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Regio- and Stereoselective Reduction of Bicyclic Imides for the Asymmetric Synthesis of Highly Substituted Pyrrolidines

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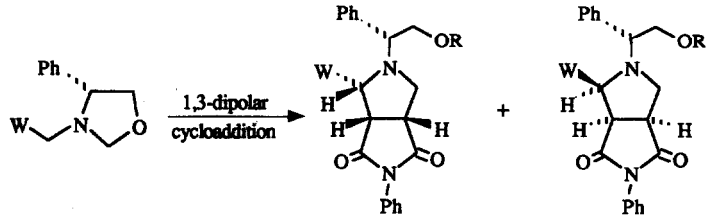
Abstract *: 1,3-dipolar cycloaddition of N-phenylmaleimide with azomethine ylides generated from α–aminonitrile or α-aminoester oxazolidines gave bicyclic imides, which were reduced regio- and stereoselectively to hydroxylactams. In the aminonitrile series, reduction with $NaBH_4/CeCl_3$ at low temperature gave a single hydroxylactam in high yield. In the aminoester series the regioselectivity was more dependent on the structure, and other conditions ($LiBEt_3H$) were found to obtain a single hydroxylactam which corresponds to a reverse regiochemistry when compared with the aminonitrile series.*

Hydroxylactams are reactive intermediates widely used in organic synthesis.[1] Such compounds are precursors of acyliminium ions permitting C-C bond formation α to the nitrogen of an amide ; this amido alkylation strategy was developed by Speckamp *et al.* allowing numerous syntheses of natural products.[1,2] Hydroxylactams may also undergo Wittig-type reactions[3] since they are in a tautomeric equilibrium with the aldehyde-amide form.

Several methods are available for the preparation of hydroxylactams. Among them are: the acid catalyzed addition of water to an enamide,[4] the reaction of primary or secondary amides with aldehydes or ketones[5] and the addition of Grignard reagents to cyclic imides.[6] The most convenient and efficient method is the selective reduction of one carbonyl group of a cyclic imide.[7] This way has been widely studied by Speckamp using sodium borohydride.[8] Further studies showed the importance of the reducing agent in determining both regio- and stereoselectivity.[9]

With the aim of synthesizing highly substituted pyrrolidines as rigid analogs of exitatory aminoacids (aspartic and glutamic acids),[10] we envisaged an amidoalkylation methodology starting from hydroxylactams derived from bicyclic imides **2** and **3** (scheme 1). These stereoisomeric imides **2** and **3** were prepared in high yield according to the asymmetric 1,3-dipolar cycloaddition recently described in our laboratory[11] using oxazolidines **1** as the ylide precursors (scheme 1). The stereochemistry of cyclic imides **2** and **3** has been determined by X-ray analysis or NMR studies.

In the present paper we which to describe the selective reduction of imides **2** and **3** which has been proved to be regio- and stereoselective to an extent depending both upon the substrate and experimental conditions.



1 2 3

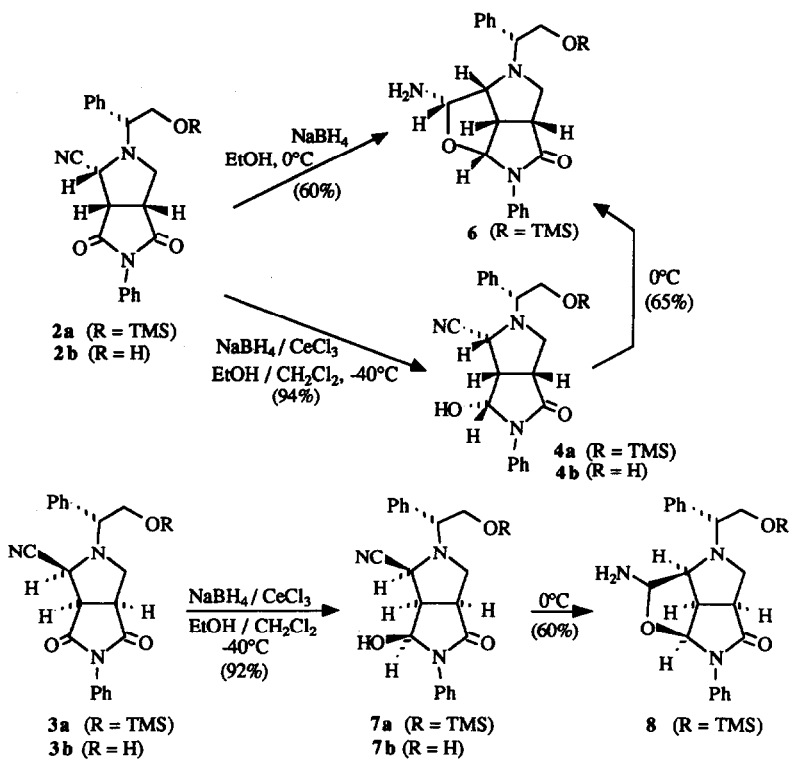
a: W = CN, R = TMS ; b: W = CN, R = H ; c: W = COOMe, R = H ; d: W = COOEt, R = H

Scheme 1

RESULTS

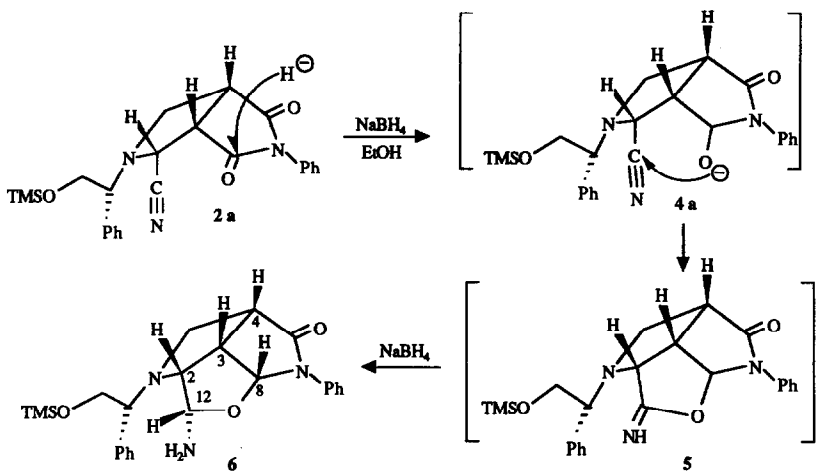
1 - Reduction of cyclic imides in the aminonitrile series.

The reduction of imides **2a** and **3a** (W = CN) was examined first. Using the procedure previously reported by Speckamp[8] namely $NaBH_4$/EtOH (with or without adding acid) a single product was formed in each case showing complete regio and stereo control (scheme 2).



Scheme 2

The compound **2a** was reduced to **6** in 60 % yield. This unexpected compound arose from a double reduction : first one carbonyl function of the imide **2a** is reduced and this is followed by an intramolecular cyclization of the oxygen of the thus-formed hydroxylactam **4a** upon the nitrile; further reduction of the resulting imidate **5** gives **6** (scheme 3). The structure and stereochemistry of compound **6** have been fully characterized. Centres C-8 and C-12 are easily identified in the NMR spectra, having respectively δ_H 4.65 and 5.90 ppm and δ_C 91.5 and 92.0. The coupling constant value $J_{H\text{-}8\ H\text{-}3}$ = 8 Hz confirmed the H-8, H-3 *cis* relationship inherent of the tricyclic structure. The formation of this single product showed that the first hydride attack on one of the two carbonyl functions was regioselective and stereoselective on the more accessible convex face of the molecule. Several attempts were made to quench the reaction after the first reduction and isolate the hydroxylactam **4a**. Variation of the reaction time, reaction temperature (-40° to 20°C) and quantity of hydride equivalent, resulted either in the formation of the tricyclic compound **6** or recovery of starting material, showing that the formation of the hydroxylactam **4a** was the slow step of the reaction.



