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SPIROAZIRIDINES FROM 4-SUBSTITUTED α-YLIDENE-γ-BUTYRO LACTONES

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Abstract – 4-Substituted α-ylidene-γ-butyrolactones produce *N*-ethoxycarbonyl-spiroaziridino γ-lactone diastereomers on treatment with $NsONHCO_2Et$ and CaO. A good stereofacial preference is observed when the ring substituent is a phenyl group. These products are precursors of α-aminolactone as pure diastereomers.

Five- and six-membered ring heterocyclic compounds have occupied a relevant place among various classes of organic compounds for their different biological activity.[1] Among them γ- and δ-lactones and their derivatives play a key role for the synthesis of natural products as steroids and pheromones.[2] Other derivatives as aziridinolactones are investigated as precursors of amino acids, particularly 4-substituted 2,3-aziridino-γ-lactones (prepared in 10 to 12 steps from carbohydrates), have been used for the enantiospecific synthesis of multisubstituted α- and β-amino acids.[3] Also spiroaziridinolactones, by aziridine ring opening, could be useful intermediates for the synthesis of α- and β-amino acids.

To the best of our knowledge there are few reports concerning synthesis of spiroaziridinolactone derivatives, even though they are an important class of synthetic targets[4] occurring in natural compounds.[5]

As a part of our research program in the area of aziridination of α,β-unsaturated esters,[6] we recently reported the synthesis of *N*-ethoxycarbonylspiroaziridino-γ-lactones from simple α-ylidene-γ-butyrolactones,[7] using $NsONHCO_2Et$ and CaO. Due to good reactivity of these substrates, we thought to extend the aziridination procedure to 4-substituted γ-butyrolactones. We supposed that the presence of a chiral carbon on the lactone ring would promote the stereoselective introduction of the aziridine ring, providing a new route to optically active spiroaziridines and α-aminolactone derivatives after ring opening and deprotection.

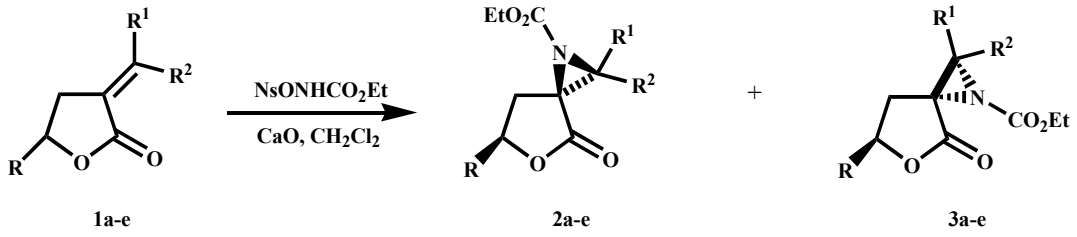
Optically active α-amino-γ-butyrolactones are useful building blocks of polypyrrolinones asymmetric synthesis.[8] The α-amino-γ-butyrolactone scaffold is present in certain biologically active molecules including immunosuppressant, antiallergic and antineoplastic agents.[9]

The aziridination reaction was performed on 4-substituted γ-butyrolactones **(1a-e)** (Scheme 1). Substrates were synthesized by different methods. Horner-Wadsworth-Emmons procedure[10] was used for **1a** starting from α-diethoxyphosphonyl-γ-valerolactone and benzaldehyde in the presence of aqueous K_2CO_3.[11]

Using the same conditions with cyclohexancarboxaldehyde, **1b** was obtained as a main product. Conversely, in the presence of NaH[12] as a base, the *Z* isomer **(1c)** was the principal product**.** Substrate **(1d)** was prepared performing Peterson's olefination[13] to the α-diphenylmethylsilyl-γ-phenyl-γ-butyrolactone using benzaldehyde as carbonyl compound. Substrate **(1e)** was synthesized in a three-step reaction sequence, consisting of Michael addition of primary nitroalkane to ethyl 2-bromoethyl acrylate, then Nef conversion of the nitro derivative and subsequent lactonization of the obtained keto ester.[14]

All compounds **(1a-e)** were purified by flash chromatography on silica gel. Their structure was confirmed by ^{1}H NMR and ^{13}C NMR analysis.

The amination reactions were carried out in CH_2Cl_2 by adding $NsONHCO_2Et$ and CaO portionwise reaching the molar ratio and the time reported in Table 1.



