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1,3-Dipolar cycloaddition of azomethine ylide from Phtaloylimidophenylalanyl-2-hydroxymethylaziridine

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Abstract: Phtaloylimidophenylalanyl-2-hydroxymethylaziridine has been used as a starting material to yield azomethine ylide through thermal opening and was then involved into 1,3-dipolar cycloaddition reactions. Different five-membered adducts were obtained and were fully identified. The latter might be considered useful starting materials for further functionalization to provide novel compounds of biological interest.

Keywords: Cycloaddition, Azomethine ylide, aziridine, oxazolidine, pyrrolidine, imidazolidine.

Introduction

In an initial work, we prepared a series of *N*-hydroxymethylaziridines[1] among which the phenylalanine derivative **1** (Fig. 1) showed the most promising biological activity according to later investigations related to breast cancer chemotherapy [2,3].

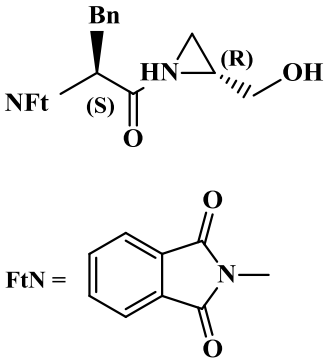

Figure 1: Phtaloylimidophenylalanyl-2-hydroxymethylaziridine **1.**

Because of this interesting behaviour, we set up this work to achieve a stereoselective synthesis of the title compound so that it could be used later as a source of azomethine. This was achieved using both (±)- and (*R*)- commercial glycidol as shown in scheme 1, starting

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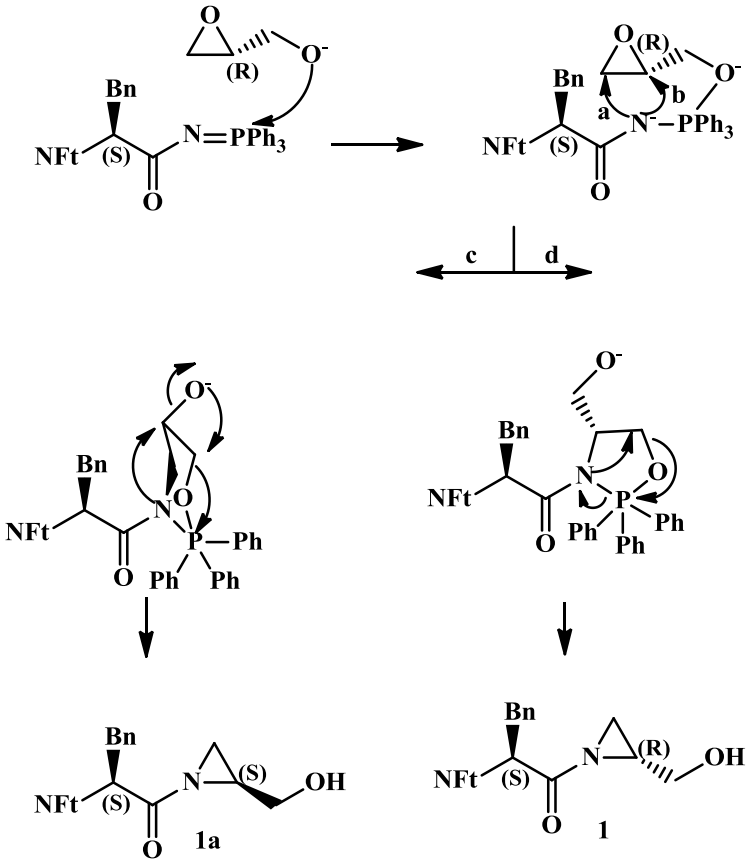
from the corresponding iminophosphorane of L-phenylalanyl azide and triphenylphosphine (Scheme 1).



Scheme 1: suggested mechanism for the stereoselective synthesis of aziridine **1**.