Scheme 3

It was found that addition of $CeCl_3$[12] to the hydride dramatically increased the reaction rate. The reduction of imide **2a** using $NaBH_4/CeCl_3$ (7:1) in CH_2Cl_2/EtOH was carried out at -40°C and it was possible to isolate hydroxylactam **4a** after a short reaction time (5 min). A single regio and stereoisomer (as shown by ^1H and ^{13}C NMR of the crude reaction mixture) was obtained in 94 % yield. If the reaction mixture was allowed to warm to 0°C before quenching, tricyclic compound **6** was isolated in 65 % yield (scheme 2). The stereochemistry of hydroxylactam **4a** was deduced by the subsequent cyclization to **6** and confirmed by NMR study ($J_{H3\text{-}H8}$ = 7 Hz).

The reduction of stereoisomeric imide **3a** proceeded as well as for **2a**. Using $NaBH_4/CeCl_3$, **3a** was reduced to hydroxylactam **7a** (94% yield) which may be further reduced to tricyclic compound **8** (scheme 2). The regio and stereochemistry of these reactions were the same as with imide **2a**. The only difference was the easy cleavage of the trimethyl silyl group since the isolated tricyclic compound was the free alcohol **8**.

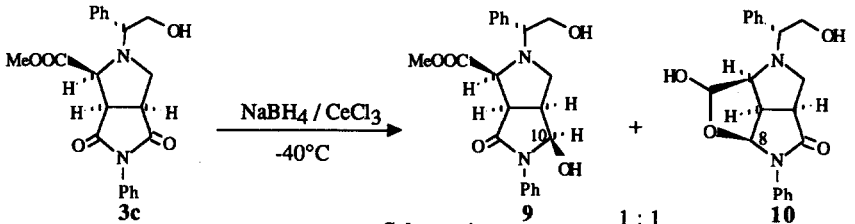
The use of $CeCl_3$ did not modify the regio- and stereochemical course of the reduction. Due to its Lewis acid properties, $CeCl_3$ can activate the more active carbonyl group thus increasing the reaction rate. The stereochemistry of **4a** corresponds to a hydride attack on the more accessible convex face of the molecule but also to the thermodynamically more stable isomer (a 11 Hz coupling constant between H-8 and OH is indicative of a hydrogen bond).

The regiochemistry is not so easy to understand for steric control due to the chiral appendage does not seem important. Furthermore, reduction of imides **2a** and **3a** in which the relative stereochemistry of the bicycle with respect to the chiral appendage was reversed gave the same regioselective reduction of the imide. Owing to the low chelating ability of $NaBH_4$ and the presence of a TMS group on the oxygen, an intramolecular transfer of hydride by the chiral appendage must be ruled out. The presence of the TMS group did not play any role in the regio- and stereoselectivity of the reaction, since $NaBH_4/CeCl_3$ reduction of desilylated compounds **2b** and **3b**[13] gave a unique hydroxylactam in each case-respectively **4b** and **7b**- with the same stereochemistry as the TMS derivatives. The major role seems to be played by the cyano group in stabilizing a conformation in which one carbonyl group is more active or accessible, as proved by the study conducted with aminoesters.

2 - Reduction of cyclic imides in the aminoester series *

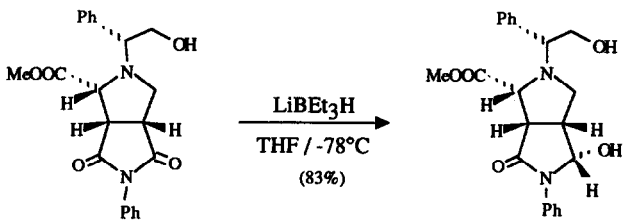
The same reduction study was undertaken with aminoester **3c** (W = CO_2Me) which possess the same stereochemistry as the aminonitrile **3a** (W = CN).

Surprisingly, the treatment of imide **3c** with the system $NaBH_4/CeCl_3$ at -40°C led to the formation of two compounds **9** and **10** as a 1:1 mixture and with a 85% yield (scheme 4). Formation of the lactol **10** was similar to the formation of tricyclic compounds **6** and **8** in the aminonitrile series. Nevertheless the formation of hydroxylactam **9** showed that the reduction proceeded with a complete lack of regiochemical control. The stereochemistry of each compound corresponded to an attack on the less hindered face of the molecule.



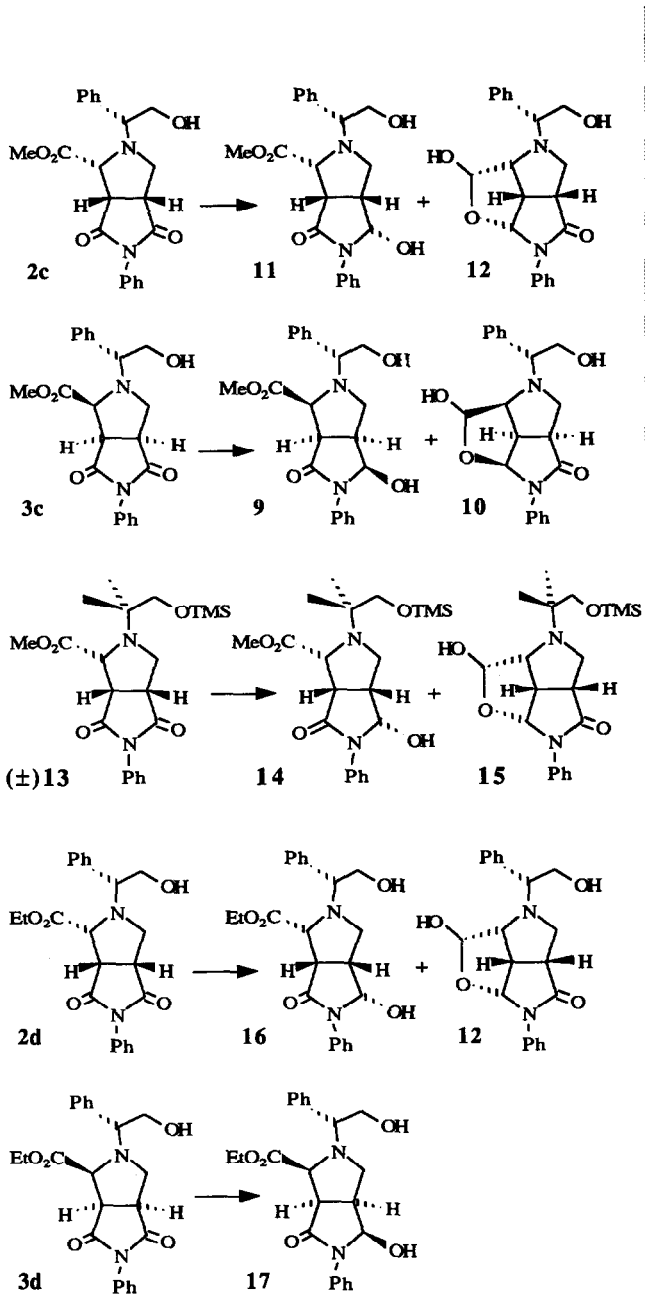
Scheme 4

In order to improve the regioselectivity of the reduction of **3c**, various reducing agents were tested. Zinc borohydride was found to be ineffective while DIBAH - in toluene or THF - at temperatures ranging from -78° to 0°C gave only complex mixtures. On the other hand when **3c** was treated with $LiBEt_3H$ (superhydride) in CH_2Cl_2 at -78°C, a 65:35 mixture of regio isomers **9** and **10** was obtained in 82% yield. The ratio was changed to 75:25 if THF was used as solvent and to 80:20 with L-selectride (sec-Bu_3LiBH) in THF at -40°C (see table). When the imide **3c** was replaced by imide **2c** a complete regio- and stereoselective reduction could be achieved using superhydride in THF at -78°C to form hydroxylactam **11** in 83% yield (scheme 5).



