

Synthesis of a Novel Class of Phosphonoaziridines as Interesting Antibacterial Agents

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Abstract: Aziridines constitute an interesting class of organic compounds because of their reactivity and the facility they can be converted into various derivatives. Our group has developed a new class of aziridines that show interesting biological activities such as antitumor and anti bacterial. This work describes new results of our ongoing research targeting new derivatives of biological interest.

Keywords: Aziridines, aza-Wittig, cancer, phosphonates, protease inhibitors, strained heterocycles.

INTRODUCTION

Heterocycles structures are found in so many fields of scientific investigation - including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well as material science- that their importance can hardly be overemphasized [1]. Therefore a long lasting effort is maintained towards the development of new synthetic protocols for the preparation of those compounds and their numerous derivatives.

Of particular importance are aziridines because of their reactivity. They are valuable synthetic intermediates that are widely used to access numerous drugs and biologically active products [2-4]. Many aziridine alkaloids show anticancer, antibacterial, and/or antimicrobial and antileishmanial activities [5-8]. Some among them behave as potential protease inhibitors [9-10]. Therefore, an assumption might be made that the presence of an aziridine moiety in natural as well as synthetic compounds structures is essential to the observed activities [11]. As a result, several syntheses are found in the literature and it is beyond the scope of this work to mention all of them [12-25].

The biological activity of aziridines is highly related to the establishment of covalent bond with DNA [26]. In a previous work we reported the synthesis of aziridinyl derivatives [27] that had antitumor activities against breast cancer cells [28]. Such a behaviour was likely due to their capacity to strengthen and modulate the immune system [29]. Thus, going on with our efforts to develop new biologically active derivatives we replaced the phtaloyl group with a phosphonate moiety, with an aim to enlarging the scope of the already observed activities [30-32]. For all these reasons, the development of processes for the synthesis of functionalized aziridines containing a phosphorus substituent may represent a useful way to access interesting compounds that might play important therapeutic roles as already being observed in literature [33-38].

We report here the synthesis of new class of aziridines through two easily accessible procedures, the first using the reaction of diethylphosphonopropionic acid **1** with glycidol and the second referring to the coupling between an aziridinetosylate with an amino acid. This would provide us with an interesting starting material for further work.

RESULT AND DISCUSSION

Syntheses

During our investigation, the target compound was **7**, "N-(diethylphosphonopropionyl) -2-hydroxymethylaziridine (Fig. 1). Preliminary antibacterial assays revealed it to be endowed with interesting antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Needless to say that those strains are globally known to withstand treatment with common antibiotics and are the source of many nosocomial diseases.

It is worth mentioning that a simple replacement of a phtaloyl moiety with phosphonyl one entails a shift of activities from antiviral to antibacterial ones. Unfortunately, the assays could not be extended to other available compounds of the same family, since the investigator in charge of biological tests left the laboratory. Therefore, the work presented here represents the synthesis of some aziridines that will serve as starting materials for the preparation of hybrids, of which work is on course, along with partial results about biological assays.

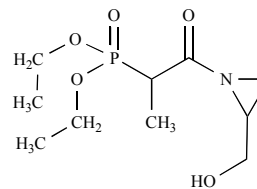
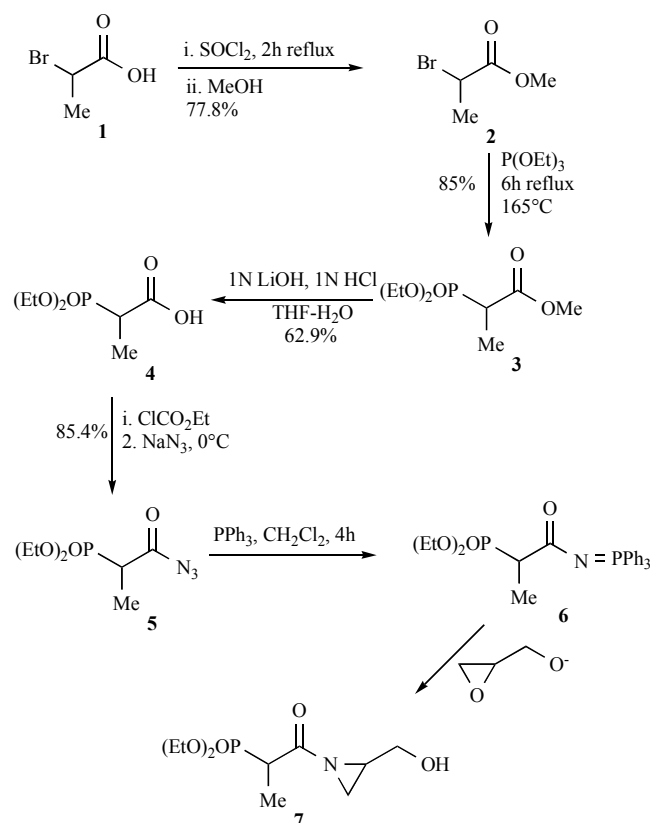


Fig. (1). Structures of Diethyl 1-(2-(hydroxymethyl)aziridin-1-yl)-1-oxopropan-2-ylphosphonate.