In order to assess the stereochemistry of **1**, the synthesis was first performed using a commercial (*R,S*)-glycidol (Aldrich, 101027992) and the reaction product was analyzed by chiral HPLC. Two main peaks with unequal percentages were observed with respective retention times 10.45 minutes and 11.24 minutes. This result suggested that either the amino acid side chain induced some stereocontrol of the reaction, or enantiomers of (*R,S*)-glycidol reacted with different rates during the process.

Therefore, we performed the same reaction with (*R*)-glycidol (Aldrich 480819) that afforded a solid (m.p. 51 °C; $[\alpha]_D^{25}$-26.5° (*c* 0.5, $CHCl_3$). HPLC showed the same peaks with same retention times but with the highest percentage at 11.24 minutes (96%) and the lowest at 10.45 minutes (4%).

This time the question was to know if once formed, a stereoisomer could be converted into its counterpart. Scheme 1 provides a sound understanding of the overall observation from mechanistic background. As a matter of fact, oxyanion from glycidol would react with iminophosphorane to afford an intermediate nitrogen nucleophile that would open epoxide ring according to pathway (a) or (b). This would lead to both five-membered- and six-membered intermediates whose decomposition would result either in the inversion of configuration (pathway c) or its retention (pathway d).

Because of hindrance generated by conformations in the six-membered intermediate, it is obvious that the five-membered intermediate would decompose faster than the six-membered

analogue, thus affording **1** as the main compound with (*S,R*) configuration while **1a** would be formed as minor counterpart with (*S,S*) configuration.

Those results induced us to attempt the synthesis of a few five-membered heterocycles from **1**, since those compounds can be easily accessed through reacting appropriate ylides with a number of dipolarophiles[4-6]. As a matter of fact, those compounds are found in a large number of best-selling pharmaceuticals and numerous synthetic pathways to access them are reported in the literature and full mention of the corresponding literature is beyond the scope of this work [7-14].

Needless to say that many synthetic approaches are described in the literature providing azomethine ylides[15-24], but their overview is beyond the scope of this work. However thermolysis of aziridines, as exemplified by literature as regards the stereochemical synthesis of natural products [25,26] was more affordable to us in order to access the targeted ylides and involve them in the cycloaddition reaction.

Taking in account the conservation of orbital symmetry [27], thermolysis of **1** would entail conrototary cleavage of C-C bond that affects the stereochemistry of the resulting azomethine **1a** displayed in scheme 3. The latter would react with such dipolarophiles as aldehydes, imines and olefins to afford oxazolidine, pyrrolidine and imidazolidine skeletons, that are found in many compounds of biological interest[28,29].

As evidence had already been given by previous studies, the way thermolysis of aziridines proceeds is subjected to steric and electronic factors. The stereochemistry of adducts mainly depends on both the configuration and the conformation of the intermediate ylide and dipolarophiles [30] as well as on steric factors during the overlap of reacting orbital during the formation of new bonds.

Actually, there are three potential conformations for bisubstituted ylides and each is named according to its shape. A ***U***-shaped conformation is often excluded because of its greatest steric hindrance but not completely discarded; an ***S***-shaped conformation stands for a half-closed conformation; and a ***W***-shaped conformation corresponds to an open system, the less hindered (Fig.2).

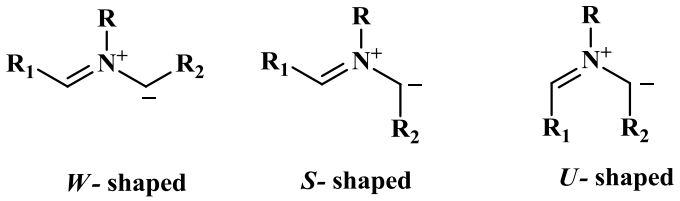
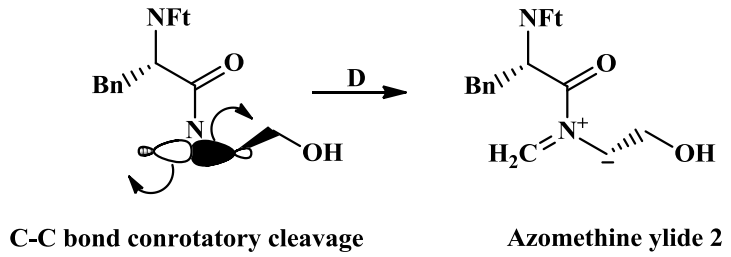