Scheme 5

* In this series, free primary alcohols were used.



	NaBH4/ CeCl3	LiBEt3H/ CH2Cl2	LiBEt3H/ THF	L-Selectride
2c → 11 + 12		11 : 12 (75/25)	11	
3c → 9 + 10	9 : 10 50/50	9 : 10 65/35	9 : 10 75/25	9 : 10 80/20
(±)13 → 14 + 15	14 : 15 50/50	14 : 15 55/45	14 : 15 65/35	14
2d → 16 + 12		16 : 12 65/35	16	
3d → 17		17		

Table : Reduction of bicyclic imide-esters using different conditions (ratios were determined from ^{1}H and ^{13}C NMR spectra of the crude reaction mixture)

This result showed the importance of the relative stereochemistry of the bicycle and the chiral chain borne at the nitrogen. The possibility of chelation of the reducing agent with the OH group seemed to be ruled out by the results obtained with racemic imide **13**. In this compound, although the hydroxyl function was protected by a TMS group reduction using different hydrides gave very similar results as those obtained from imide **3c** (see table).

Finally the reduction of ethyl esters **2d** and **3d** was examined. While ester **2d** afforded the same results to those obtained with the methyl analog **2c** (see table), ester **3d** was reduced to a single hydroxylactam **17** by treatment with $LiBEt_3H$ in CH_2Cl_2 while methyl ester **3c** gave mixture of hydroxylactam and lactol (**9** and **10**) regardless of the reducing agent.

Thus in each case (except **3c**) conditions were found for the reduction of aminoester-imide to a single hydrolactam (see table). The determination of the exact stereochemistry of reduced compounds indicates an attack upon the more accessible face of the molecule.

The difference in regiochemistry between the aminonitrile and aminoester series is not fully understood.

Conditions have been found to obtain pure hydroxylactams from aminonitrile-imides as well as from aminoester-imides. Then bicyclic imides resulting in 1,3-dipolar cycloaddition of **1** with phenylmaleinide can be reduced regio- and stereoselectively in good yield. Both regioisomers of hydroxylactams can be obtained using aminonitrile or aminoesters imides.

EXPERIMENTAL

200 MHz ^1H and 50 MHz ^{13}C NMR spectra were recorded on a Brüker AC-200 instrument.250 MHz ^1H and 62.5 MHz ^{13}C NMR spectra were recorded on a Brüker AC-250 instrument. The chemical shifts are given in ppm from TMS. IR spectra were recorded in solution ($CHCl_3$) on a NICOLET 205 IR-FT. Mass spectra were recorded on AEI MS 9 (CI) and MS 5O (EI) spectrometers. Melting point were measured with a Kofler apparatus. TLC was carried out on silica 60F-254 (Merck, Art 5554). Elemental analysis were carried out by the Microanalytical Service Laboratory in the Institut de Chimie des Substances Naturelles. Optical rotations were measured using a Perkin Elmer 241 polarimeter. TMSOTf, N-phenylmaleimide, i-Pr_2NEt, $LiBEt_3H$ 1M solution in THF and L-Selectride 1M solution in THF were purchased from Aldrich Chemical Co. N-phenylmaleimide was recrystallized from cyclohexane and iPr_2NEt was distilled before use. CH_2Cl_2 is distilled from P_2O_5 and THF from sodium-benzophenone. Reactions were carried out on argon atmosphere with oven dried equipments.

R-(-)-4-phenyl-3-oxazolidineacetonitrile 1a :

To a solution of R-(-)-phenylglycinol (2.05 g, 15 mmol) and potassium cyanide (0.97 mg, 15 mmol) in 60 ml of water at pH 3 (adjusted with 6 g of citric acid) was added at room temperature 18.3 ml of 37% aqueous formaldehyde. The solution was stirred for 1 h, neutralized with Na_2CO_3 (pH = 9) and extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. Purification by flash chromatography on silica (85:5 hexane/AcOEt) gave oxazolidine **1a** (2.5 g, 13.3 mmol) as a colorless oil (yield = 88%).

$[\alpha]_D$= -173° (c 1.4, $CHCl_3$) ; **^1H NMR** (200MHz, $CDCl_3$) : 3.55 (1H, d, J=17Hz, H-6), 3.65 (1H, d, J=17Hz, H-6), 3.75 (1H, t, J=8Hz, H-5), 3.98 (1H, t, J=8Hz, H-4), 4.35 (1H, t, J=8Hz, H-5), 4.45 (1H, d, J=3Hz, H-2), 4.80 (1H, d, J=3Hz, H-2), 7.40 (5H, m, H) ; **^{13}C NMR** ($CDCl_3$) : 37.5 (C-6), 65.3 (C-4), 74.1 (C-5), 85.3 (C-2), 114.8 (CN), 127.4, 128.4, 128.9, 137.1 ; **IR** (cm^{-1}) : 2220 ; **MS** (EI) : m/z= 188 (M^+,25), 158 (M^+-CH_2O, 100), 157 (M^+-CH_2OH, 90), 132 (158-HCN, 12), 118 (55) ; **Anal.** calcd. for : $C_{11}H_{12}N_2$, C 69.96, H 6.36, N 14.84 ; Found, C 70.02, H 6.33, N 14.56.

R-(-)-Methyl 4-phenyl-3-oxazolidineacetate 1c

To a solution of R-(-)-phenylglycinol (4.5 g, 33 mmol) in 200 ml of THF were added methyl bromoacetate (3.25 ml, 35 mmol) and iPr_2NEt (6.3 ml, 36 mmol). The reaction mixture was stirred overnight, and then filtered through a silica pad. The

solvent was distilled off to give a colorless oil which was dissolved in 200 ml of toluene. Paraformaldehyde (1g) was added and the mixture was refluxed in a Dean-Stark apparatus for 1 h. After distillation of the solvent, the reaction mixture was purified on silica using heptane/AcOEt 75:25 as solvent to give 6.3 g of oxazolidine **1c** as a colorless oil (yield 86%).
$[\alpha]_D$= -134° (c 1, $CHCl_3$) ; **^{1}H NMR** (200MHz, $CDCl_3$) : 3.3 (d, J=11.5Hz, 1H, H-6), 3.5 (d, J=11.5Hz, 1H, H-6), 3.65 (s, 3H, CH_3), 3.75 (t, J=7.5Hz, 1H, H-5), 4.0 (t, J=7.5Hz, 1H, H-4), 4.25 (t, J=7.5Hz, 1H, H-5), 4.35 (d, J=3.5Hz, 1H, H-2), 4.9 (d, J=3.5Hz, 1H, H-2), 7.35 (m, 5H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 51.2 (CH_3), 52.2 (C-6), 66.3 (C-4), 73.1 (C-5), 86.4 (C-2), 127.2, 127.5, 128.3, 138.9 (C arom), 170.5 (C=O) ; IR (cm^{-1}) : 1750; **MS** (EI) m/z= 221 (M^+, 24), 190 (28), 162 (M^+-COOMe, 100), 148 (62) ; **Anal.** calcd. for : $C_{12}H_{15}NO_3$, C 65.14, H 6.83, N 6.33 ; Found : C 64.86, H 6.97, N 6.55.