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Scheme 1. Synthesis of *N*-(diethylphosphonopropionyl)-2-hydroxymethylaziridine.

to afford a colorless oil, before reacting with triethyl phosphite according to Arbuzov reaction, to afford the phosphonate **3** in good yield. **3** was hydrolyzed with a 1N LiOH in tetrahydrofuran (THF)-water solution to yield 2-(diethoxy phosphoryl)propionic acid **4**.

The latter was converted into an acylazide **5**, after reaction with ethyl chloroformate and sodium azide. The azide was used without further purification in the next step to yield the iminophosphorane. The generation of the non-isolated iminophosphorane was monitored by the evolution of nitrogen from the reaction solution.

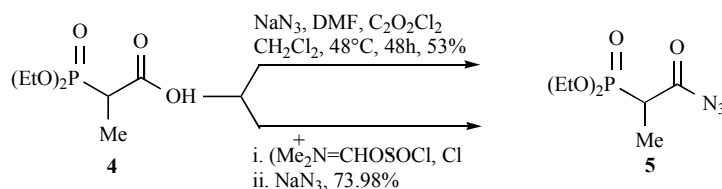
Afterwards, glycidol alcoholate, *in situ* generated by treatment of glycidol with sodium hydride in dry ether, was dropwise added to the iminophosphorane solution. The reaction was left to proceed under nitrogen to yield the target compound. The reaction could be monitored by the progressive formation of a white solid corresponding to triphenylphosphine oxide, as could be checked later with an authentic commercial sample (Aldrich).

The conversion of an acyl azide into an aziridine is believed to occur according to mechanism we already

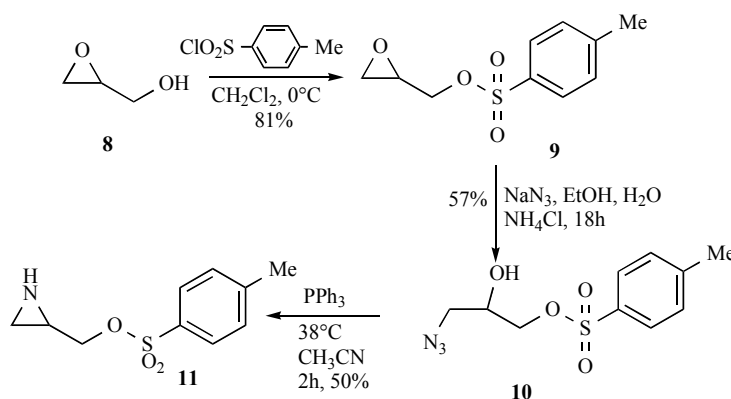
suggested in our previous work [27]. After quenching the reaction mixture with an aqueous solution of ammonium chloride and removal of triphenylphosphine oxide, the compound was purified on a silica gel column using petroleum ether (b.p. 40-60°C)-dichloromethane. Satisfactory IR, ¹H-NMR, and ¹³C-NMR characteristics were obtained.

N-acylazide could also be prepared through a direct reaction of sodium azide in dimethylformamide (DMF) and with an acylchloride in dry dichloromethane, or according to a literature protocol [39].

As related to the synthesis of aziridines, we also prepared *N*-acyl-2-tosylmethylaziridine from *O*-tosylglycidol. The latter was first converted into an azido alcohol and further transformed into an aziridine by means of triphenylphosphine according to literature [40]. This compound showed more potent antibacterial activity as compared to compound **7**. Probably the tosylate moiety could contribute to this enhanced activity, and this needs to be verified during further studies.



Scheme 2. Synthesis of Diethyl 1-azido-1-oxopropan-2-ylphosphonate.



Scheme 3. Synthesis of aziridin-2-ylmethylbenzenesulfonate.

1. Synthesis of aziridin-2-ylmethylbenzenesulfonate 11

The *O*-protection of glycidol **8** with *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine (TEA), led to **9** in good yield (Scheme 3). The solution of **9** in ethanol and water was treated with ammonium chloride and sodium azide to give the azido alcohol **10** that was reacted in the next step with a solution of triphenylphosphine in anhydrous tetrahydrofuran (THF) to provide **11** in high yield. Compound **11** was purified on a silica gel column eluted with dichloromethane (CH₂Cl₂)-methanol (MeOH) (v/v: 1:1).