1a-e 2a-e 3a-e

Scheme 1. Aziridination of α-ylidene-γ-butyrolactones **(1)**

The reaction produced spiroaziridines **(2a-e)** and **(3a-e)** in the yields and diastereomeric ratios shown in Table 1. Traces of **2b** and **3b** were detected upon reaction of **1c**. All diastereomers were easily isolated by flash chromatography with more than 90% purity.

All products (**2a-e)** and **(3a-e)** have been characterized by GC-MS, IR, ^{1}H, ^{13}C NMR spectral analysis, and the spectral data are in agreement with the reported structure.

As far as the stereoselectivity of the reaction is concerned, we observed only a slight stereofacial preference when the methyl group was the ring substituent. With the phenyl group we had a good substrate-controlled diastereoselective aziridination.

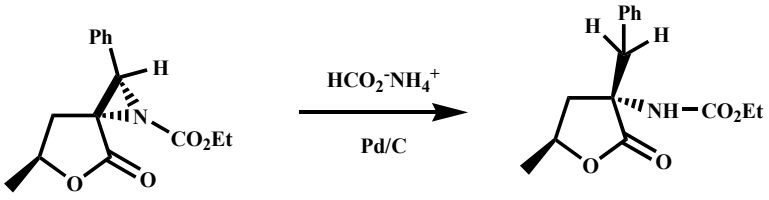
Table1. Aziridination of α-ylidene-γ-butyrolactones **(1)**. Conditions and yields.

Substrates	R^1	R^2	R	Molar ratio **1:**$NsONHCO_2Et$:CaO	Diastereomeric Ratio **3 : 2**	**3 + 2** Total Yields %
1a	Ph	H	Me	1:5:5	67:33	38
1b	C_6H_{11}	H	Me	1:7:7	58:42	52
1c	H	C_6H_{11}	Me	1:7:7	60:40	45
1d	Ph	H	Ph	1:7:7	85:15	37
1e	H	H	CH_2Ph	1:5:5	50:50	32

We think that the ratio of the diastereomeric spiroaziridines always favors the products **(3a-d)**, derived from the attack of the aminating reagent *anti* to the substituent. We suppose that the no-stereoselectivity for **1e** could depend on the absence of the substituent on the double bond.

In conclusion, we observed that starting from 4-substituted α-alkylidene-γ-butyrolactones it was possible to obtain, by a simple aziridination reaction, both diastereomers of *N*-ethoxycarbonylspiroaziridino-γ-lactones substituted with an alkyl or phenyl group on the five-membered ring. Furthermore we analyzed the effect of these substituents on the stereoselectivity of the aziridination reaction.

Moreover the treatment of **3a** with ammonium formate in the presence of palladium catalyst[15] allowed us to obtain **4a** in good yield.



3a **4a**

Scheme 2

This last reaction pathway confirms the possibility of obtaining stereoselectively 4-substituted α-amino-γ-butyrolactone derivatives which also are precursors of multisubstituted α-amino acids.[3]

EXPERIMENTAL

GC-MS spectra were done on a HP G1800A GCD System with a capillary column (phenylmethylsilicone, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Microanalyses were carried out on a CE Instruments EA1110. ^{1}H-NMR and ^{13}C-NMR spectra were obtained in $CDCl_3$ on a Gemini 200

spectrometer, with $CHCl_3$ as internal standard. IR spectra in CCl_4 were recorded on a Perkin-Elmer 1600 Series FTIR spectrophotometer.

Synthesis of α-ylidene-γ-valerolactones (1a-c). Method A.[11] To a stirred solution of the α-diethoxyphosphonyl-γ-valerolactone (1.40 g, 6.0 mmol) in THF (6 mL), a 7M potassium carbonate aqueous solution (1.30 g, 9.0 mmol) was added dropwise. After 1 h at rt, the aldehyde (12.0 mmol, benzaldehyde for **1a** and cyclohexancarboxaldehyde for **1b** and **1c**), was added and the resulting mixture was heated to 70 °C. The mixture was stirred for several hours (5 h for **1a** and 15 h for **1b-c**), then was extracted with ether and washed with brine. The organic layer was dried (Na_2SO_4). After evaporation of solvent the reaction mixture was purified by flash chromatography on silica gel (hexane:ether=9:1) to obtain 0.70 g (62%) of **1a** (*E*) [16] or 0.43 g (37%) of **1b** and 0.27 g (23%) of **1c**.