Figure 2: ylide conformations

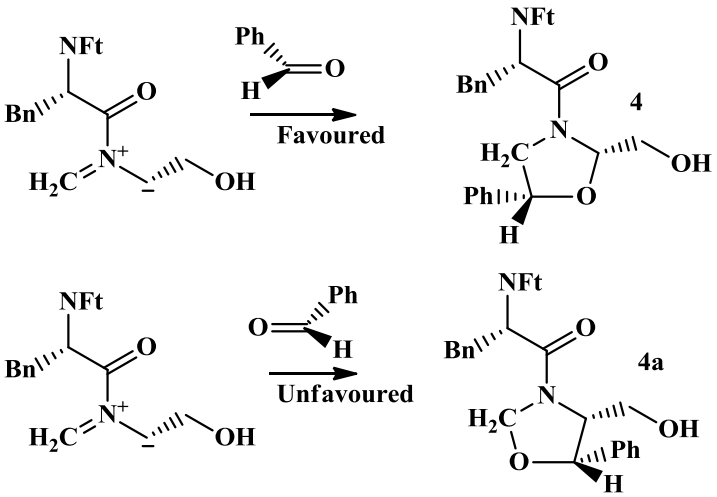
The ***S***-shaped conformation is stable and reactive when the ylide is stabilized by an electrowidrawing group[31], so that it usually leads to single regioisomers [32,33]. It has been observed that single stereoisomers were obtained when the reaction proceeds through a concerted process, while it leads to mixtures of stereoisomers as a result of existing mixture of conformations, or when reaction proceeds through a stepwise mechanism. It is also worth mention that the geometry of the dipole and steric factors during the approach of dipole and dipolarophile control the stereochemistry of the final product.

Being a monosubstituted ylide, our ylide cannot be assigned any of these conformations; but its geometry is much more close to a ***W***-shaped conformation than the two remaining ones (scheme 2).



Scheme 2: Thermolysis of **1** and geometry of ylide **2**.

As described in scheme 3, the reaction would lead to a single stereoisomer and a single regioisomer at the same time because of less steric hindrance between azomethine **2** and dipolarophile.



Scheme 3: 1,3-Dipolar cycloaddition of **2** with benzaldehyde.

During this work, other regio- and stereoisomers were not observed either because they were not formed or they could not be detected.

Results and Discussion

1,3-Dipolar cycloaddition with benzaldehyde.

Thermolysis of aziridine **1** in the presence of benzaldehyde in refluxing toluene for 50 h was expected to afford **3**; the latter was obtained in 60.5% yield as a single regioisomer (Fig. 3).

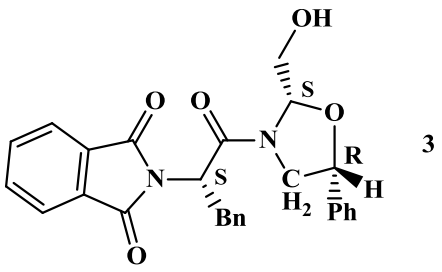


Figure 3: structure of **3**.

The regiochemistry of **3** was first determined by its ^{1}H NMR spectrum, focusing our attention on signals at 3.55, 3.64 and 4.20 ppm. As a matter of fact a doublet of doublet (dd) was observed at 4.20 (J = 6.0Hz, J = 5.4Hz) for H_5 while two distinct dd were located at 3.55(J = 8.7Hz, J = 5.4Hz, H_4) and 3.64 (J = 8.7Hz, J = 6.0Hz, H_4). It is worth mention that dd of H_2 appeared at 5.13(J = 5.4Hz, J = 3.3Hz) coupled with hydroxymethyl protons, and the observed values of coupling constants were in accordance with Karplus J constants for *cis* and *trans* vicinal coupling in oxazolidines[34]. Besides NOESY relationship was observed between H4' and aromatic proton but not between H_2 and H_5 (Figure 3). Those data along with coupling constants gave evidence for the suggested regiochemistry. All those observations are in favour of a *cis* coupling between H_4 and H_5, while $H_{4'}$ is *trans*-coupled to H_5.