2. Diethylphosphonopropionyl-2-tosylmethylaziridine 12

Diethylphosphonopropionic acid was reacted either with thionyl chloride in the presence of TEA to yield an acyl chloride that was reacted with **11** to give **12** (50%), or coupled in the presence of dicyclohexylcarbodiimide (DCC) with unprotected aziridine **11** to give the same compound in high yield (90%).

This strategy enabled us use 2-methyltosylate aziridine **11** as building block to obtain different functionalized aziridines. The same approach was successfully applied to generate aziridines from *N*-phtaloylamino acids **13**. Phenylalanine and tyrosine were chosen as a models, since in our initial work in this field [27], aziridine from the former amino acid showed the best biological profile [28], whereas tyrosine is claimed to behave as a residue of utmost importance in many receptors [41]. Derivatives **13** were prepared according to a modified literature procedure [42] and were recrystallized. They were further converted into aziridines **14** according to both methods previously described in the last section. After work-up, the phtaloyl

group (Ft) could be removed from the protected amino acid moiety of **14a** by treatment with hydrazine hydrate according to literature [43], affording **15a** with a free amino group for a potential peptide growth.

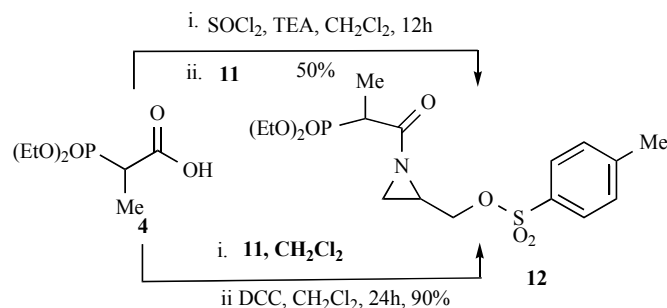
Preliminary Biological Tests

Compound **7** was submitted to biological assays on *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922 (gram negative bacteria), *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212 (gram positive bacteria). The assays were carried out by disc diffusion on agar medium, where compound **7** showed medium to medium activity on *Pseudomonas aeruginosa*, and a weak one on *Staphylococcus aureus*. Gentamycin and Ciprofloxacin were used as references (Rahmoun, N. *Unpublished results 2011*. Détermination du pouvoir antibactérien d'une aziridine nouvellement synthétisée au Laboratoire COSNA).

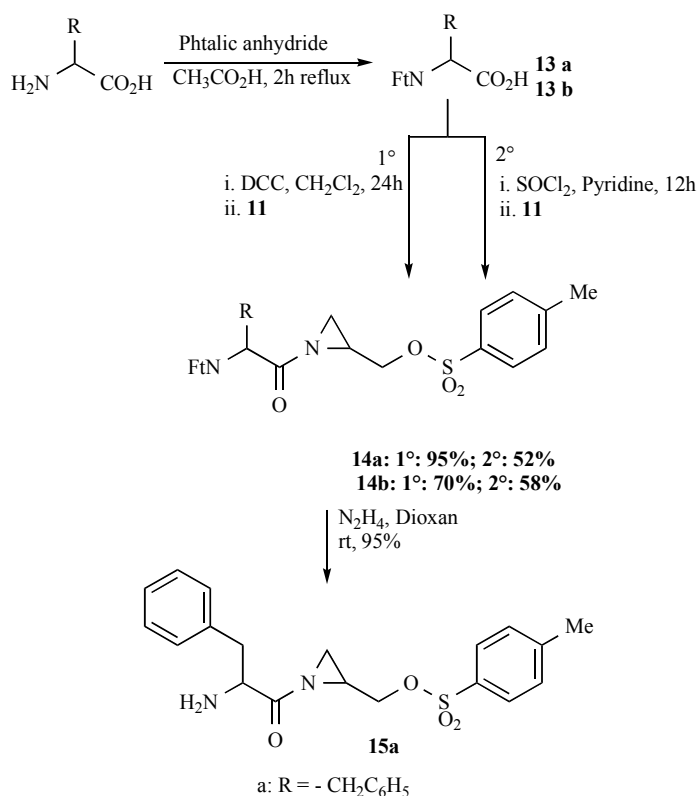
As compared to the previous activity of phtaloyl aziridines, the results is interesting in such a way that it enables us modify or fix various groups on our aziridines to extend the scope of their biological activity. That is why compound **7** is already engaged in such a work. However, much work is still to be carried out on compound **7** and derivatives as related to assess as accurately as possible the Minimal Inhibitory Concentrations (MIC), the antibacterial effect versus concentration, as well as the biological pathway targeted by this aziridine and derivatives.

CONCLUSION

Numerous synthetic methods are found in the literature and allow easy accesses to various aziridines. It is worth



Scheme 4. Synthesis diethylphosphonopropionyl-2-tosylmethylaziridine.