(*E*)-α-Cyclohexylmethylene-γ-valerolactone (1b) [17]: IR (CCl_4): 1682, 1756 cm^{-1}; ^{1}H-NMR: δ 0.80-1.30, 1.60-1.80 (2 m, 11H, c-(C*H*$_2$)$_5$, -CH$_2$C*H*CH$_2$-), 1.45 (d, 3H, CH_3, *J* = 6.2 Hz), 2.40 (ddd, 1H, CH(CH$_3$)CH*H*, *J* = 16.7, 5.9, 2.9 Hz), 3.05 (ddd, 1H, CH(CH$_3$)C*H*H, *J* = 16.7, 7.8, 2.7 Hz), 4.65 (m, 1H, OC*H*(CH$_3$)), 6.60 (dt, 1H, C*H*=C, *J* = 9.71, 2.8Hz); ^{13}C-NMR: δ 22.1, 25.3, 25.6, 31.3, 31.4, 32.6, 39.3, 73.8, 124.5, 145.3, 171.3; ms: *m/z*(%) 194 (16), 113 (100), 95 (80).

(*Z*)-α-Cyclohexylmethylene-γ-valerolactone (1c) [17]: IR (CCl_4): 1670, 1770 cm^{-1}; ^{1}H-NMR: δ 1.00-1.55; 1.60-1.80 (2 m, 11H, c-(C*H*$_2$)$_5$, -CH$_2$C*H*CH$_2$-); 1.40 (d, 3H, CH_3, *J* = 6.2 Hz); 2.50 (ddd, 1H, CH(CH$_3$)CH*H*, *J* = 15.8, 7.4, 2.1 Hz); 3.00 (ddd, 1H, CH(CH$_3$)C*H*H, *J* = 15.8, 6.6, 2.4 Hz); 4.60 (m, 1H, OC*H*(CH$_3$)), 6.00 (dt, 1H, C*H*=C, *J* = 9.9 2.2 Hz); ^{13}C-NMR: δ 21.7, 25.3, 25.8, 32.4, 32.5, 35.7, 36.8, 73.5, 122.9, 148.9, 168.9; ms: *m/z*(%) 194 (66), 81 (100), 67 (65).

Synthesis of α-ylidene-γ-valerolactones (1b-c). Method B.[12] To NaH (60%, 0.116 g, 2.8 mmol) in dry DME (1.4 mL), α-diethoxyphosphonyl-γ-valerolactone (0.524 g, 2.2 mmol) in dry DME (0.4 mL) was added dropwise with stirring, under argon at 0°C. After 1 h at rt, a solution of cyclohexancarboxaldehyde (0.36 g, 3.2 mmol) in DME (0.2 mL) was added at 0°C. After 3 h at rt, the mixture was poured into saturated aqueous ammonium chloride and the aqueous phase was extracted with ether. The combined organic phases were washed with brine and dried (Na_2SO_4). After evaporation of solvent the reaction mixture was purified by flash chromatography on silica gel (hexane:ether=9:1) to obtain 0.03 g (7%) of **1b** and 0.14 g (33%) of **1c**.

Synthesis of (*E*)-α-benzylidene-γ-phenyl-γ-butyrolactone (1d). To a stirred 2M solution of LDA in THF (2 mL, 8.0 mmol), α-diphenylmethylsilyl-γ-phenyl-γ-butyrolactone (2 g, 5.6 mmol) in THF (6 mL) was added dropwise, under argon at -78°C. After 1 h at -78°C, benzaldehyde (0.59 g, 5.6 mmol) was added and the mixture was stirred for an additional 1 h at rt. After this period the mixture was heated to 70°C for 1 h, then trimethylchlorosilane (0.91 g, 8.4 mmol) was added to silylate the lithium diphenylmethylsiloxide formed and thereby facilitate product purification. The reaction mixture was

diluted with hexane, washed with water and 10% aqueous ammonium chloride, and dried over Na_2SO_4. After solvent removal at reduced pressure, the product was purified by flash chromatography on silica gel (hexane:ethyl acetate=9:1) to obtain 0.87 g (62%) of **1d** (*E*).[18]

General procedure for the aziridination reaction of 1a-e. To a stirred solution of the substrate **(1a-e)** (3.0 mmol) in CH_2Cl_2 (0.6 mL), $NsONHCO_2Et$ (0.87 g, 3.0 mmol) and CaO (0.17 g, 3.0 mmol) were added, every 1 h, reaching the molar ratio substrate:reagent reported in Table 1. After 8 h under stirring, pentane was added and after filtration, the solid residue was washed with a pentane-CH_2Cl_2 mixture (8:2). The organic phases were combined, concentrated in vacuo and the residue was purified by flash chromatography on silica gel (hexane: ether= 8:2) to yield **2a-e** and **3a-e** in the ratio and in the yield reported in Table 1.