R-(-)-Ethyl-4-phenyl-3-oxazolidineacetate 1d

The same procedure as for **1c** with ethyl bromoacetate from 4.5 g of R-(-)-phenylglycinol was used. (Yield 85%).
$[\alpha]_D$= -119.4° (c 0.78, $CHCl_3$) ; **^{1}H NMR** (250MHz, $CDCl_3$) : 1.3 (t, J=7Hz, 3H, CH_3 ester), 3.3 (d, J=17Hz, 1H, H-6), 3.5 (d, J=17Hz, 1H, H-6), 3.7 (t, J=8Hz, 1H, H-5), 4.0 (t, J=8Hz, 1H, H-4), 4.1 (q, J=7Hz, 2H, CH_2 ester), 4.25(t, J=8Hz, 1H, H-5), 4.4 (d, J=3.5Hz, 1H, H-2), 4.9 (d, J=3.5Hz, 1H, H-2), 7.35 (m, 5H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 13.6 (CH_3 ester), 52.2 (C-6), 60.0 (CH2 ester), 66.1 (C-4), 72.8 (C-5), 86.2 (C-2), 127.0 127.3 128.1 138.8 (C arom), 169.7 (C=O) ; **IR** (cm^{-1}) : 1737 ; **MS** (EI) : m/z=235 (M^+, 40), 206 (40), 162 (M^+-COOEt, 100), 148 (162-CH_2, 70) ; **Anal.** calcd. for. : $C_{13}H_{17}NO_3$, C 66.36, H 7.28, N 5.95 ; Found : C 66.51, H 7.35, N 5.73.

Cycloaddition (standard procedure)

To a solution of oxazolidine **1** (1 mmol), N phenylmaleimide (1.3 mmol) and iPr_2NEt (2 mmol) in dry CH_2Cl_2 (10 ml) cooled to -78°C under Ar atmosphere was added dropwise Me_3SiOTf (1.2 mmol). The solution was stirred at -78°C for 4 h and then was allowed to warm to room temperature. In the aminonitrile series, silylated cycloadduct were separated by a flash chromatography on silica (Heptane/AcoEt 80:20 to 60:40). In the aminoester series, the crude reaction mixture was desilylated using MeOH/citric acid (pH-3). The solution was stirred overnight, neutralised with aqueous Na_2CO_3, extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. Desilylated cycloadducts were separated by flash chromatography on silica (Heptane/AcOEt 50:50).

Aminonitrile cycloadducts 2a and 3a

Standard cycloaddition procedure from oxazolidine **1a** (1.9 g, 10 mmol) followed by flash chromatography on silica gave respectively 1.0 g (24%) of a mixture of two cycloadducts (with H_2H_3 trans-relationship), 1.8 g (44%) of imide **2a** and 1.3 g (32%) of imide **3a** (yield 95%).
Imide **2a** : **mp** 172 °C (hexane-CH_2Cl_2) ; $[\alpha]_D$= -113.5° (c 1, $CHCl_3$) ; **^{1}H NMR** (200MHz, $CDCl_3$) : 0.15 (9H, s, TMS), 2.7 (1H, dd, J=7Hz, 10Hz, H-5), 3.25 (1H, t, J=10Hz, H-5), 3.5 (1H, dt, J=7Hz, 10Hz, H-4), 3.9 (4H, m, H-3, H-6, H-7), 5.05 (1H, d, J=8Hz, H-2), 7.4 (10H, m, H arom) ; **^{13}C NMR** : -0.8 (CH_3-TMS), 42.6 (C-4), 48.8 (C-3), 52.3 (C-5), 55.4 (C-2), 66.8 (C-7), 67.2 (C-6), 114.4 (CN), 126.8 (arom), 127.5 (arom), 128.4 (arom), 128.9 (arom), 129.1 (arom), 129.3 (arom), 131.5 (C arom), 138.4 (C arom), 173.2 (C=O), 175.5 (C=O) ; **IR** (cm^{-1}) : 1720, 1260 ; **MS** (EI) : m/z= 433 (M^+,4), 331 (30), 330 (M^+ -CH_2OTMS, 100) ; **Anal.** calcd.for. : $C_{24}H_{27}N_3O_3Si$, C 66.48, H 6.27, N 9.69 ; Found : C 66.51, H 6.37, N 9.61
Imide **3a**: **mp** 176°C (hexane-ethyl acetate) ; $[\alpha]_D$= -118.5° (c 1, $CHCl_3$) ; **^{1}H NMR** (400MHz, $CDCl_3$) : 0.05 (9H, s, TMS), 3.11 (1H, dd, J=5Hz, 10Hz, H-5), 3.6 (2H, m, H-3, H-4), 3.7 (1H, t, J=10Hz, H-5), 3.8 (2H, m, H-6, H-7), 3.9 (1H, d, J=8Hz, H-2), 3.95 (1H, dd, J=4Hz, 7.5Hz, H-7), 7.4 (10H, m, H arom) ; **^{13}C NMR** : 0.2, (CH_3-TMS), 44 (C-4), 46.8 (C-3), 50.8 (C-5), 55.3 (C-2), 65.6 (C-7), 66.9 (C-6), 114 (CN), 126.6 (arom), 128.1 (arom), 128.4 (arom), 128.8 (arom), 128.9 (arom), 129.2 (arom), 131.4 (C arom), 137.3 (C arom), 173 (C=O), 175.7 (C=O) ; **IR** (cm^{-1}) : 1720, 1260 ; **MS** (EI) : m/z= 433 (M^+,3), 330 (M^+-CH_2OTMS, 100) ; **Anal.** calcd.for. : $C_{24}H_{27}N_3O_3Si$, C 66.48, H 6.27, N 9.69 ; Found : C 66.29 , H 6.37, N 9.68.

Aminonitrile cycloadducts 2b and 3b

Citric acid (100 mg) was added to a solution of silylated compound **2a** (resp. **3a**) (100 mg, 0.23mmol) in CH_2Cl_2 (1 mL) and MeOH (5mL), and the mixture was stirred overnight. After neutralization with aqueous $NaHCO_3$ up to pH8, extraction with CH_2Cl_2 and flash chromatography on silica (AcOEt/hexane 50:50), desilylated compound **2b** (resp. **3b**) was obtained as a white amorphous solid. (78 mg, 94% yield).

2b: ^{1}**H NMR** (200MHz, $CDCl_3$): 3.1 (dd, J=9, 4Hz, 1H, H-5), 3.4 (dt, J=9, 1Hz, 1H, H-4), 3.55 (m, 2H, H-3, H-5), 3.9 (m, 4H, H-2, H-6, H-7), 7.4 (m,10H, H arom.); **MS** (CI): m/z= 362 (MH^+), 335.

3b: ^{1}**H NMR** (200MHz, $CDCl_3$): 2.7 (dd, J=10, 7Hz, 1H, H-5), 3.2 (t, J=9Hz, 1H, H-3), 3.4 (m, J=9, 7Hz, 1H, H-4), 3.8 (m, 4H, H-5, H-6, H-7), 4.8 (d, J=8Hz, 1H, H-2), 7.4 (m, 10H, H arom.); **MS** (CI): m/z= 362 (MH^+), 335.

Amino-methylester cycloadducts 2c and 3c

Standard cycloaddition procedure from oxazolidine **1c** (2.2 g, 10 mmol) followed by desilylation step and flash chromatography on silica (AcOEt/Heptane 50:50) gave respectively 1.55 g of imide **3c** and 1.80 g of imide **2c** (yield 85%) (without desilylation, the two cycloadducts were unseparable).

