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Palladium(II)-Catalyzed Formation of γ-Butyrolactones from 4-Trimethylsilyl-3-alkyn-1-ols : Synthetic and Mechanistic Aspects

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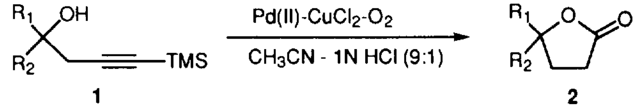
Abstract : γ-butyrolactones are obtained in good yields from 4-trimethylsilyl-3-alkyn-1-ols *via* Wacker-type oxidation reaction. A mechanism is proposed for this transformation : it involves two successive *trans*-hydroxypalladations followed by a [PdXSiMe3] *syn*-elimination and explains why the presence of the silyl group is essential in such a process. Copyright © 1996 Elsevier Science Ltd

Introduction

The discovery of new methods for the preparation of γ-lactones[1] is still a current topic of interest due to the presence of this functionality in a number of natural products.

The most common way to prepare γ-lactones remains the cyclization of γ-hydroxy acids and many methods have been described to obtain these last compounds in enantioenriched form.[2] They can also "*inter-alia*" be obtained by selective reduction of butenolides issued from the metal-catalyzed carbonylation of propargylic or allylic alcohols.[3]

In this paper, we report the results of the study of a new method of preparation of diversely substituted γ-lactones based on a heterocyclization of trimethylsilyl homopropargylic alcohols related to the Wacker process depicted in Scheme 1.[4]

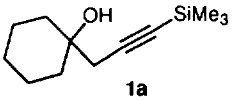
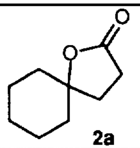
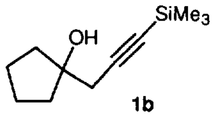
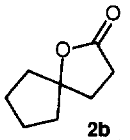
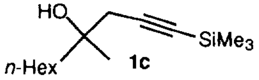
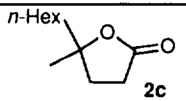
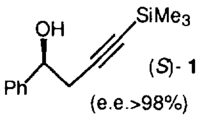
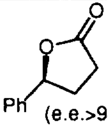
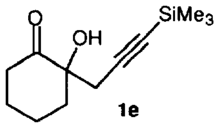
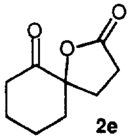
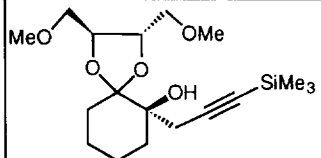
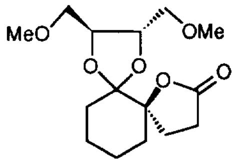
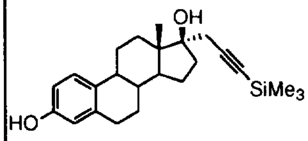
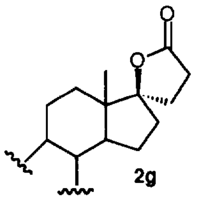


R_1, R_2 = H, Ph, alkyl, cycloalkyl

Scheme 1

A set of various acetylenic alcohols **1**, easily prepared by addition of the lithium salt of trimethylsilyl propyne to their corresponding ketones, was by this process cleanly transformed to lactones **2**. A systematic

Table 1 : Pd(II)-Catalyzed γ-Butyrolactone Formation from Substituted 4-Trimethylsilylbut-3-yn-1-ols **1**

Entry	Substrate	Catalyst	Solvent	Reaction Time	γ-butyrolactone	Isolated Yield (%)
1	 **1a**	PdClNO2(MeCN)2	MeCN-1N HCl	16h	 **2a**	68
2 3	 **1b**	Pd(OAc)2 PdClNO2(MeCN)2	MeCN-1N HCl MeCN-1N HCl	20h 16h	 **2b**	72 74
4 5	 **1c**	Pd(OAc)2 PdClNO2(MeCN)2	MeCN-1N HCl MeCN-1N HCl	22h 16h	 **2c**	54 53
6	 (*S*)- **1d** (e.e.>98%)	PdClNO2(MeCN)2	MeCN-1N HCl	16h	 (*S*)- **2d** (e.e.>98%)	58
7 8	 **1e**	PdClNO2(MeCN)2 PdClNO2(MeCN)2	MeCN-1N HCl wet DMF	16h 72h	 **2e**	34[a] 50
9	 (d.e.=80%) **1f**	PdCl2(PhCN)2	wet DMF	96h	 (d.e.=80%) **2f**	68
10	 **1g**	Pd(OAc)2	MeCN-1N HCl	16h	 **2g**	83

[a] 26% of the diketone 3 was also formed

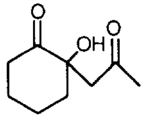
study on the influence of the experimental conditions has shown that the best results were obtained when alcohols **1** were treated with 5% of $PdClNO_2(MeCN)_2$ or $Pd(OAc)_2$ in the presence of 25% of $CuCl_2$, in a slightly acidic medium and under an air atmosphere[4]. In Table 1 are listed some examples of this reaction which lead in all the cases to lactones **2** with acceptable to good yields.