Scheme 5. Coupling of aziridines with Phenylalanine and Tyrosine.

mention that most of those methods are based on the conversion of an amino group into the corresponding aziridine. By contrast, our synthetic procedure targets the carboxylic group and its transformation into acyl aziridines, while the amino group is either protected or replaced by a phosphonate. As compared to our initial work [27], the present study has allowed us develop a second class of aziridines of interesting biological activities, represented by compound 7. The phthaloyl derivatives were active against breast cancer cells [28] whereas phosphonate showed antibacterial activity. Work is going on for the diversification of the initial work, especially for the search of targeted cancer chemotherapy, through the synthesis of hybrids.

EXPERIMENTAL SECTION

All the reactions with dry solvents were carried out under dry nitrogen. THF was dried over sodium/benzophenone and freshly distilled before use; CH₂Cl₂ was distilled and dried over phosphorus pentoxide (P₂O₅). Triethylphosphite P(OEt)₃ was distilled before use under reduced pressure. IR spectra were collected from a Mattson Genesis II FTIR. NMR spectra were recorded in CDCl₃ on a Bruker 300MHz instrument, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constant (J) values in Hertz (Hz). GC analysis was performed on a Shimadzu 17A CPG chromatograph using a 30m DB-35 column. Melting points were determined on an Electrothermal T1A F3.15A instrument. Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH₂Cl₂, MeOH and ether. Elemental analysis was performed only for solids on a LECO CHN 900 instrument.

Methyl-2-bromopropionate 2

To 2-bromopropionic acid (20 g, 0.13 mol), thionyl chloride (23.32g, 0.196mol) was added at room temperature. The reaction mixture was heated under reflux for 2 h. The mixture was cooled and methanol (0.261mol) was very slowly added with stirring and cooling, and the reaction was left for 30min. Excess methanol and thionyl chloride were removed in vacuo, and dichloromethane (50 ml) was added. The organic layer was washed respectively with a 5% solution of sodium bicarbonate (20ml), a saturated solution of sodium chloride (20 ml) and then dried over calcium sulfate. The dry solution was filtered and evaporated under vacuum to afford a residue that was purified by distillation under reduced pressure to afford a colorless oil (77.77%). bp = 50°C, 12mm Hg.; IR cm⁻¹ neat: 1743.95 (C=O), 1160.03 (C-O), 673.81(C-Br). GC analysis, retention time (Rt) = 7.22 mn. ¹H RMN, δ CDCl₃: 300MHz: 1.95(d, J= 6.5Hz, 3H, CH₃CH), 3.69 (s, 3H, OCH₃), 4.49 (s, 2H, BrCH₂CO). ¹³C RMN, δ CDCl₃: 23.90, 50.87, 160.02, 190.90

Methyl 2-(diethoxy phosphoryl)propanoate 3

Methyl 2-bromopropionate (35mmol) was introduced under nitrogen into a dry flask and then heated on reflux at 120 °C in a fume cupboard. Triethylphosphite (35mmol) was slowly added over a period of 35 mn. When the addition was completed the reaction mixture was refluxed for 6h and checked for completion by gas chromatography. At the end, the mixture was distilled under vacuo to afford a colorless oil. Yield 85%; bp = 140°C, 12mmHg; GC: retention time 24.25mn; Rf=0.32 on silica gel plate F₂₅₄ (Merck) AcOEt/CH₂Cl₂ (5:1). IR cm⁻¹ neat 1740.16 (C=O), 1165.95 (C-O), 1024.98 (P=O), 965.51 (P-O).

^1H RMN δ CDCl_3 300MHz: 1.29 (t, $\text{CH}_3\text{CH}_2\text{OP}$, $J=1.5\text{Hz}$), 1.39 (d, CH_3CH , $J=7.5\text{Hz}$), 3.68(s, OCH_3), 4.06(q, CH_3CH , $J=1.5\text{Hz}$), 4.11(q, POCH_2CH_3 , $J=6.9\text{Hz}$).

^{13}C RMN, δ CDCl_3 : 3.45, 16.29, 43.98, 50.99, 62.19, 169.97. ^{31}P RMN δ CDCl_3 200MHz: -1 (^{31}P)

2-(diethoxy phosphoryl)propionic acid 4

To a mixture of tetrahydrofuran and water (v/v: 81ml/40ml), ester (23mmol) was introduced under magnetic stirring and an aqueous solution of 1N LiOH (24mmol) was added. The mixture was stirred for 1h at 0°C and left to stand overnight at room temperature. It was extracted with ethyl acetate; the aqueous layer was collected, and acidified with a 1N HCl aqueous solution to pH 2. Extraction was then carried out with ethyl acetate; the aqueous solution was saturated with salt, and extracted for a last time. The organic extracts were combined, dried over CaSO_4 , filtered and concentrated in vacuo. Yield 62.96%. IR cm^{-1} neat 3405.66 (O-H), 1735.64 (C=O), 1456.64 (C-O), 1024.33 (P=O), 973.51 (P-O).