Imide **2c**: $[\alpha]_D$= +26.5 (c 2, $CHCl_3$) ; ^{1}**H NMR** (200MHz, $CDCl_3$) : 2.9 (s, 1H, OH), 3.0 (dd, J=8Hz, 9.5Hz, 1H, H-5), 3.3 (dt, J=8Hz, 2Hz, 1H, H-4), 3.5 (dd, J=2Hz, 9.5Hz, 1H, H-5), 3.7 (m, 1H, H-3), 3.75 (s, 3H, CH_3 ester), 3.85 (m, 3H, H-2, H-6 et H-7), 4.0 (dd, J=5Hz, 9Hz, 1H, H-7), 7.35 (m, 10H, H arom) ; ^{13}**C NMR** ($CDCl_3$) : 43.7 (C-4), 48.1 (C-3), 52.6 (OCH_3), 53.4 (C-5), 62.6 (C-7), 64.0 (C-2), 66.2 (C-6), 126.6, 128.5 128.7, 128.8, 129.1, 129.3, 132.0, 135.1 (C arom), 171.0, 175.2, 176.8 (C=O) ; **IR** (cm^{-1}) : 1718, 1743 ; **MS** (CI) : m/z= 395 (MH^+, 100), 363 (MH^+-CH_3OH, 45).

Imide **3c**:$[\alpha]_D$= -61.0 (c 1.5, $CHCl_3$) ; ^{1}**H NMR** (200MHz, $CDCl_3$) : 2.45 (dd, J=8Hz, 10Hz, 1H, H-5), 2.8 (s, 1H, OH), 3.3 (t, J=8Hz, 1H, H-4), 3.5 (t, J=8Hz, 1H, H-3), 3.65 (dd, J=3.5Hz, 10Hz, 1H, H-7), 3.7 (d, J=10Hz, 1H, H-5), 3.75 (d, J=8Hz, 1H, H-2), 3.84 (s, 3H, CH_3 ester), 4.0 (m, 2H, H-6 et H-7), 7.35 (m, 10H, H arom); ^{13}**C NMR** ($CDCl_3$) : 43.4 (C-4), 46.8 (C-3), 48.7 (C-5), 52.5 (OCH_3), 61.9 (C-7), 64.6 (C-2), 65.6 (C-6), 128.4, 128.6,, 128.7, 128.8, 129.1, 129.2, 131.9, 133.8 (C arom), 170.4, 175.1, 177.1 (C=O) ; **IR** (cm^{-1}) : 1720, 1740 ; **MS** (CI) : m/z= 395 (MH^+, 100), 363 (MH^+-CH_3OH, 100).

Amino ethyl ester cycloadducts 2d and 3d :

Standard cycloaddition procedure from oxazolidine **1d** (6.4 g, 27 mmol) followed by desilylation and flash chromatography on silica (50:50 AcOEt/Heptane) gave respectively 4.4 g of imide **3d** and 4.9 g of imide **2d** (yield 85%).

Imide **2d**: ^{1}**H NMR** (250MHz, $CDCl_3$) : 1.4 (t, J=7Hz, 3H, CH_3), 3.0 (t, J=8Hz, 1H), 3.3 (t, J=8Hz, 1H), 3.5 (m, 2H), 3.7-4 (m, 4H), 4.1 (q, J=7Hz, CH_2 ester), 7.35 (m, 5H, H arom) ; ^{13}**C NMR** ($CDCl_3$) : 14.0 (CH_3), 43.7, 48.1 (C-3, C-4), 53.2 (C-5), 61.8, 62.5 (CH_2 ester, C-7), 64.1 (C-2), 65.9 (C-6), 126.6, 128.3, 128.6, 128.7, 129.0, 129.2, 132.1, 135.5 (C arom), 171.2, 175.3, 177.1 (C=O) ; **IR** (cm^{-1}) : 1737, 1714 ; **MS** (CI) : m/z= 409 (MH^+, 100), 289 (MH^+-$CHPhCH_2OH$+H, 40), 287 (MH^+-$CHPhCH_2OH$-H, 40).

Imide **3d**: **mp** 157°C ; $[\alpha]_D$= -122.5° (c 0.4, $CHCl_3$) ; ^{1}**H NMR** (250MHz, $CDCl_3$) : 1.3 (t, J=7Hz, 3H, CH_3), 2.4 (t, J=9Hz, 1H, H-5), 3.2 (t, J=9Hz, 1H, H-4), 3.4 (t, J=9Hz, 1H, H-3), 3.5 (d, J=10Hz, 1H, H-5), 3.6 (d, J=9.5Hz, 1H, H-2), 3.7 (m, 1H, H-7), 3.9 (dd, J=10Hz, 4Hz, 1H, H-6), 4.0 (t, J=10Hz, 1H, H-7), 4.3 (m, 2H, CH_2 ester), 7.35 (m, 10H, H arom) ; ^{13}**C NMR** ($CDCl_3$) : 14.0 (CH_3 ester), 43.4, 46.7 (C-3,C-4), 48.6 (C-5), 61.8 61.9 (CH_2 ester, C-7), 64.5 (C-2), 65.7 (C-6), 126.4, 128.3, 128.6, 128.8, 129.1, 131.9, 133.8 (C arom), 170.0, 175.0, 177.2 (C=O) ; **IR** (cm^{-1}) : 1714, 1737 ; **MS** (CI) : m/z= 409 (MH^+, 100), 363 (MH^+-EtOH, 20), 289 (MH^+-$CHPhCH_2OH$+H, 40), 287 (MH^+-$CHPhCH_2OH$-H, 40) ; **Anal.** calcd. for. : $C_{23}H_{24}N_2O_5$: C 67.64, H 5.88, N 6.86 Found : C 67.58, H 5.95, N 7.01.

Imide 13

Standard cycloaddition procedure from 1.9 g (10.9 mmol) of methyl 4-(gem-dimethyl)-3-oxazolidine acetate (obtained from 2-amino-2-methyl propanol in 49% yield using the procedure described for oxazolidine **1c**).gave imide **13** (3.55 g, 8.5 mmol) as a single isomer (yield 78%).

^{1}**H NMR** (200MHz, benzene) : 0.85 (s, 3H, CH_3), 0.95 (s 3H, CH_3), 2.6 (td, J=3.5Hz, 9Hz, 1H, H-4), 2,8 (t, 9 Hz, 1H, H-5), 3.0 (t, J=9Hz, H-5), 3.25 (s, 2H, H-7), 3.35 (s, 3H, OCH_3), 3.55 (dd, J=3.5Hz, 9Hz, 1H, H-3), 4 (d, J=9Hz, 1H, H-2),

7.2 (m, 4H, H arom), 7.5 (d, J=10Hz, 1H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 21.8, 22.4 (CH_3), 44.8, 48.3 (C-3, C-4), 48.4 (C-5), 52.0 (OMe), 57.3 (C-6), 63.2 (C-2), 69.1 (C-7), 126.7, 128.6, 129.1, 132.2 (C arom), 173.1, 175.9, 177.4 (C=O) ; **IR** (cm^{-1}) : 1714, 1740 ;**MS** (CI) : m/z= 419 (MH^+,100); 315 (10).

Reduction of imides with $NaBH_4$-$CeCl_3$ system ; standard procedure A :

To a cooled (-40°C) solution of bicyclic imide (**2** or **3**) in 1.5:1 EtOH/CH_2Cl_2 (25 ml for 1.2 mmol) were sequentially added $CeCl_3$-$7H_2O$ (1 equiv) and $NaBH_4$ (7 equiv). After 5 min the crude reaction mixture was poured into cold water (75 ml for 1.2 mmol) and then extracted with CH_2Cl_2. After washing the organic phase with water and drying (Na_2SO_4), the solvent was evaporated to give hydroxylactam as a waxy solid which was pure enough for use without further purification.

Reduction of imides with $NaBH_4$-$CeCl_3$ system ; standard procedure B :

The general procedure A was used and after 5 min at -40°C the mixture was allowed to warm to 0°C. After 2 h at this temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2. After drying (Na_2SO_4) and evaporation of the solvent the crude product was purified by flash chromatography (Heptane-AcOEt) to give pure tricyclic derivative.