Some comments can be added to the results reported on Table 1 :

* The presence of the trimethylsilyl group is crucial for the success of the lactonization. The same reaction on the desilylated homopropargylic alcohols leads to an untractable mixture of compounds where the corresponding lactones **2** were completely absent.

* The reaction occurs with complete retention of the configurational integrity when diastereo- or enantioenriched alcohols **1** are used (entries 6 and 9). We recently used[5] this result to determine the absolute configuration of the levorotatory isomer of **1e** (obtained by resolution of the diastereomeric camphanates of racemic alcohol) by its transformation to the previously described lactone *(R)*-**2e**.

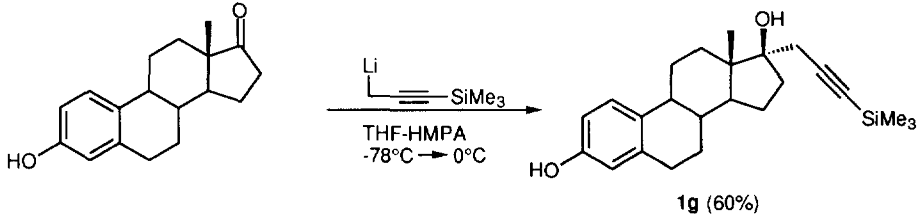
* Generally, the lactone **2** is the only isolated reaction product. However, in the case of **1e** and depending on the experimental conditions, it was sometimes accompanied by up to 26% of the diketone **3**, the origin of which having been previously explained.[4]



3

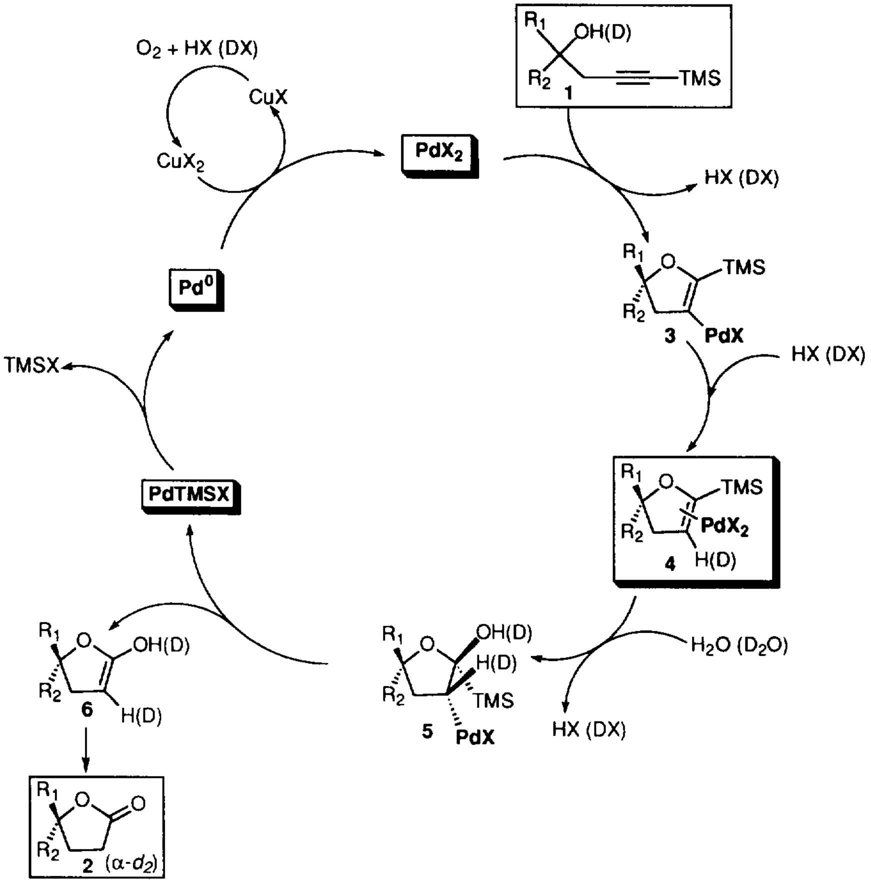
* A typical example of the synthetic interest of the methodology is the rapid and efficient synthesis from estrone of the biologically interesting steroidal γ-butyrolactone **2g**. Very recently,[6] this spirolactone was found to be a potent inhibitor of 17β-hydroxysteroid dehydrogenase (17β-HSD), an enzyme that plays an essential role in the biosynthesis and metabolism of steroid hormones.

Previous preparations of **2g** were realized in five to six step sequence[6] in about 30% overall yields from estrone. The cyclization of homopropargylic alcohol **1g**, prepared in 60% yield from estrone (Scheme 2), afforded **2g** in 83% yield, thus accessible from estrone in two steps and 50% overall yield.



Scheme 2

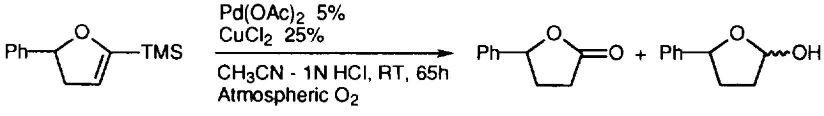
Because of this unexpected behaviour of compounds **1** under the Wacker oxidation conditions, we thought that a thorough mechanistic study seemed worthwhile. Based on literature informations dealing with oxypalladation reactions of unsaturated systems, it appeared that the synthesis of γ-butyrolactones **2** from alcohols **1** must likely proceed by the reaction pathway shown in Scheme 3. We decided to verify the main steps of this catalytic sequence and also to determine the role of the trimethylsilyl group.