2-Phenyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (2a): Pale yellow oil; IR (CCl_4): 1745, 1786 cm^{-1}; ^{1}H-NMR: δ 1.30 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 1.50 (d, 3H, $OCH(CH_3)$, *J* = 6.3 Hz), 2.10 (m, 2H, $CH_2CH(CH_3)$), 4.05 (s, 1H, NCH), 4.25 (q, 2H, OCH_2CH_3, *J* = 7.2 Hz), 4.55 (m, 1H, $OCH(CH_3)$), 7.30-7.50 (m, 5H, arom.); ^{13}C-NMR: δ 14.2, 21.8, 31.5, 48.4, 49.6, 63.1, 73.9, 126.9, 128.5, 128.7, 128.8, 128.9, 133.1, 159.7, 171.9; ms: *m/z*(%) 275 (<1), 143 (81), 117 (100), 103 (72), 90 (61), 89 (67); Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.51; H, 6.30; N, 5.12.

2-Phenyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (3a). Pale yellow oil; IR (CCl_4): 1744, 1786 cm^{-1}; ^{1}H-NMR: δ 1.30 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 1.50 (d, 3H, $OCH(CH_3)$, *J* = 6.3 Hz), 1.60 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 14.2, 5.8 Hz), 2.50 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 7.2, 14.2 Hz), 4.10 (s, 1H, NCH), 4.25 (q, 2H, OCH_2CH_3, *J* = 7.2 Hz), 4.92 (m, 1H, $OCH(CH_3)$), 7.30-7.50 (m, 5H, arom.); ^{13}C-NMR: δ 14.2, 21.9, 31.6, 48.5, 49.6, 63.2, 74.9, 127.1, 128.6, 128.7, 128.9, 129.9, 133.1, 159.7, 171.9; ms: *m/z*(%) 275 (<1), 143 (83), 117(100), 103 (74), 90 (61); Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.53; H, 6.28; N, 5.16.

2-Cyclohexyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (**2b**): Pale yellow oil; IR (CCl_4): 1740, 1786 cm^{-1}; ^{1}H-NMR: δ 1.00-1.80 (m, 11H, c-$(CH_2)_5$, $-CH_2CHCH_2-$), 1.23 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 1.60 (d, 3H, $OCH(CH_3)$, *J* = 6.3 Hz), 2.09 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 13.9, 6.5 Hz), 2.46 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 13.9, 7.5 Hz); 2.66 (d, 1H, -NC*H*, *J* = 9.0 Hz) 4.09-4.46 (m, 2H, OCH_2CH_3), 4.57 (m, 1H, $OCH(CH_3)$); ^{13}C-NMR: δ 14.3, 21.8, 25.4, 26.1, 29.5, 29.7, 30.7, 32.2, 38.3, 46.9, 51.1, 62.8, 74.9, 160.2, 172.9; ms: *m/z*(%) 281 (2), 95 (100), 67 (63); Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.08; H, 8.29; N, 4.93.

2-Cyclohexyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (**3b**): Pale yellow oil; IR (CCl_4): 1740, 1786 cm^{-1}; ^{1}H-NMR: δ 1.00-1.80 (m, 11H, c-$(CH_2)_5$, $-CH_2CHCH_2-$), 1.27 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 1.50 (d, 3H, $OCH(CH_3)$, *J* = 6.3 Hz), 2.00 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 13.9, 6.8 Hz), 2.50 (dd, 1H, $CH(CH_3)CH$*H*, *J* = 13.9, 7.4 Hz); 2.75 (d, 1H, NC*H*, *J* = 8.8 Hz) 4.20 (m, 2H,

OC*H*$_2$CH$_3$), 4.95 (m, 1H, OC*H*(CH$_3$); ^{13}C-NMR: δ 14.2, 22.0, 25.4, 26.1, 29.5, 30.6, 30.7, 32.9, 38.3, 47.3, 50.8, 62.9, 75.1, 160.2, 172.9; ms: *m/z*(%) 281 (2), 95 (100), 67 (63); Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.06; H, 8.30; N, 4.93.