Reduction of imides with superhydride ; standard procedure C :

To the imide dissolved in CH_2Cl_2 or THF (15 ml for 1 mmol) cooled to -78°C was added 1.5 equiv. of a 1 M THF solution of $LiBEt_3H$. The reaction requires 10 to 60 min to go to completion. Excess of reagent was destroyed by addition of a saturated NH_4Cl aqueous solution at -78°C and the reaction mixture was extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the solvent were followed by purification by flash chromatography on silica (AcOEt/heptane).

Reduction of imides with L-selectride ; standard procedure D :

To the imide dissolved in THF (15 ml for 1 mmol) and cooled to -40°C were added 2 equiv. of $LiB(sec\text{-}Bu)_3H$. One more equiv. was added every 2 h. The complete reduction required about 7 h. Hydrolysis with dilute H_2O_2 followed by extraction with CH_2Cl_2, drying (Na_2SO_4), distillation of the solvent and flash chromatography on silica (heptane/AcOEt) gave hydroxylactam or/and lactol.

Hydroxylactam 4a :

Bicyclic imide **2a** (525 mg, 1.2 mmol) was reduced to hydroxylactam **4a** isolated as an oil (500 mg, 94% yield) using standard procedure A.

$[\alpha]_D$= -52.9° (c 4, $CHCl_3$) ; **^{1}H NMR** (200MHz, $CDCl_3$) : 0.2 (s, 9H, $SiMe_3$), 3.1 (m, 3H, 2 H-5, H-4), 3.3 (m, 1H, H-3), 3.8 (dd, J=4Hz, 10Hz, 1H, H-7), 3.85 (d, J=6Hz,.1H, H-2), 4.15 (dd, J=4Hz, 10Hz, 1H, H-6), 4.4 (t, J=10Hz, 1H, H-7), 5.5 (d, J=11Hz, 1H, OH), 5.8 (dd, J=7Hz, 11Hz, 1H, H-8), 7.35 (m, 8H, H arom), 7.7 (d, J=7.5Hz, 2H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 43.2 (C-4), 43.9 (C-3), 51.1 (C-5), 51.9 (C-2), 63.8 (C-7), 65.8 (C-6), 83.8 (C-8), 116.8 (CN), 124.1 124.6 128.4 128.6 129.0 136.4 136.7 (C arom), 172.9 (C=O) ; **IR** (cm^{-1}) : 1695 ; **MS** (CI) : m/z= 436 (MH^+, 100), 410 (MH^+-CN, 100), 391 (5) ; **Anal.** calcd. for : $C_{24}H_{29}N_3O_3Si$; C 69.40, H 5.82, N 11.56 ; Found : C 69.15, H 5.77, N 11.32.

Tricyclic compound 6 :

General procedure B from bicyclic imide **2a** (210 mg, 0.48 mmol) gave tricyclic compound **6** (136 mg ; 65%yield) as a waxy solid.

$[\alpha]_D$= -24.9° (c 0.5, $CHCl_3$) ; **^{1}H NMR** (400MHz, $CDCl_3$) : 0.2 (s, 9H, $SiMe_3$), 3.1 (m, 2H, H-4, H-5), 3.4 (dd, J=2Hz, 9Hz, 1H, H-2), 3.5 (m, 1H, H-3), 3.55 (d, J=9Hz, 1H, H-5), 3.80 (t, J=6.5Hz, 1H, H-6), 3.90 (dd, J=6Hz, 10.5Hz, 1H, H-7), 4.05 (dd, J=7Hz, 10Hz, 1H, H-7), 4.65 (d, J=2Hz, 1H, H-12), 5.9 (d, J=6.5Hz, 1H, H-8), 7.35 (m, 8H, H arom), 7.8 (d, J=7.5Hz, 2H, H arom) ; **^{13}C NMR** ($CDCl_3$) : -0.5 ($SiMe_3$), 46.4 46.7 (C-3, C-4), 55.0 (C-5), 65.3 (C-7), 67.8 (C-6), 73.1 (C-2), 91.5 92.0 (C-8, C-12), 122.6 125.9 127.9 128.6 128.9 129.0 137.9 140.5 (C arom), 174.4 (C=O) ; **IR** (cm^{-1}): 1695 (C=O) ; **MS** (CI) : 438 (MH^+.100), 421 (MH^+-NH3.10) .

Hydroxylactam 7a :

Bicyclic imide **3a** (250 mg, 0.58 mmol) was reduced using general procedure A to hydroxylactam **7a** (92% yield).
^{1}H NMR (200MHz, $CDCl_3$) : 0.1(s, 9H, $SiMe_3$), 2.5 (t, J=9.5Hz, 1H, H-5), 2.9 (t, J=9Hz, 1H, H-4), 3.0 (m, 2H, H-3, H-5), 3.2 (d, J=6Hz, 1H, H-2), 3.6 (dd, J=4Hz, 10Hz, 1H, H-7), 3.9 (t, J=10Hz, 1H, H-6), 4.1 (dd, J=4Hz, 10Hz, 1H, H-7), 5.5 (dd, J=7Hz, 11Hz, 1H, H-8), 5.7 (d, J=11Hz, 1H, OH), 7.35 (m, 8H, H arom), 7.7 (d, J=5.7Hz, 2H, H arom) ; **^{13}C NMR** ($CDCl_3$) : -0.4 ($SiMe_3$), 42.0 (C-4), 43.4 (C-3), 46.2 (C-2), 52.6 (C-5), 61.9 (C-7), 63.8 (C-6), 84.4 (C-8), 116.1 (CN), 122.8 123.5 126.3 128.8 128.9 133.5 137.1 (C arom), 172.9 (C=O) ; **IR** (cm^{-1}) : 1695 (C=O) ; **MS** (CI) : m/z= 436 (MH^+, 100), 410 (MH^+-CN, 100) .

Tricyclic compound 8

Bicyclic imide **3a** (250 mg, 0.58 mmol) was reduced using general procedure B to tricyclic compound **8** (60% yield).
^{1}H NMR (400MHz, DMSO) : 2.5 (m, 2H), 3.3 (m, 3H), 3.8 (m, 3H), 5.2 (m, 1H), 5.7 (m, 1H), 7.35 (m, 8H), 7.67 (m, 2H) ; **^{13}C NMR** (DMSO) : 44.9 45.3 (C-3, C-4), 55.8 (C-5), 64.4 (C-7), 69.3 (C-6), 72.4 (C-2), 91.8 (C-8), 93.5 (C-10), 122.1 125.3 127.3 128.3 128.9 139.9 (C arom), 175.3 (C=O) ; **IR** (cm^{-1}) : 1695 (C=O) ; **MS** (CI) : m/z= 366 (MH^+, 90), 349 (MH^+-NH3, 100) ; **Anal.** calcd. for : $C_{21}H_{23}N_3O_3$: C 69.02, H 6.34 ; Found : C 68.95, H 6.50.

Hydroxylactam 4b:

Bicyclic imide **2b** (45 mg, 0.12mmol) was reduced using standard procedure A and 2.5 equiv. of $CeCl_3$-$7H_2O$. Because of its unstability, crude product **4b** (30mg, oil) was analyzed without further purification.
^{1}H NMR (200MHz, $CDCl_3$): 2.6 (t, J=10Hz, 1H, H-5), 3.0 (dt, J=10, 2Hz, 1H, H-4), 3.1 (m, J=6, 4.5Hz, 1H, H-3), 3.2 (dd, J=10, 2Hz, 1H, H-5), 3.335 (d, J=4.5Hz, 1H, H-2), 3.8 (dd, J=10, 5Hz, 1H, H-7), 4.0 (t, J=10Hz, 1H, H-6), 4.2 (dd, J=10, 5Hz, 1H, H-7), 5.5 (d, J=6Hz, 1H; H-8), 5.7 (s, 1H, OH), 7.4 (m, 10H, H arom.); **^{13}C NMR** ($CDCl_3$): 42.0, 43.4 (C-3, C-4), 46.1, 52.6 (C-2, C-5), 61.7, 64.0 (C-6, C-7), 84.3 (C-8), 116.4 (CN), 123.3, 126.4, 128.9, 129.8, 132.9 (C arom.), 173.9 (CO); **MS** (CI): m/z= 364 (MH^+), 337.