Scheme 3

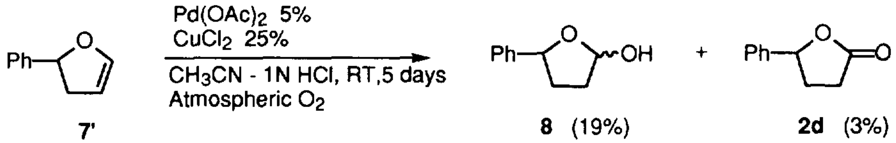
In the first place, in order to demonstrate that the η^2-olefin complex **4** was an intermediate in the γ-butyro lactone formation, we synthesized 5-phenyl-2-trimethylsilyl-4,5-dihydrofuran **7** from the commercially available γ-phenyl-γ-butyrolactone.[7,8]

Under the reaction conditions previously used for **1**, the vinylsilane **7** afforded the expected lactone **2d** in 38% yield along with the lactol **8** in 36% yield (Scheme 4).



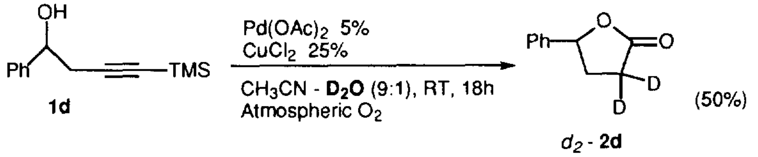
Scheme 4

The formation of the lactone **2d** from **7** provides a good support that a silylated 4,5-dihydrofuran is an intermediate in the mechanistic pathway. It is noticeable that a lactol was never detected in the cyclization of **1**, probably because cyclic enol ether **4** is then a transient species involved in a catalytic cycle. In the present case (Scheme 4) only 5% of **7** can be complexed with palladium(II) which undergoes a slow transformation to compound **2d**. Consequently, a fraction of **7**, in the presence of diluted HCl, can be protodesilylated and hydrated to the lactol **8**. This hypothesis was verified by using compound **7'** which in the same reaction conditions, gave the lactol **8** in 19% yield accompanied by 3% of the lactone **2d** and by polymers (Scheme 5).



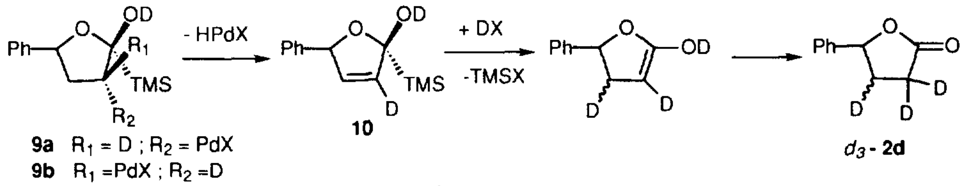
Scheme 5

Next, we examined the cyclization of compound (±)-**1d** in the presence of D_2O (Scheme 6). The double deuterated lactone **2d** was obtained in 50% yield. The position and number of deuterium atoms, determined by ^{1}H and ^{13}C NMR analyses, are consistent with the mechanism proposed in Scheme 3.



Scheme 6

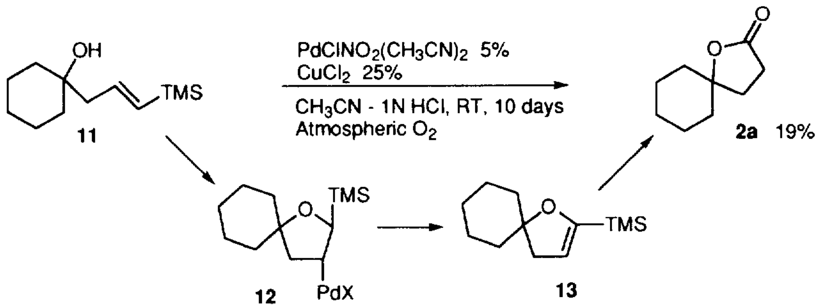
This result rules out the formation of γ-butyrolactones from the σ-complex **5** by [HPdX] elimination (Scheme 3). Indeed, if β-hydride elimination took place rather than a [PdX/SiMe$_3$] elimination[9] from **9a** this would then lead to the formation of the intermediate **10** which after protodesilylation and 1,3-deuterium shift would furnish the trideuteriolactone d$_3$-**2d** (Scheme 7). Moreover, this experiment shows that hydroxypalladation of **7** is a *trans* process. Indeed, the *cis*-addition would give **9b** where palladium is *trans* to the silicon. The β-hydride elimination would be then favored giving **10** and ultimately *d*$_3$-**2d**.



Scheme 7

On the basis of the mechanistic pathway depicted in Scheme 3, we imagined another possible access to γ-butyrolactones from (E)-1-substituted-4-trimethylsilylbut-3-en-1-ols.