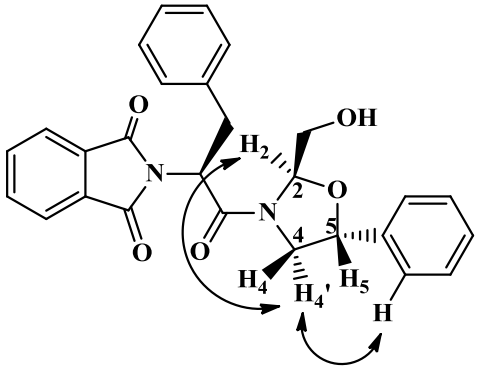
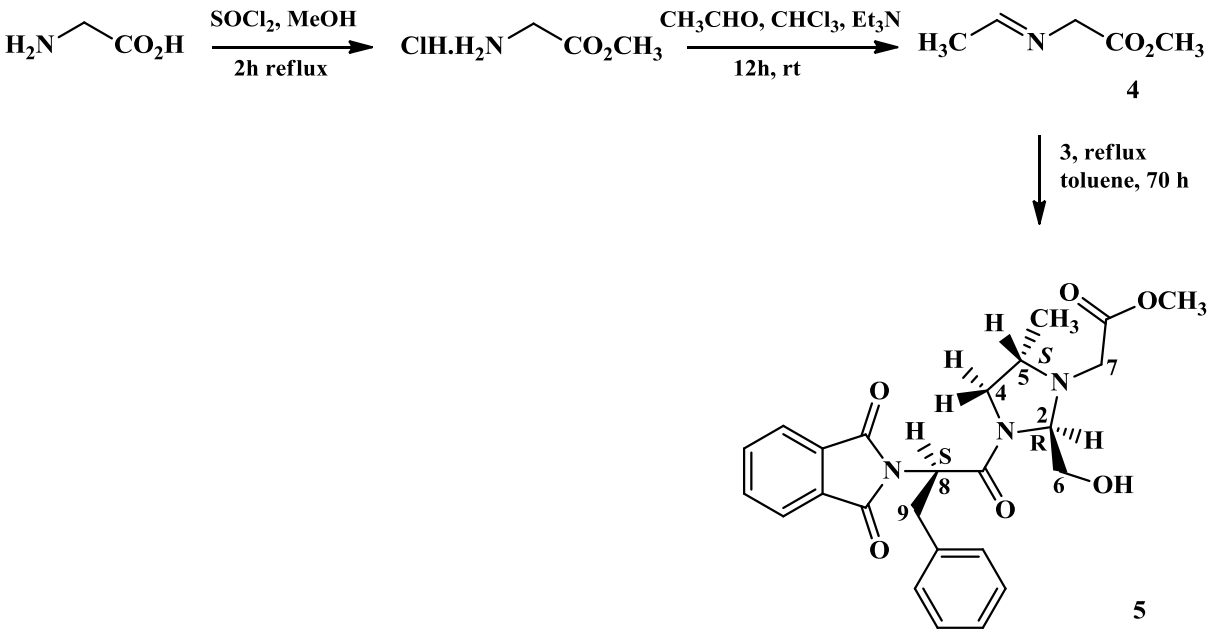


Figure 4: NOESY correlation for oxazolidine **3**.

1,3-Dipolar cycloaddition with imine

Only few reactions leading to imidazolidines from azomethine ylides from various sources and imines are found in the literature[31,35,36]. In order to explore the reactivity of our azomethine with imines, the synthesis of imine **4** as a model was achieved to access imidazoline **5.** Methyl 2-(ethylideneamino) acetate **4** was prepared in a moderate yield (52.77%) from the corresponding glycine methylester hydrochloride and then reacted with aziridine **1** to provide **5** (Scheme 4).