^1H RMN δ CDCl_3 300MHz: 1.28 (t, $\text{CH}_3\text{CH}_2\text{OP}$, $J=1.5\text{Hz}$), 1.33(d, CH_3CH , $J=7.2\text{Hz}$), 3.68(q, CH_3CH , $J=1.5\text{Hz}$), 4.06(q, POCH_2CH_3 , $J=6.9\text{Hz}$), 9.95(s, OH). ^{13}C RMN, δ CDCl_3 : 3.19, 16.29, 46.48, 176.99.

Diethyl 1-azido-1-oxopropan-2-ylphosphonate 5

To a well stirred and cooled solution of carboxylic acid (13,5mmol), dry CH_2Cl_2 , and dry TEA (1.47g, 14,6mmol) were added under nitrogen. A solution of ethyl chloroformate (2.058 g, 18,9mmol) in dry CH_2Cl_2 was added over 15 min. The reaction was allowed to react at $0-5^\circ\text{C}$ for 20 min and a solution of sodium azide (1.58g, 24mmol) in 10ml of cold water was added dropwise. After standing at 0°C for 1h, the mixture was poured onto crushed ice and extracted with CH_2Cl_2 (3 x 50ml). The combined organic layers were washed with water and dried over calcium sulfate. The solvent was removed under reduced pressure maintained at 40°C and the oily yellow residue was used in the next reaction without further purification. Yield: 85.41%; IR cm^{-1} neat: 2138.10 (N_3), 1735.59(C=O), 1024.75(P=O). ^1H RMN δ CDCl_3 300MHz: 1.30(d, $J=7.2\text{Hz}$, 3H, CH_3), 1.39(t, $J=6.9\text{Hz}$, 6H, OCH_2CH_3), 3.95 (q, $J=7.2\text{Hz}$, 1H, O=P-CH(CH_3)-CON $_3$), 4.10(q, $J=6.9\text{Hz}$, 4H, OCH_2CH_3). ^{13}C RMN, δ CDCl_3 : 3.79, 16.29, 42.98, 61.77, 179.78.

Diethyl 1-(2-hydroxymethyl)aziridin-1-yl)-1-oxopropan-2-ylphosphonate 7

General Procedure

Solution A

N-acylazide (4.04g, 22,9mmol) was introduced under nitrogen in a dry flask containing dry dichloromethane (100mL). The solution was cooled (0°C) and triphenylphosphine (6.03g, 22,9mmol) was fractionally added and the solution was stirred for 2h.

Solution B

In a separate flask, sodium hydride (0.6g, 24,7mmol) previously washed with ether was introduced in ether (50 mL) and the suspension was stirred under nitrogen. A solution of glycidol (1.7g, 22,9mmol) in dry ether (50mL)

was added dropwise over 20 min to the cooled suspension. After the addition was complete, the mixture was stirred for an additional 30 min. Solution B was then siphoned off under nitrogen into a constant pressure dropping funnel mounted on the reaction flask containing solution A. B solution was then added dropwise to solution A, of which flask was cooled in an ice bath. The mixture was warmed up to 50°C for 1.5 h and cooled to room temperature. A 10% aqueous solution of ammonium chloride was added and the mixture was extracted with dichloromethane (3x25 mL). The organic extracts were combined and dried over anhydrous CaSO_4 . After removal of the solvent, the residue was dissolved in icy anhydrous ether (100 mL) and triphenylphosphine oxide was filtered off under suction.

This operation was repeated until no solid separated from the ethereal solution. After removal of the solvent, the residue was purified on a silica gel column using petroleum ether (bp $40-60^\circ\text{C}$) and dichloromethane (4:1). The resulting compound was stored in the cold under dry nitrogen. Crystallization occurred after standing at room temperature for 6 months (m.p. 83°C). Yield: 62.38%; IR cm^{-1} (KBr pellet): 3473.52(O-H), 1669.65(C=O), 1022.52(P=O).

^1H RMN δ CDCl_3 300MHz: 1.22 (d, CH_3 , $J=3.3\text{Hz}$), 1.27 (t, $\text{CH}_3\text{CH}_2\text{OP}$, $J=4.2\text{Hz}$), 1.34(d, CHCH_2N , $J=9\text{Hz}$); 2.99(m, CH), 3.29(dd, CH_2OH , $J=1.2\text{Hz}$, $J=0.6\text{Hz}$), 3.31(dd, CH_2OH , $J=1.8\text{Hz}$, $J=3.6\text{Hz}$), 3.64(s, OH), 4.11(q, CH_3CH , $J=3.9\text{Hz}$), 4.18(q, POCH_2CH_3 , $J=2.1\text{Hz}$). ^{13}C RMN δ CDCl_3 : 13.89(CH_3), 14.47(CH_3CH_2), 29.06(CH_2), 34.87(CH), 53.9(CH), 62.38 (CH_2O), 77.09(COH), 170.63(C=O).