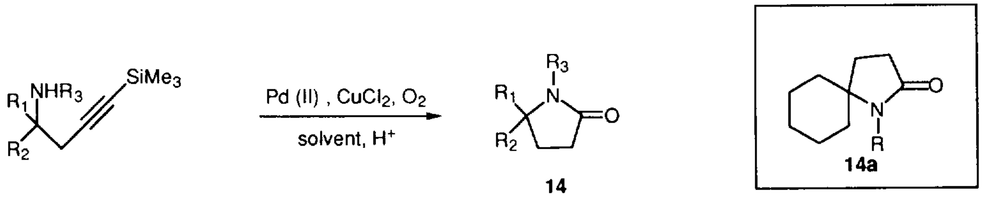
Indeed, the σ-complex **12** obtained by *trans*-hydroxypalladation of **11** can suffer a regioselective *syn* -elimination of [HPdX][10] to furnish the vinylsilane **13** which by the pathway described in Scheme 3 must afford the γ-butyrolactone **2a**. Thus, (E)-1-[3-(trimethylsilyl)allyl]-1-cyclohexanol[11] **13**, subjected to Wacker conditions produced the expected lactone **2a** in only 19% yield[12] (Scheme 8). Because of the slow cyclization of **11** into **2a** (10 days), we assume that the acidity of the reaction mixture can favor a partial prodesilylation of **11** giving rise to other unstable Wacker oxidation products.



Scheme 8

Consequently, it seems that all these experiments (Schemes 4 to 8) strongly support the hypothetic mechanism described in Scheme 3 : the cyclization of 1-substituted-4-trimethylsilylbut-3-yn-1-ols **1** promoted by Pd(II) occurs *via* intermediate **4** which, after hydroxypalladation, suffers a [PdX/SiMe$_3$] *syn*-elimination to afford lactones **2**. We have also shown that the hydroxypalladation of 2-trimethylsilyl-4,5-dihydrofuran is a *trans* process which is consistent with the results of Bäckvall and Stille[13] on simple olefins. Lastly, in the presence of D$_2$O, the cyclization of compounds **1** constitutes an easy and very mild access to α,α'-dideuterated γ-butyrolactones.

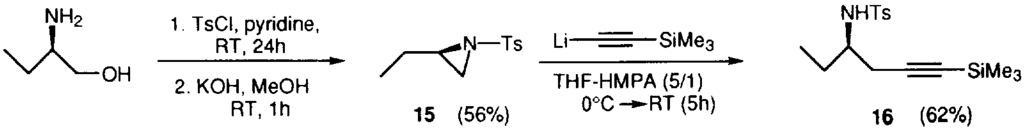
We tried to extend the cyclization process to homopropargylic amines in order to prepare γ-lactams **14** as described in Scheme 9.



Scheme 9

Our main target was then to open a new entry to the 1-azaspiro[5,4]decane skeleton, by preparation of the spirolactam **14a**. This interest was drawn by the known biological activity of compounds of this azaspirane family[14] as well as the homologous 1-azaspiro[5,5] family to which histrionicotoxin and its congeners are related.[15]

Referred to the literature[16], we were able to obtain the tosylamine **16** from (*R*)-(-)-2-aminobutanol by the three step sequence depicted in Scheme 10.



Scheme 10

Unfortunately, all the attempts to transform **16** to the corresponding γ-lactam **14** were unsuccessful whatever were the catalyst and the solvent. In the majority of runs the starting material was partially recovered at room temperature while at higher temperatures an intense degradation without any formation of the expected product was observed.

Experimental section

General. ^1H NMR spectra were recorded in $CDCl_3$ (δ_H = 7.25 ppm) at ambient probe temperature on a Bruker AC 200 (200MHz) spectrometer. Data are presented as follows : chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperature on Bruker AC 200 (50.3 MHz) in $CDCl_3$ used as reference (δ_c 77.00 ppm). IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer using 5mm sodium chloride plates. Wavelengths of maximum absorbance (√max) are quoted in cm^{-1}. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at the sodium D line (589 mm). Melting points were determined on a Büchi 530 apparatus and are uncorrected. Combustion analyses were performed by the Service Central de Microanalyse, CNRS, Solaize.

Reagents and solvents were purified by standard means. Acetonitrile, dichloromethane, dimethylformamide and pyridine were distilled from calcium hydride ; diethyl ether and tetrahydrofuran were distilled from sodium wire / benzophenone and stored under a nitrogen atmosphere.

General procedure for the preparation of 4-trimethylsilyl-3-alkyn-1-ols (1a, 1b, 1c)

To a solution of the lithium salt of 1-trimethylsilylpropyne (12.5 mmol) in Et_2O (37 ml) containing TMEDA (1.9 ml, 12.5 mmol) cooled to -60°C, was added under nitrogen a solution of ketone (10 mmol) in Et_2O (15 ml). The reaction mixture was warmed up to -25°C (1h) and acetic acid (7 ml) then water (22 ml) were added slowly. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were successively washed with saturated $NaHCO_3$ solution, water, dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash chromatography.

