and 125.9, 129.2 and 129.3, 153.8, 171.3 and 171.5; CIMS (NH_3) m/z (relative intensity) : 242 (MH^+, 70), 186 (100). Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94. Found : C, 59.89; H, 8.09.

(-)-(2R)-N-Benzyloxycarbonyl-2-N-methyl-N-methoxycarbamoylmethyl-2,5-dihydropyrrole (20). 400 mg of **15** are thermolyzed to give 195 mg (60%) of amide **20** as a colourless solid : mp 65°C; $[\alpha]_D^{20}$ = -169 (c 0.8, $CHCl_3$); IR ($CHCl_3$) 1705, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.45 (m, 1H), 3.12 (s, 3H), 3.35 (m, 1H), 3.49 and 3.69 (2s, 3H), 4.05-4.35 (m, 2H), 4.45 (m, 2H), 5.2 (m, 2H), 5.8 (m, 1H), 6.0 (m, 1H), 7.4 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) (two distinct conformers) δ 31.9, 36.2 and

37.6, 53.2 and 53.6, 60.7 and 60.9, 61.2 and 61.5, 66.6 and 66.9, 124.9 and 125.1, 127.8 and 127.9, 128.1, 128.4 and 128.5, 130.4 and 130.5, 136.6 and 136.7, 154.2 and 154.4, 172.1 and 172.4; CIMS (NH_3) m/z (relative intensity) : 305 (MH^+, 100). Anal. calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found : C, 63.07; H, 6.74; N, 9.07.

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