The regio- and stereochemical assignments of **5** were achieved the same way as for compound **3**. Thus, the ^{1}H NMR analysis showed two dd, the former at 3.53(J = 8.7Hz, J = 3.3 Hz, $H_{4'}$), and the latter at 3.59(J = 8.7Hz, J = 5.7 Hz, H_4). Other significant signals were the following: 4.29 ppm for H_2 (dd, J = 5.4 Hz, J = 2.4 Hz), 3.77 ppm (dd, J = 11.8 Hz, J = 5.4Hz, 1H, H_6) and 4.01(dd, J =11.8 Hz, J = 2.4 Hz, 1H, $H_{6'}$); 3.63 (m, H_5) and finally 1.25 ppm (d, J = 7.2Hz) for the methyl group on C5. The observed coupling constant values $J_{5\text{-}4'}$ = 3.3 Hz is lower than the value of coupling constant $J_{4\text{-}5}$ = 5.7 Hz indicating *trans* relationship between $H_{4'}$ and H_5, entailing that methyl group on C5 was *cis* versus $H_{4'}$.



Scheme 4: Synthesis of Imidazolidine **5** (Methyl-2-(3-(2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl)-2-(hydroxymethyl)-5-methylimidazolidine-1-yl)acetate).

NOESY of **5** was also recorded and the stereochemistry was assigned unambiguously. The ^{1}H-^{1}H NOESY correlation is shown in Figure 5 where a cross peak was observed between the dd at 4.29 (H_2) and the doublet at δ =1.25 (methyl group) advocating for the location of those protons on the same face of the imidazoline ring. No correlation was observed between H_2 and H_5 thus indicating a *trans* relationship between methyl and alkoxy groups. Besides cross peaks were observed between dd at 5.15 ppm (H_8) with dd at 3.59 ppm ($H_{4'}$) and the doublet at 1.25 ppm, giving evidence for a *cis* relationship between these protons.

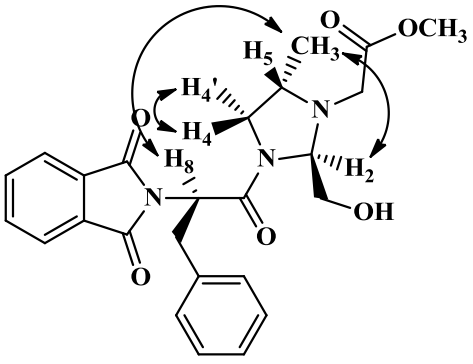
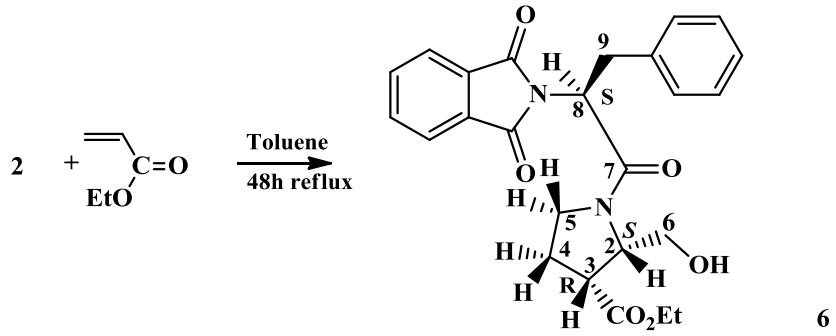


Figure 5: NOESY correlations for **5**.

Of particular importance were ^{13}C-NMR signals of methine carbon atoms of the imidazoline ring respectively at δ 76.68 (**C4**), 77.53(**C2**), 62.04(**C5**), whereas δ 77.10 was attributed to **C6** and the carbonyl chemical shift was located at 168.84. In addition, HMBC showed correlations between protons and corresponding ^{13}C carbon atoms Table 2. It is worth mention that no reaction occurred with the ester group as a dipolarophile.

1,3-Dipolar cycloaddition with ethyl acrylate.

Finally cycloaddition of azomethine **2** with ethyl acrylate was performed as shown in scheme 5.



6

Scheme 5: Synthesis of Pyrrolidine **6** (Ethyl 1-(2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl)-2(hydroxymethyl)pyrrolidine-3-carboxylate).