1-Hydroxy-1-(3-trimethylsilylprop-2-ynyl)cyclohexane (1a). Et_2O-petroleum ether, (1:7) ; amorphous solid (55% yield) ; IR (neat) 3360, 2160, 1240, 830, 755 ; ^1H NMR : 0.15 (s, 9H, $Si(CH_3)_3$), 1.22-1.66 (m, 10H, $5CH_2$), 1.84 (s, 1H, OH), 2.38 (s, 2H, $\underline{CH_2}$-C≡C) ; ^{13}C NMR : 0.1, 23.8, 27.2, 35.9 (2C), 38.3 (2C), 71.8, 89.8, 104.6. These spectroscopic data are identical with those reported in the literature.[17]

1-Hydroxy-1-(3-trimethylsilylprop-2-ynyl)cyclopentane (1b). Et_2O-petroleum ether, (1:7) ; white solid (69% yield) ; mp 58-59°C ; IR (neat) 3400, 2160, 1260, 840, 740. ^1H NMR : 0.19 (s, 9H), 1.6-1.95 (m, 8H, $4CH_2$), 2.03 (s, 1H, OH), 2.54 (s, 2H, $\underline{CH_2}$-C≡C) ; ^{13}C NMR : 0.1, 24.1 (2C), 32.9, 39.1 (2C), 80.8, 87.0, 103.9 ; Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28 ; H, 10.27. Found : C, 66.61 ; H, 10.41.

4-Hydroxy-4-methyl-1-(trimethylsilyl)dec-1-yne (1c). Et_2O-petroleum ether, (1:10) ; oil (65% yield) ; IR (neat) 3420, 2170, 1250, 840, 760 ; ^1H NMR : 0.18 (s, 9H), 0.9 (t, 3H, J=6.7Hz, CH_3), 1.26 (s, 3H, CH_3), 1.28 (m, 8H, $4CH_2$), 1.42-1.65 (m, 2H, CH_2), 1.92 (s, 1H, OH), 2.40 (s, 2H, $\underline{CH_2}$-C≡C) ; ^{13}C

NMR : 0.1, 14.1, 22.6, 24.0, 26.4, 29.8, 31.8, 33.8, 41.2, 71.7, 87.9, 103.5 ; Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93 ; H, 11.74. Found : C, 70.30 ; H, 11.91.

2-Hydroxy-2-(3-trimethylsilylprop-2-ynyl)cyclohexanone (1e). Prepared as described in ref. 18.

(S)-1-Phenyl-4-trimethylsilylbut-3-yn-1-ol (1d). To a solution of trimethylsilylacetylene (1.28 g ; 13 mmol, 1.5 equiv) in THF (20 ml) cooled to -70°C, was added under nitrogen *n*-BuLi (2.3 M in hexane, 13 mmol). After stirring at -70°C for 10 min, BF_3-Et_2O (1.62 ml, 13 mmol) was added. The reaction mixture was stirred at this temperature for 10 min and (*R*)-phenyloxirane (1 ml, 8.8 mmol) was added. The mixture was stirred for 30 min at -70°C and then allowed to warm up to -25°C (1 h). Saturated NH_4Cl solution (30 ml) was added and the aqueous phase was extracted three times with Et_2O (3 x 20 ml). The combined ethereal layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (Et_2O-petroleum ether (8:1) to give first **1d** (0.45 g, 24%) as an oil : $[\alpha]^{20}_D$ - 32.3 (c 4.2, $CHCl_3$) ; IR (neat) 3380, 3080, 3060, 2960, 2900, 2180, 1600, 1250, 845, 755, 695 ; ^1H NMR : 0.19 (s, 9H, $Si(CH_3)_3$), 2.66 (d, 2H, J=6.4Hz, $C\underline{H}_2$-C≡C), 2.73 (brd, 1H, J=2.8Hz, OH), 4.75-5.05 (m, 1H, $C\underline{H}OH$), 7.25-7.6 (m, 5H, Ph) ; ^{13}C NMR : 0.02, 31.0, 72.3, 87.8, 103.1, 125.8, 127.8, 128.3, 142.6. The next fraction was constituted of 2-phenyl-4-trimethylsilylbut-3-yn-1-ol (0.43 g, 23%) obtained as a white solid ; mp 40-41°C ; IR (KBr) 3400, 3080, 3060, 3025, 2960, 2920, 2895, 2170, 1600, 1585, 1250, 1040, 840, 760, 700 ; ^1H NMR : 0.24 (s, 9H, $Si(CH_3)_3$), 2.07 (t, 1H, J=6.7Hz, OH), 3.75 (m, 2H, $C\underline{H}_2OH$), 3.91 (t, 1H, J=6.7Hz, $C\underline{H}$ Ph), 7.28-7.6 (m, 5H, Ph) ; ^{13}C NMR : 0.13, 42.4, 67.6, 89.4, 105.0, 127.4, 127.9, 128.7, 137.7 ; Anal. Calcd for $C_{13}H_{18}OSi$: C, 71.50 ; H, 8.31. Found : C, 71.25 ; H, 8.39.