2-Cyclohexyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (2c): Pale yellow oil; IR (CCl_4): ν C=O 1734, 1790 cm^{-1}; ^{1}H-NMR: δ 1.00-1.84 (m, 10H, c-(C*H*$_2$)$_5$), 1.30 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.1 Hz), 1.57 (d, 3H, OCH(C*H*$_3$), *J* = 6.2 Hz), 2.00-2.16 (m, 2H, CH(CH$_3$)C*H*H, -CH$_2$C*H*CH$_2$-), 2.48 (d, 1H, -NC*H*, *J* = 9.4 Hz), 2.56 (m, 1H, CH(CH$_3$)CH*H*), 4.20 (m, 2H, OC*H*$_2$CH$_3$), 4.72 (m, 1H, OC*H*CH$_3$); ^{13}C-NMR: δ 14.4, 21.2, 25.2, 25.3, 26.1, 30.0, 30.8, 34.2, 35.3, 46.8, 55.3, 62.9, 74.1, 159.8, 171.4; ms: *m/z*(%) 281 (2), 95 (100), 55(62), 41 (69); Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.08; H, 8.27; N, 4.94.

2-Cyclohexyl-6-methyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (3c): Pale yellow oil; IR (CCl_4): 1743, 1782 cm^{-1}; ^{1}H-NMR: δ 1.00-1.86 (m, 11H, c-(C*H*$_2$)$_5$, CH(CH$_3$)C*H*H), 1.30 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.1 Hz), 1.48 (d, 3H, OCH(C*H*$_3$), *J* = 6.4 Hz), 2.04-2.18 (m, 1H, -CH$_2$C*H*CH$_2$-), 2.48 (d, 1H, NCH, *J* = 9.4 Hz), 3.00(dd, 1H, CH(CH$_3$)C*H*H, *J* = 13.3, 8.3 Hz), 4.20 (m, 2H, OC*H*$_2$CH$_3$), 4.88 (m, 1H, OCH(CH$_3$)); ^{13}C-NMR: δ 14.4, 22.0, 25.2, 25.3, 26.2, 29.9, 30.9, 32.6, 35.3, 45.1, 55.2, 62.9, 73.8, 159.7, 171.6; ms: *m/z*(%) 281 (2), 95 (100), 67 (64), 41 (68); Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.05; H, 8.28; N, 4.92.

2-Phenyl-6-phenyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (2d): Pale yellow oil; IR (CCl_4): 1744, 1786 cm^{-1}; ^{1}H-NMR: δ 1.40 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.2 Hz), 2.43 (m, 2H, CH(Ph)C*H*$_2$), 4.17 (s, 1H, NC*H*), 4.32 (q, 2H, OC*H*$_2$CH$_3$, *J* = 7.2 Hz), 5.47 (t, 1H, OC*H*Ph, *J* = 7.8 Hz), 7.17-7.47 (m, 10H, arom.); ^{13}C-NMR: δ 14.2, 32.3, 49.3, 49.5, 63.3, 78.7 124.5, 125.9, 127.3, 128.6, 128.7, 128.8, 128.9, 133.0, 139.1, 159.7, 172.0; ms: *m/z*(%) 337 (1), 130 (70), 117 (100), 115 (82), 103 (75), 91 (68); Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.25; H, 5.72; N, 4.18.

2-Phenyl-6-phenyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (3d): Pale yellow oil; IR (CCl_4): 1744, 1790 cm^{-1}; ^{1}H-NMR: δ 1.40 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.1 Hz), 2.00 (dd, 1H, CH(Ph)C*H*H, *J* = 14.3, 6.4 Hz), 2.80 (dd, 1H, CHPhCH*H*, *J* = 14.3, 7.9 Hz), 4.17 (s, 1H, NC*H*), 4.32 (q, 2H, OC*H*$_2$CH$_3$, *J* = 7.1 Hz), 5.80 (t, 1H, OC*H*Ph, *J* = 7.7 Hz), 7.17-7.40 (m, 10H, arom.); ^{13}C-NMR: δ 14.3, 32.8, 48.6, 49.5, 63.4, 79.1, 124.5, 125.5, 127.1, 128.6, 128.7, 128.8, 128.9, 132.9, 138.9, 159.7, 172.0; ms: *m/z*(%) 337 (1), 130 (70), 117 (100), 115 (82), 103 (75), 91 (68); Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.23; H, 5.65; N, 4.12.