Hydroxylactam 7b; lactone 18:

Bicyclic imide **3b** (45 mg, 0.12mmol) was reduced using standard procedure A and 2.5 equiv. of $CeCl_3$-$7H_2O$. Unresolved ^{1}H NMR spectrum was obtained with the crude reaction mixture, purification on silica (AcOEt as solvent) gave lactone **18** (10mg).
^{1}H NMR (200MHz, $CDCl_3$): 2.8 (dd, J=9, 6Hz, 1H, H-5), 3.2 (m, 2H, H-4, H-5), 3.8 (m, 1H, H-3), 4.0 (m, 2H, H-6, H-7), 4.1 (t, J=6Hz, H-7), 4.4 (d, J=8.5Hz, 1H, H-2), 6.0 (d, J=7.5Hz, 1H, H-8), 7.4 (m, 10H, H arom.); **^{13}C NMR** ($CDCl_3$): 42.2, 45.5 (C-3, C-4), 54.8 (C-5), 61.7, 64.8, 65.1 (C-2, C-6, C-7), 91.0 (C-8), 123.0, 127.1, 128.1, 128.3, 129.0, 129.2, 137.9 (C arom.), 173.6, 174.2 (CO); **IR** (neat, cm^{-1}): 1775, 1710; **MS** (CI): m/z= 365 (MH^+), 363, 245, 243.

Hydroxylactam 9 and tricyclic lactol 10 :

Procedure A applied to ester **3c** (200 mg, 0.51 mmol) gave after flash chromatography (65:35 AcOEt/heptane) hydroxylactam **9** (43% yield) and lactol **10** (42%).
9 : ^{1}H NMR (200MHz, $CDCl_3$) : 2.4 (dd, J=5Hz, 9Hz, 1H, H-5), 3.0 (m, 1H), 3.4 (m, 2H), 3.55 (d, J=8Hz, 1H, H-2), 3.65 (m, 2H, H-6, H-7), 3.7 (s, 3H, O-CH_3), 3.9 (m, 1H, H-7), 5.5 (d, J=7Hz, 1H, H-10), 7.35 (m, 10H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 38.7 (C-4), 48.5 (C-5), 49.1 (C-3), 52.8 (OCH_3), 63.0 (C-7), 64.5 66.6 (C-2,C-6), 85.9 (C-10), 123.7 126.3 128.8 129.0 135.0 137.5 (C arom), 172.0 172.3 (C=O) ; **IR** (cm^{-1}) : 1737, 1695 ; **MS** (CI) : m/z= 397 (MH^+, 100), 379 (MH^+-H_2O, 15), 365 (MH^+-MeOH, 30) ; **Anal.** calcd. for : $C_{22}H_{24}N_2O_5$: C 66.65, H 6.10, N 7.06 ; Found : C 66.61, H 6.29, N 6.79.
10 : ^{1}H NMR (200MHz, $CDCl_3$) : 2.5 (m, 2H), 3.0 (dd, J=7Hz, 9Hz, 1H), 3.4 (m, 2H), 3.65 (m, 1H), 3.9 (m, 2H), 5.7 (d, J=2.5Hz, 1H, H-12), 6.0 (d, J=7Hz, 1H, H-8), 7.35 (m, 10H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 43.4 45.1 48.2 52.4 62.5 71.7 (C-2, C-3, C-4, C-5, C-6, C-7), 93.7 (C-8), 101.6 (C-12), 122.4 123.8 126.4 128.2 128.8 129.3 132.0 134.7 (C arom), 174.7 (C=O) ; **MS** (CI) : m/z= 367 (MH^+, 100), 349 (MH^+-H_2O, 20).

Hydroxylactam 14 and tricyclic lactol 15 :

Procedure A applied to ester **13** (200 mg, 0.48 mmol) gave a 1:1 mixture of **14** and **15** (as deuced from ^1H and ^{13}C NMR spectra) which were difficult to separate. A small amount of pure hydroxylactam **14** was obtained by chromatography.
^1H NMR (400MHz, C_6D_6) : 0.0 (s, 9H, TMS), 0.7 (s, 3H, CH_3), 0.9 (s, 3H, CH_3), 2.0 (m, 1H, H-4), 2.1 (dd, J=5Hz, 9Hz, 1H, H-5), 2.8 (t, J=10Hz, 1H, H-3), 3 (d, J=9Hz, 1H, H-5), 3.2 (AB, 2H, H-7), 3.4 (s, 3H, OCH_3), 3.7 (d, J=10Hz, 1H, H-2), 5.2 (dd, J=7Hz, 10Hz, 1H, H-10), 6.0 (d, J=11Hz, 1H, OH), 7.3 (m, 4H, H arom), 8.0 (d, J=10Hz, 1H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 0.2 ($SiMe_3$), 39.6 (C-4), 47.6 (C-5), 49.6 (C-3), 52.3 (OMe), 57.4 (C-6), 61.7 (C-2), 69.1 (C-7), 86.4 (C-10), 124.5 126.2 128.9 137.7 (C arom), 172.6 174.1 (2 C=O) ; **IR** (cm^{-1}) : 1695, 1740; **MS** (CI) : m/z= 421 (MH^+,100), 403 (MH^+-H_2O, 10) ; **MS** (IE) : m/z= 317 (M^+ -CH_2OTMS, 80), 287 (100) .

Reduction of imide-ester 2c : hydroxylactam 11

Imide **2c** (250 mg, 0.68 mmol) was reduced with $LiBEt_3H$ using standard method C in THF during 40 min. Hydroxylactam **11** (207 mg, 0.52 mmol ; 83%) was obtained as amorphous solid after purification by flash-chromatography on silica (AcOEt as solvent).
$[\alpha]_D$= +68.1° (c 1, $CHCl_3$) **^1H NMR** (200MHz, $CDCl_3$) : 2.8 (dd, J=5Hz, 10Hz, 1H, H-5), 3.0 (m, 1H, H-4), 3.3 (dd, J=9Hz, 10.5Hz, 1H, H-3), 3.45 (d, J=10Hz, 1H, H-5), 3.6 (d, J=10.5Hz, 1H, H-2), 3.65 (s, 3H, OCH_3), 3.85 (m, 2H, H-6, H-7), 4.0 (dd, J=6Hz, 9Hz, 1H, H-7), 5.55 (d, J=6.5Hz, 12.5Hz, 1H, H-10), 5.65 (d, J=12.5Hz, 1H, OH), 7.35 (m, 10H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 39.2 (C-4), 49.5 (C-3), 52.4 (C-5), 52.8 (OCH_3), 62.6 67.6(C-2,C-6 and C-7 -two signals), 86.0 (C-10), 123.8 126.4 128.3 128.6 129.0 129.4 134.8 137.4 (C arom), 172.0 173.3 (C=O) ; **IR** (cm^{-1}) : 1728, 1695; **MS** (CI) : m/z= 397 (MH^+, 20), 379 (MH^+-H_2O, 100), 365 (MH^+-MeOH, 35) .