(2S,3S,6S and 6R)-2,3-Dimethoxy-6-hydroxy-6-(3-trimethylsilylprop-2-ynyl)-1,4-dioxaspiro [4.5]decane (1f). To a solution of **1a** (0.22 g ; 0.98 mmol) and (*S,S*)-1,4-dimethoxy-2,3-butanediol (0.17 g, 1.3 mmol, 1.15 equiv) in CH_2Cl_2 (4 ml) was added slowly at 0°C under nitrogen chlorotrimethylsilane (0.52 ml, 4.1 mmol, 4.2 equiv). The reaction mixture was allowed to warm up to room temperature and stirred at this temperature for 11 h. To the mixture were successively added CH_2Cl_2 (20 ml) and saturated $NaHCO_3$ solution (15 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic extracts were washed with brine (30 ml) and finally dried (Na_2SO_4). The residue was purified by flash chromatography (Et_2O - CH_2Cl_2 - petroleum ether, 1:1:6) to give the less polar diastereomer (0.05 g, 14%) obtained as a yellow oil (de 93%) : IR (neat) 3460, 2170, 1245, 2960, 840, 755 ; ^1H NMR : 0.15 (s, 9H, $Si(CH_3)_3$), 1.25-2.05 (m, 8H, $4CH_2$), 2.50 (d, 1H, J=17Hz, $C\underline{H}$-C≡C) ; 2.76 (d, 1H, $C\underline{H}$-C≡C), 2.98 (s, 1H, OH), 3.37 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.4-3.56 (m, 3H, $C\underline{H}_2OCH_3$), 3.64-3.73 (m, 1H, $C\underline{H}_2OCH_3$), 3.98 (dt, 1H, J=8.4 and 3.5Hz, $C\underline{H}OR$), 4.17 (quint, 1H, J=4.5Hz, $C\underline{H}OR$) ; ^{13}C NMR : 0.2, 21.7, 23.0, 26.4, 33.5, 34.8, 59.4, 59.6, 73.0, 74.9, 76.4, 77.3, 77.7, 87.1, 103.4, 111.3. The next fraction was a mixture of the two diastereomers (0.033 g, 9%). The third fraction was constituted of the other diastereomer (0.07 g, 20% ; de 80%) : ^1H NMR : 0.13 (s, 9H, $Si(CH_3)_3$), 1.30-1.96 (m, 8H, $4CH_2$), 2.44 (s, 1H, OH) ; 2.49 (d, 1H, J=17Hz, $C\underline{H}$-C≡C), 2.65 (d, 1H, J=17Hz, $C\underline{H}$-C≡C), 3.37 (s, 3H, OMe), 3.38 (s, 3H, OMe), 3.42-3.62 (m, 4H, $2C\underline{H}_2OCH_3$), 3.70-4.11 (m, 2H, $C\underline{H}OR$) ; ^{13}C NMR : 0.13, 20.8, 23.0, 27.6, 33.4, 34.0, 59.4, 59.5, 73.4, 74.3, 74.9, 77.8, 77.9, 87.2, 103.4, 111.6 ; Anal. Calcd for $C_{18}H_{32}O_5Si$ (mixture of diastereomers) : C, 60.64 ; H, 9.05. Found : C, 60.64 ; H, 8.97.

3,17β-Dihydroxy-17α-(3-trimethylsilylprop-2-ynyl)-1,3,5(10)-estratriene (1g). To a solution of estrone (0.37 g ; 1.4 mmol) in THF (10 ml) cooled to -78°C was added under nitrogen a solution of the lithium salt of 1-trimethylsilylpropyne (5.6 mmol, 4 equiv) [prepared from trimethylsilylpropyne (0.62 g) and *tert*-BuLi (1.6M in hexane, 3.5 ml)]. The reaction mixture was stirred at -78°C for 4h and then at room temperature for 16 h. The mixture was cooled down to 0°C and saturated NH_4Cl solution (30 ml) was added. The aqueous layer was extracted three times with AcOEt (40 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt, petroleum ether, 1:8) to give **1g** (0.32 g, 60% yield) as a foam : IR (KBr) 3350, 2170, 1255, 890, 870, 845, 760 ; ^1H NMR : 0.19 (s, 9H, $Si(CH_3)_3$), 0.96 (s, 3H, CH_3), 1.2-1.95 (m, 9H) ; 2.0-2.7 (m, 6H), 2.75-2.90 (m, 2H, CH_2-6), 3.75 (s, 1H, OH), 6.08 (s, 1H, OH), 6.58 (d, 1H, J=2.4Hz, CH-4), 6.65 (dd, J=2.6 and 4Hz, CH-2), 7.15 (d, 1H, J=8.4Hz, CH-1) ; ^{13}C NMR : 0.1, 14.4, 23.2, 26.3, 27.4, 29.6, 30.5, 32.2, 36.2, 39.5, 43.7, 46.3, 49.8, 82.3, 88.4, 104.1, 112.8, 115.3, 126.4, 132.2, 138.1, 153.7.

General procedure for the preparation of γ-lactones (2a-g).

To a solution of 4-trimethylsilyl-3-alkyn-1-ols (10 mmol) in CH_3CN-1N HCl (9:1, 37 ml) or DMF containing 1% of water (30 ml) were added 5 mole % of Pd(II) and 25 mole % of $CuCl_2$ (0.335 g). The mixture was stirred at room temperature under air, for 16 h to 96 h depending on the substrate. The reaction mixture was concentrated *in vacuo*, diluted with Et_2O, washed twice with water and dried (Na_2SO_4). The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:2).