Microanalysis: calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_5\text{P}$: C 45.28%, H 7.60% N 5.28%. Found: C 45.24%, H 7.59, N 5.25%

Oxiran-2-ylmethyl 4-methylbenzenesulfonate 9

Dry triethylamine (10.9g, 0.1081mol) and p-toluenesulfonyl chloride (20.61g, 0.11mol) were added to a stirred solution of glycidol (2g, 27,02mmol) in dry CH_2Cl_2 , under nitrogen at 0°C . The reaction mixture was stirred at room temperature overnight. After the reaction completion, the resulting mixture was diluted with CH_2Cl_2 and washed once with an aqueous solution of NH_4Cl . The organic layer was dried over Na_2SO_4 , and the solvent removed under reduced pressure. The glycidol tosylate was obtained as a pasty mass in a good yield (81.16%) IR cm^{-1} 1366.22(S=O), 1176.69 (C-O), 915.22 (S-O), 687.75-665.05 (OTs).

^1H RMN δ CDCl_3 300MHz: 2.41(s, CH_3), 2.55(d, $J=13.8\text{Hz}$, 2H, CH_2), 2.75 (m, 1H, CH), 3.89(dd, $J=6.3\text{Hz}$, $J=5.1\text{Hz}$, CH_2OTs), 4.2(dd, $J=6.3\text{Hz}$, $J=5.1\text{Hz}$, CH_2OTs), 7.3(d, $J=8\text{Hz}$, 2H, Ar), 7.70(d, $J=8\text{Hz}$, 2H, Ar). ^{13}C RMN δ CDCl_3 : 21.29 (CH_3), 43.89, 50.66, 128.20, 130.49, 139.98, 144.39.

3-azido-2-hydroxypropyl 4-methylbenzenesulfonate 10

A solution of glycidol (2g, 8,8mmol) in ethanol (20ml) and water (18ml) was treated with ammonium chloride (0.5g, 9,61mmol) and sodium azide (0.62g, 9,62mmol). The resulting mixture was heated at $70-75^\circ\text{C}$ during 18h. The mixture was cooled to room temperature and treated with a 5% aqueous sodium bicarbonate solution. Ethanol was removed in vacuo. The aqueous residue was extracted with ethyl acetate and the combined extracts were washed with

brine and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded the azido alcohol (57%). IR cm^{-1} : 3387.31 (O–H), 1356.78(S=O), 1177.09 (C–O), 932.53 (S–O), 714.5–667.07 (OTs).

^1H RMN δ CDCl_3 : 300MHz: 1.25(dd CH_2N_3 , J= 26.7Hz, 1H, J= 7.2Hz), 1.37(dd, J= 26.7Hz, J= 7.2Hz, 1H, CH_2N_3), 2.48(s, CH_3), 3.41(m, 1H), 3.54(s broad, OH), 4.10(dd, J=16Hz, 7.2Hz, 1H, $\text{CH}_2\text{CHOTsOH}$), 4.26 (dd, J= 16Hz, 7.2Hz, 1H, $\text{CH}_2\text{CHOTsOH}$), 7.69(d, J= 8.1Hz, 2H, Ar), 7.37(d, J= 8.1Hz, 2H, Ar).

^{13}C RMN δ CDCl_3 : 21.29, 52.89, 70.69, 71.00, 128.29, 130.49, 140.29, 144.38.

Aziridin-2-ylmethylbenzenesulfonate 11

To a solution (1.25g, 4.99mmol) of azido alcohol in anhydrous THF, a solution of triphenylphosphine (1.33g, 5.06mmol) in anhydrous THF was added dropwise. The addition was accompanied by a vigorous evolution of nitrogen. After nitrogen evolution has ceased. The solution was heated for 16h under reflux at 70°C under nitrogen. The mixture was concentrated in vacuo to afford aziridine tosylate as a yellow oil (90%). The oil was purified on a silica gel column using CH_2Cl_2 -MeOH (1:1). IR cm^{-1} neat: 3362.53 (N–H), 1363.15 (S=O), 1119.20 (C–O), 931.10 (S–O), 722.28–696.32 (OTs).

^1H RMN δ CDCl_3 : 300MHz: 1.27(s, NH), 1.99(d, J=13.8Hz, CH_2), 2.26–2.34 (m, CH), 2.48(s, CH_3), 3.66(dd, J= 13.2Hz, J=4.5Hz, 1H, CH_2OTs), 4.20(dd, J=13.2Hz, J=4.5Hz, 1H, CH_2OTs), 7.4(d, J= 3Hz, 2H, CH_2OTs), 7.60(d, J= 3Hz, 2H, CH_2OTs).