6-Benzyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (2e): Pale yellow oil; IR (CCl_4): 1744, 1786 cm^{-1}; ^{1}H-NMR: δ 1.30 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.2 Hz), 2.15 (s, 1H, NHC*H*H), 2.20 (dd, 1H, CH(CH$_2$Ph)C*H*H, *J* = 13.9, 5.7 Hz), 2.52 (s, 1H, NC*H*H), 2.60 (dd, 1H CH(CH$_2$Ph)C*H*H, *J* = 13.9, 7.8 Hz), 3.10 (m, 2H, CH$_2$Ph), 4.20 (q, 2H, OC*H*$_2$CH$_3$, *J* = 7.2 Hz), 5.10 (m, 1H, OC*H*(CH$_2$Ph), *J* = 7.8

Hz), 7.20-7.40 (m, 5H, arom.); ^{13}C-NMR: δ 14.2, 31.7, 36.1, 41.4, 42.7, 63.1, 78.0 127.4, 128.9, 129.9, 134.9, 160.0, 172.5; ms: *m/z*(%) 275 (1), 104 (98), 91 (100); Anal. Calcd for $C_{15}H_{17}NO_4$: C, 64.44; H, 6.22; N, 5.09. Found: C, 64.47; H, 6.28; N, 5.11.

6-Benzyl-4-oxo-5-oxa-1-ethoxycarbonyl-1-azaspiro[2,4]bicycloheptane (3e): Pale yellow oil; IR (CCl_4): 1744, 1790 cm^{-1}; ^{1}H-NMR: δ 1.30 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 2.40 (m, 1H, $CH(CH_2Ph)CHH$), 2.82 (s, 1H, $NCHH$), 3.07 (m, 2H, CH_2Ph), 3.30 (dd, 1H $CH(CH_2Ph)CHH$, *J* = 13.8, 6.9 Hz) 4.20 (q, 2H, OCH_2CH_3, *J* = 7.2 Hz), 4.90 (m, 1H, $OCHCH_2Ph$), 7.20-7.40 (m, 5H, arom.); ^{13}C-NMR: δ 14.3, 32.1, 36.3, 41.7, 42.6, 63.2, 78.4 127.2, 128.8, 129.5, 135.6, 160.0, 172.4; ms: *m/z*(%) 275 (1), 91 (100); Anal. Calcd for $C_{15}H_{17}NO_4$: C, 64.44; H, 6.22; N, 5.09. Found: C, 64.46; H, 6.25; N, 5.11.

Aziridine ring opening reaction of 3a. The reaction was performed according to the reported procedure,[15] obtaining a total conversion of **3a** to **4a**.

(3-Benzyl-5-methyl-2-oxotetrahydrofuran-3-yl)carbamic acid ethyl ester (4a): Pale yellow oil; ^{1}H-NMR : δ 0.82 (d , 3H, $OCH(CH_3)$, *J* = 5.9 Hz), 1.19 (t, 3H, OCH_2CH_3, *J* = 7.2 Hz), 2.04 (dd, 1H, $CH(CH_3)CHH$, *J* = 6.4, 13.9 Hz), 2.59 (dd, 1H, $CH(CH_3)CHH$, *J* = 8.5, 13.9 Hz), 2.91 (d, 1H, $CHHPh$, *J* = 13.2), 3.16 (d, 1H, $CHHPh$, *J* = 13.2), 4.06 (q, 2H, OCH_2CH_3, *J* = 7.2 Hz), 4.70 (m, 1H, $OCHCH_3$), 5.17 (br s, 1H, NH), 7.10-7.34 (m, 5H, arom.); ^{13}C-NMR: δ 14.4, 20.9, 38.5, 43.5, 61.5, 61.9, 74.4, 127.7, 128.8, 129.9, 130.5, 134.0, 155.3, 176.9; ms: *m/z*(%) 277 (1), 186 (100), 114 (67), 91 (80); Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.95; H, 6.94; N, 5.01.

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