1-Oxaspiro[4.5]decan-2-one (2a). Oil (68% yield). Its spectroscopic data are identical to those reported in the literature.[19]

1-Oxaspiro[4.4]nonan-2-one (2b). Oil (74% yield). Its spectroscopic data agreed with the corresponding values reported in the literature.[20a,b]

5-(n-Hexyl)-5-methyl-2-oxotetrahydrofuran (2c). Oil (53% yield). Its IR and ^1H NMR spectroscopic data are in good agreement with those described in the literature[21]. ^{13}C NMR : 14.0, 22.5, 23.7, 25.6, 29.1, 29.4, 31.6, 32.9, 40.9, 86.9, 176.8.

(S)-5-Phenyl-2-oxotetrahydrofuran (2d). Oil (58% yield). $[\alpha]^{20}_D$ - 35.5 (c 2.9, $CHCl_3$) [lit.[22] of (R) enantiomer $[\alpha]^{25}_D$ + 35.5 (c 2.5, $CHCl_3$). Its spectroscopic data are identical to those reported in the literature.[2,22]

1-Oxaspiro [4.5] decan-2.6-dione (2e). In CH_3CN - 1N HCl (9:1), flash chromatography of the residue using a mixture of Et_2O-hexane-AcOEt (1:2:1) gave first 2-hydroxy-(2-oxopropyl)cyclohexanone **3** (0.025 g, 26%) as an oil ; IR (neat) 3450, 1715 ; ^1H NMR : 1.50-2.09 (m, 6H, $3CH_2$), 2.25 (s, 3H, CH_3), 2.28-2.45 (m, 1H, $C\underline{H}CO$), 2.56 (d, 1H, J=16.1Hz, $C\underline{H}COCH_3$), 2.78-2.92 (m, 1H, $C\underline{H}CO$), 3.01 (d, 1H, J=16Hz, $C\underline{H}COCH_3$), 4.86 (s, 1H, OH) ; ^{13}C NMR : 22.2, 29.5, 32.7, 38.9, 42.4, 49.5, 79.5, 210.9, 213.4. The second fraction was constituted of pure **2e** (0.032 g, 34%) which displays identical spectral data with that reported in the literature.[23]

(2S,3S)-2,3-dimethoxymethyl-1,4,14-trioxadispiro[4.4.4.0]tetradecan-13-one (2f). Oil (68%) ; IR (neat) 1775 ; ^{1}H NMR : 1.30-2.10 (m, 9H), 2.45-2.80 (m, 3H), 3.38 (s, 6H, 2OCH$_3$), 3.42-3.62 (m, 4H, 2CH$_2$OCH$_3$), 3.90-4.00 (m, 1H, C$\underline{H}$OR), 4.01-4.16 (m, 1H, C$\underline{H}$OR) ; ^{13}C NMR : 21.5, 22.5, 28.3, 29.2, 33.6, 36.0, 59.4, 59.6, 72.5, 72.7, 78.0, 78.3, 88.4, 110.7, 177.4 ; Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98 ; H, 8.05. Found : C, 59.65 ; H, 8.00.

3-Hydroxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (2g). Colorless needles (83%) ; mp 243-245°C (acetone/hexane) [lit.^{6b} mp 244-246°C (acetone/hexane)]. Its spectroscopic data (IR, ^{1}H and ^{13}C NMR) are in perfect agreement with those reported in the literature^{6b}.

(3-$^{2}H_{2}$)-5-Phenyl-2-oxotetrahydrofuran (d$_2$-2d). Cyclization was performed in a mixture of CH$_3$CN-D$_2$O (6:1). After a usual work-up, the residue was purified by flash-chromatography (Et$_2$O-petroleum ether, 1:5) to give (*d*$_2$-**2d**) (50% yield, 94% d$_2$ by ^{13}C NMR) ; IR (film) : 2160 (CD), 1770 (lactone) ; ^{1}H NMR : 2.11 (dd, 1H, J=7 and 12Hz, C$\underline{H}$-CD$_2$), 2.57 (dd, 1H, C$\underline{H}$-CD$_2$), 5.44 (t, 1H, J=7.5Hz, C$\underline{H}$Ph) ; 7.13-7.43 (m, 5H, Ph) ; ^{13}C NMR : 28.3, 30.7, 81.1, 125.2, 128.3, 128.6, 139.3, 177.2.

Formation of the γ-butyrolactone (2d) from the vinylsilane (7).

To a solution of 7^{7,8} (0.07 g, 0.32 mmol) in CH$_3$CN-1N HCl (9:1, 2 ml) were added Pd(OAc)$_2$ (0.004 g, 5 mole %) and CuCl$_2$ (0.011 g, 25 mole %). The reaction mixture was stirred under air for 65 h at room temperature. The mixture is concentrated *in vacuo* and the residue was purified by flash chromatography (Et$_2$O-petroleum ether, 1:5) to give first the lactol **8** [oil, 0.019 g (36%)] ; IR (film) 3400, 3080, 3060, 3020, 2940, 755, 700 ; ^{1}H NMR (mixture of α and β anomers) : 1.65-2.75 (m, 4H, 2CH$_2$), 3.16 (s, 0.55H, OH), 3.20 (s, 0.45H, OH), 5.01 (q, 0.45H, J=6 and 8Hz, C$\underline{H}$OH), 5.26 (t, 0.55H, J=6.9Hz, C$\underline{H}$OH), 5.63 (brs, 0.45H, C$\underline{H}$Ph), 5.78 (q, 0.55H, J=1.5 and 4Hz, C$\underline{H}$Ph), 7.15-7.60 (m, 5H,Ph). The next fraction was pure **2d** (0.02 g, 38%) obtained as an oil which has identical spectral data with those reported in the literature.^{2,22}