^{13}C RMN δ CDCl_3 : 21.29, 22.68, 29.79, 76.28, 128.27, 130.48, 140.29, 144.39.

General Procedure for the Aziridinepeptides

Method 1

To a well stirred and cooled solution of acid (1equiv.), and 2-methyl aziridine tosylate (1equiv.) was added a solution of dicyclohexylcarbodiimide (DCC) (1equiv.) in CH_2Cl_2 , over period of 15 min. The reaction was allowed to react at 0°C for 24h. At the end, the dicyclohexylurea (DCU) was filtered and washed with cold CH_2Cl_2 . The organic layers were combined and dried over CaSO_4 . The solvent was removed under reduced pressure to afford a yellow oil was obtained in good 90% yield. The residue was purified on a silica gel column using petroleum ether (45–46°C)–MeOH (1:4).

Method 2

To a solution of the carboxylic acid (1equiv) dissolved in CH_2Cl_2 , SOCl_2 (1equiv.) was added slowly at room temperature. The reaction mixture was heated under reflux for 2 h. Once the mixture was cooled, a solution of 2-methyl aziridine tosylate (1equiv) in CH_2Cl_2 was added dropwise, and the reaction was left for 12h at room temperature. The solvent was removed in vacuo, and dichloromethane (50 ml) was added. The organic layer was washed with 20ml of brine and then dried over calcium sulfate, filtered and evaporated under vacuum to yield the aziridine. An example of identification is given for the compound obtained after the coupling of 2-(diethoxyphosphoryl)propionic acid with aziridine 11.

Diethylphosphonopropionyl-2-tosylmethylaziridine 12

IR (KBr): 1728.87(C=O), 1366.79(S=O), 1119.96 (C–O), 1023.46(P=O), 932.07 (S–O), 723.31–695.46 (OTs).

^1H RMN δ CDCl_3 , 300MHz: 1.27(d, J=5.1Hz, 3H, CH_3CH), 1.29(t, J= 7.1Hz, 6H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.70(d, J= 4.5Hz, 2H, CH_2N), 1.75–1.79(m, 1H, CHN), 2.34(s, 3H, CH_3Ts), 3.68(dd, J=13.2Hz, J=4.5Hz, CH_2N), 3.88(dd, J=13.2Hz, J=4.5Hz, 1H, CH_2N), 4.01(q, J= 3.9Hz, 1H, CHCH_3), 4.09(q, J= 2.4Hz, 4H, POCH_2CH_3), 7.75(d, J= 3Hz, 2H, Ar), 7.46(d, J= 3Hz, 2H, Ar).

^{13}C RMN δ CDCl_3 : 4.38, 16.29, 21.28, 29.35, 30.56, 42.51, 61.78, 73.58, 128.25, 130.48, 144.76, 177.19.

N-phtalimidophenylalanine 13a

Phenylalanine (0.121mol) was suspended in glacial acetic acid (100mL) and phthalic anhydride (0.12 mol) was added. The mixture was refluxed for 2 h until all the solids dissolved and then cooled to room temperature and afterwards in an ice bath. The solid was filtered under suction and recrystallized from ethanol and water (4:1). The compound was identical to an authentic commercial sample from Aldrich. mp = 183°C Yield: 83%; IR (KBr):3269.43 (O–H), 1771.55(C=O phtaloyl), 1748.50(C=O) 1102.05 (C–O). ^1H RMN δ CDCl_3 , 300MHz: 3.6(d, CH_2 , J=7.5Hz), 5.24(t, CH, J=7.5Hz), 7.25(s, 5H, Ph), 7.79(s, 4H, Ft), 7.91(s, CO_2H).

N-Phtalimidotyrosine 13b

The same procedure for the synthesis as above mentioned for 13a, except for the reflux time duration that was 24h.

Mp=149°C. ^1H RMN δ CDCl_3 , 300MHz: 3.21(dd, J= 8.5Hz, 4.1Hz, 1H, NCH- CH_2), 3.46(dd, J= 8.5Hz, 4.1Hz, 1H, NCH- CH_2), 4.80(m, 1H, NCH), 5.30(s, 1H, OH), 6.65(d, J= 6.5Hz, 2H, ArOH), 7.08(d, J= 6.5Hz, 2H, ArOH), 7.80–7.84 (m, 4H, Ar).

^{13}C RMN δ CDCl_3 : 33.48, 60.86, 112.75, 126.19, 120.64, 127.18, 128.17, 152.65, 171.69.