Reduction of imide-ester 2d : hydroxylactam 16

Imide **2d** (200 mg; 0.49 mmol) was reduced with $LiBEt_3H$ in THF using standard procedure. Purification by flash-chromatography (AcOEt as solvent) gave hydroxylatam **16** (164 mg ; 0.40 mmol, 82%) as amorphous solid.
^1H NMR (200MHz, $CDCl_3$) : 1.25 (t, J=7Hz, 3H, CH_3), 2.8 (dd, J=5Hz, 10Hz, 1H, H-5), 3.0 (m, 1H, H-4), 3.3 (t, J=10Hz, 1H, H-3), 3.4 (d, J=10Hz, 1H, H-5), 3.6 (d, J=10Hz, 1H, H-2), 3.8-4 (m, 3H, H-6, H-7), 4.0 (q, J=7Hz, 2H, CH_2 ester), 5.5 (d, J=7Hz, 1H, H-10), 7.4 (m, 10H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 13.8 (CH_3), 39.4 49.5 52.4 (C-3, C-4, C-5), 62.1 62.8 63.2 (CH_2 ester, C-2, C-7), 67.8 (C-6), 86.7 (C-10), 122.5 123.7 126.4 128.3 128.6 128.9 129.4 135.2 137.4 (C arom), 172.1 172.9 (C=O) ; **IR** (cm^{-1}) : 1737, 1700; **MS** (CI) : m/z= 411 (MH^+, 100), 393 (MH^+-H_2O, 40), 365 (MH^+-EtOH, 20) .

Reduction of imide-ester 3d : hydroxylactam 17

Imide **3d** (1g, 2.45 mmol) was reduced with $LiBEt_3H$ in CH_2Cl_2 using standard procedure C. After flash-chromatography on silica (AcOEt as solvent) pure hydroxylactam **17** (0.8 g ; 1.95 mmol ; 80%) was obtained as a waxy solid.
$[\alpha]_D$= -64.6 (c 1.5, $CHCl_3$) ; **^1H NMR** (200MHz, $CDCl_3$) : 1.3 (t, J=7Hz, 3H, CH_3), 2.5 (dd, J=5Hz, 10Hz, 1H, H-5), 3.1 (m, 1H, H-4), 3.4 (m, 2H, H-3 et H-5), 3.7 (d, J=10Hz, 1H, H-2), 3.9 (m, 2H, H-6, H-7), 4.1 (dd, J=7Hz, 11Hz, 1H, H-7), 4.4 (m, 2H, CH_2 ester), 5.5 (d, J=7Hz, 1H, H-10), 7.35 (m, 10H, H arom) ; **^{13}C NMR** ($CDCl_3$) : 14.9 (CH_3), 39.8 (C-3), 49.7 (C-5), 49.9 (C-4), 63.0 64.0 (CH_2 ester, C-7), 65.6 (C-2), 67.8 (C-6), 86.7 (C-10), 124.4 127.0 129.3 129.6 136.3 136.7 (C arom), 172.6 172.8 (C=O) ; **IR** (cm^{-1}) : 1737, 1700 ; **MS** (CI) : m/z= 411 (MH^+, 100), 393 (MH^+-H_2O, 30), 365 (MH^+-EtOH, 20) ; **Anal.** calcd. for : $C_{23}H_{26}N_2O_5$: C 67.30, H 6.38, N 6.82 ; Found : C 67.74, H 6.71, N 6.42.

REFERENCES AND NOTES

1 - a) Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4367. b) Zaugg, H.E. *Synthesis*, **1984**, 85.

2 - a) Hiemstra, H.; Speckamp, W.N. *"The Akaloids"*, Brossi, A, Eds, N.Y., **1988**, *32*, chap. 4 ; b) Speckamp, W.N.*"Stereoselective Synthesis of Natural Products"*, Bartmann, W. Eds, Amsterdam, **1978**, *7*, 52.; c) Hiemstra, H.; Sno, M.H.A.M.; Vijn, R.J.; Speckamp, W.N. *J. Org. Chem.*, **1985**, *50*, 4014 ; d) Hiemstra, H.; Klaver, W.J.; Speckamp, W.N. *J. Org. Chem.*, **1984**, *49*, 1151 ; e) Fischer, M.J.; Overman, L.E. *J. Org. Chem.*, **1990**, *55*, 1447 ; f) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.*, **1981**, *103*, 1172.

3 - a) Oostveen, A.R.C.; De Boer, J.J.J.; Speckamp, W.N. *Heterocycles*, **1977**, *7*, 171 ; b) Wakabayashi, T.; Saito, M. *Tetrahedron Lett.*, **1977**, 93 ; c) Shishido, E.; Sukegawa, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1*, **1987**, 993.

4 - Wilkens, H.J.; Troxler, F. *Helv. Chem. Acta*, **1975**, *58*, 1512.

5 - a) Einhorn, A.; Mauermayer, T. *Annal Chem.*, **1905**, *343*, 282 ; b) Zoller, U.; Ben Ishai, D. *Tetrahedron*, **1975**, *31*, 836 ; c) Gormley, G.; Chan, Y.Y.; Fried, J. *J. Org. Chem.*, **1980**, *45*, 1447 ; d) Wuonola, M.A.; Woodward, R.B. *Tetrahedron*, **1976**, **32**, 1085 ; e) Confalone, P.N.; Ko, S.S. *Tetrahedron Lett.*, **1984**, *25*, 947.

6 - a) Evans, D.A.; Thomas, E.W.; Cherpeck, R.E. *J. Am. Chem. Soc.*, **1982**, *104*, 3695 ; b) Wrobel, T.; Cybulski, J.; Dabrowski, Z. *Synthesis*, **1977**, 686.

7 - a) Horii, Z.I.; Iwata, C.; Tamura, Y. *J. Org. Chem.*, **1961**, *26*, 2273 ; b)Uhle, F.C. *J. Am. Chem. Soc.*, **1961**, *83*, 1460.

8 - a) Hubert, J.C.; Steege, W.; Speckamp, W.N.; Huisman, H.O. *Synth. Commun.*, **1971**, 103 ; b) Hubert, J.C.; Winjberg, J.B.P.A.; Speckamp, W.N. *Tetrahedron*, **1975**, *31*, 1437 ; c) Winjberg, J.B.P.A.; Shoemaker, H.E.; Speckamp, W.N. *Tetrahedron*, **1978**, *34*, 179 ; d) Hiemstra, H.; Vijn, R.J.; Speckamp, W.N. *J. Org. Chem.*, **1988**, *53*, 3882 ; e) Vijn R.J.; Hiemstra, H.; Kok, J.J.; Knotter, M.; Speckamp, W.N. *Tetrahedron*, **1987**, *43*, 5019.

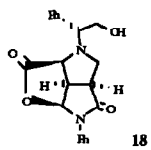
9 - a) Winterfeld, E. *Synthesis*, **1975**, 617 ; b) Miller, S.A.; Chamberlin, A.R. *J. Org. Chem.*, **1989**, *54*, 2502.

10- Johnson, R.L.; Koerner, J.F. *J. Med. Chem.* **1988**, *31*, 2057.

11- a) Rouden, J.; Royer, J.;Husson H.-P. *Tetrahedron Lett.*, **1989**, *30*, 5133 ; b) Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.*, **1991**, *31*, 1531 ; c) Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron : Asym.*, **1991**, *2*, 1189.

12- $CeCl_3$ has already been used in association with $NaBH_4$ by Krief A. and al. (Boss III, Louvain La Neuve, July 1990) in order to invert stereoselectivity of the reduction of an imide. see also: Atta-ur-Rahman; Ghazala, M; Sultana, N.; Bashir, M. *Tetrahedron Lett.*, **1980**, *21*, 1773.

13- In these cases more than 2 equiv. of $CeCl_3$ were needed to observe a clean reaction. Reduction products **4b** and **7b** were found to be unstable. Hydroxylactam **4b** could be analyzed without further purification whereas hydroxylactam **7b** could not, being transformed into lactone **18** during flash chromatograpy on silica gel.



18