(S)-2-Ethyl-1-paratoluenesulfonylaziridine (15). To a well-stirred solution of *p*-toluenesulfonyl chloride (7.4 g, 38.8 mmol, 2.1 equiv) in pyridine (20 ml) cooled to -15°C, was added slowly a solution of (R)-(-)-2-aminobutanol (1.65 g, 18.5 mmol) in pyridine (5 ml). The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. The reaction was carefully quenched with cold 1N HCl (60 ml) and extracted with Et$_2$O (3 x 75 ml). The combined organic layers were successively washed with 1N HCl (3 x 50 ml), saturated NaHCO$_3$ solution and dried (Na$_2$SO$_4$). After concentration *in vacuo* the residue was used for the next step without further purification. To the solution of N,O-ditosyl compound in MeOH (50 ml) was added slowly at room temperature KOH solution (3.1 g, 55.5 mmol, 3 equiv) in MeOH (30 ml). After stirring 1 h, water (150 ml) and Et$_2$O (150 ml) were added. The aqueous phase was extracted three times by Et$_2$O (3 x 120 ml). The combined organic phases were washed with saturated NH$_4$Cl solution, then water and dried (Na$_2$SO$_4$). After concentration *in vacuo*, the residue was purified by flash chromatography (petroleum ether-AcOEt, 9:1) to give the aziridine **15** (2.32 g, 56%) as a white solid ; mp 34-35°C ; $[\alpha]^{20}_{D}$ -11 (c 1.4, CHCl$_3$) ; ^{1}H NMR : 0.83 (t, 3H, J=7.4Hz, CH$_3$), 1.20-1.48 (m, 1H, C$\underline{H_2}$CH$_3$), 1.50-1.72 (m, 1H, C$\underline{H_2}$CH$_3$), 2.07 (d, 1H, J=4.4Hz, C$\underline{H_2}$N) ; 2.43 (s, 3H, PhC$\underline{H_3}$) ; 2.62 (d, 1H, J=6.8Hz, C$\underline{H_2}$N) ; 2.70 (m, 1H, C$\underline{H}$N) ; 7.33 (d, 2H, J=8.6Hz, Ph) ; 7.85 (d, 2H, J=8.5Hz, Ph) ; ^{13}C NMR : 10.7, 21.5, 24.4, 33.5, 41.6, 127.6, 129.6, 135.1, 144.4 ; Anal. Calcd for $C_{11}H_{15}NO_2Si$: C, 58.64 ; H, 6.71 ; N, 6.22 ; O, 14.2. Found : C, 58.72 ; H, 7.03 ; N, 6.22, O, 14.59.

(S)-4-Paratoluenesulfonylamino-1-trimethylsilylpent-1-yne (16). To a cooled (0°C) solution of trimethylsilylacetylene (1.3 g, 13.3 mmol, 3 equiv) in a mixture THF-HMPA (5:1, 12 ml) was added *n*-BuLi (2.2 M in hexane, 6.05 ml, 13.3 mmol). The reaction mixture was stirred for 30 min at 0°C and was added dropwise to a solution of the aziridine **15** (1 g, 4.4 mmol) in a mixture of THF-HMPA (5:1, 12 ml). The mixture was allowed to warm up to room temperature and stirred for 7 h. The reaction was quenched with saturated NH_4Cl solution and the aqueous phase was extracted three times with Et_2O (3x50 ml). The combined ethereal extracts were washed with water dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel gave **16** (0.88 g, 62%) as a white solid : mp 100-101°C ; $[\alpha]^{20}_D$+ 128.5 (c 1.1, $CHCl_3$) ; IR (KBr) 3240, 2180, 1600, 1250, 840, 815, 760 ; ^1H NMR : 0.13 (s 9H, $Si(CH_3)_3$), 0.8 (t, 3H, J=7.4Hz, CH_3), 1.4-1.69 (m, 2H, $C\underline{H_2}$-CH_3) ; 2.22 (dd, 1H, J=6 and 16.5Hz, $C\underline{H}$-C≡C), 2.33 (dd, 1H, J=4.3 and 16.5Hz, $C\underline{H}$-C≡C), 2.42 (s, 3H, $PhCH_3$), 3.14-3.32 (m, 1H, $C\underline{H}N$), 4.86 (d, 1H, J=8.8Hz, NH), 7.29 (d, 2H, J=8.3Hz, Ph), 7.75 (d, 2H, J=8Hz, Ph) ; ^{13}C NMR : -0.05, 10.1, 21.5, 25.8, 27.0, 53.3, 88.2, 101.7, 127.0, 129.7, 138.1, 143.3 ; Anal. Calcd for $C_{16}H_{25}NO_2Si$: C, 59.40 ; H, 7.79 ; N, 4.33 ; S, 9.91. Found : C, 59.33 ; H, 7.86 ; N, 4.31, S, 9.96.

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