(1-(2-(1,3-dioxoisindolin-2-yl)-3-phenylpropanoyl)aziridin-2-yl)methyl 4- methylbenzenesulfonate 14a

Pasty product. 1771.75(C=O Ft), 1710.04 (C=O aziridine), 1349.17(S=O), 1186.10 (C–O), 723.93–683.38 (OTs). ^1H RMN δ CDCl_3 , 300MHz: 1.66(dd, J= 8.7Hz, J= 4.5Hz, 1H, NCH), 1.41(dd, J= 8.7Hz, J= 4.5Hz, 1H, NCH), 1.71(m, 1H, NCH), 2.31(s, 3H, CH_3Ph), 3.21–3.84(m, 4H, CH_2Ph , CH_2O), 5.16(m, 1H, CONCH), 7.23–7.7.26(m, 3H, Ar), 4.36(d, J=6Hz, 2H), 7.81–7.86(m, 4H, Ar).

^{13}C RMN δ CDCl_3 : 18.29, 26.38, 27.57, 32.01, 57.28, 70.56, 120.65, 122.85, 125.62, 126.55, 129.17, 136.18, 141.38, 164.86. Elemental analysis: calcd for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$: C 64.27%, H 4.79%, N 5.55%. Found: C 63.87%, H 4.75%, N 6.01%.

(1-(2-(1,3-dioxoisindolin-2-yl)-3-(4-hydroxyphenyl)propanoyl)aziridin-2-yl) methyl 4- methylbenzenesulfonate 14b

mp = 201°C. IR (KBr): 3328.41 (O–H), 1775.61(C=O of Ft), 1626.75 (C=O of aziridine), 1311.81(S=O), 1127.16 (C–O), 972.25 (S–O), 723.93–683.38 (OTs).

¹H RMN δ, CDCl₃, 300MHz: 1.36(dd, J= 8.9Hz, J= 4.1Hz, 1H, NCH), 1.64(dd, J= 8.9Hz, J=4.1Hz, 1H, NCH), 1.70(m, 1H, NCH), 2.31(s, 3H, CH₃Ph), 3.20(dd, J=8.5Hz, 4.01Hz, 1H, CH₂Ph), 3.46(dd, J=8.5Hz, 4.01Hz, 1H, CH₂Ph), 3.59(dd, J= 7Hz, J=3.5Hz, 1H, CH₂O), 3.83(dd, J= 7Hz, J=3.5Hz, 1H, CH₂O), 5.15(m, 1H, 1H, NCHCO), 5.30(s, broad, 1H, OH), 7.24-4.26(m, 4H, ArOH, Ph), 7.36(d, J=6Hz, 2H, Ph), 7.83-7.85(m, 4H, Ar). ¹³C RMN δ CDCl₃: 18.27, 26.35, 32.19, 57.18, 70.55, 112.75, 115.09, 120.66, 125.29, 127.49, 129.08, 141.39, 151.65, 164.85,

Elemental analysis: calcd for C₂₇H₂₄N₂O₇S: C 62.30%, H 4.65%, N 5.38%. Found: C 61.99, H 5.01%, N 5.32%.

N-phenylalanyl-2-tosylmethylaziridine 15a

mp = 198°C. IR(KBr): (N-H), 1659.13 (C=O aziridine), 1329.22(S=O), 1081.37 (C-O), 965.45 (S-O), 720.13-682.09 (OTs).

¹H RMN δ CDCl₃, 300MHz: 1.28(dd, J=5.1Hz, J=2.1Hz, 1H, NCH₂CH), 1.72(dd, J=5.1Hz, J=2.1Hz, 1H, NCH₂CH), 1.78-1.81(m, 1H, NCH₂CH), 2.48(s, 3H, CH₃), 3.24(d, J= 3.9Hz, 1H, CH₂Ph), 3.26(d, J=3.9Hz, 1H, CH₂Ph), 3.55(dd, J=8.1Hz, J=2.7Hz, 1H, CH₂OTs), 3.76(dd, J=8.1Hz, J=2.7Hz, 1H, CH₂OTs), 4.14-4.18(m, 1H, PhCH₂CHNH₂), 5.44(d, J=1.5Hz, 2H, CHNH₂), 7.28(d, J=4.2Hz, Ph), 7.30(d, J=1.8Hz, 2H, Ph), 7.41(t, J=1.2Hz, 2H, Ph), 7.47(d, J=1.5Hz, 2H, Ts), 7.76(d, J=3Hz, 2H, Ts).

¹³C RMN δ CDCl₃: 16.29, 25.39, 24.38, 25.37, 34.01, 46.55, 110.75, 126.28, 124.18, 125.48, 135.27, 140.36, 150.66.

Elemental analysis: calcd for C₁₉H₂₂N₂O₅S: C 58.45%, H 5.68%, N 7.17%. Found C 57.56%, H 5.70%, 6.99%.

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