^{1}H NMR of **6** displayed the following characteristics: a signal at δ 1.25 (m, 2H, H_4), another multiplet at δ 2.58(ddd, *J*=6 Hz, 3.6 Hz, 3.3 Hz, 1H, H_3), and the last one at δ 3.63 (m, 2H, H_5). A signal at δ 4.22(ddd, *J* = 5.1 Hz, *J* = 3.6 Hz, *J* = 1.8 Hz, H_2) along with two dd, the former at δ 3.35(δδ, *J* = 11.1 Hz, J = 1.8 Hz, H_6), and the latter at δ 3.59(dd, *J* = 11.1 Hz, *J* = 5.1 Hz, $H_{6'}$).

NOESY allowed us assess the stereochemistry of **6** as shown in figure 6. The signal at 4.22ppm (ddd, H_2) showed relationship with the multiplet at δ 2.58 (H_3), and the multiplet at δ 2.20 (H_4). All these data gave strong evidence for a *cis* relationship between H_2, H_3 and H_4.

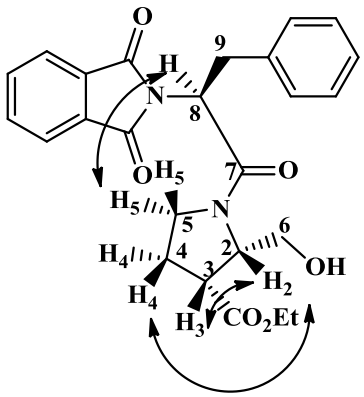


Figure 6: NOESY correlations for **6**.

In order to confirm these assignments, a COSY NMR spectrum of **6** showed only a vicinal coupling between H_2 (δ 4.24) and H_3 (δ 2.58). This confirms the observed regioselectivity of the reaction. HMBC revealed correlations between H_3 (δ 2.58) and C_3 (53.45 ppm). Besides another interaction was also observed between H_6 (3.35, dd, 3.59, dd) and C_6 (76.82ppm).

Conclusion

Under thermolysis conditions phtaloylimidophenylalanyl-2-hydroxymethylaziridine affords azomethine that undergoes stereoselective and regioselective 1,3-dipolar cycloaddition reaction to yield interesting novel five-membered heterocycles because of a concerted cycloaddition reaction. Our results highlight for the first time the behaviour of this aziridine and could pave the way to further studies in this field.

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Experimental

All reactions with dry solvents were carried out under dry nitrogen. $CHCl_3$ was distilled and stored over P_2O_5.Toluene was distilled and dried over sodium wires before use. I.R spectra were performed on a Mattson Genesis II FTIR instrument. NMR spectra were recorded in $CDCl_3$ on a Bruker 300MHz, Bruker Avance 400 MHz and/or 500MHz instrument using tetramethylsilane (TMS) as an internal standard. 13C NMR spectra are collected at 75 MHz on same instruments. Chemical shifts are given in δ (ppm) and J values in Hertz (Hz). Melting points were determined on an Electrothermal T1A F3.15A apparatus. Column chromatography was achieved on silicagel 230-270 mesh (Merck) using appropriate solvent or mixture of solvents (dichloromethane, methanol or ether). Chiral HPLC was performed on a Shimadzu SCL-10VP, LC-10AD instrument with a UV detector (210 nm) using a Chromatopack C-R6A (250mmx4, 6mm, 100Å porosity) column. A mixture af acetonitrile and water was used (40% initial concentration of acetonitrile up to 90%, with 20 minutes gradient). Microanalysis was achieved on a LECO CHN-900 instrument.

General procedure for the synthesis of aziridine from protected aminoacyl azide

Starting materials, namely, phtaloylimido phenylalanine and its azide derivatives were prepared according to literature[37].

Synthesis of aziridine 1.

In a three-necked flask was dissolved under nitrogen *N*-protected aminoacyl azide (25 mmol) in dry dichloromethane (100 ml) and the solution was cooled at 0 °C with stirring. Then trphenylphosphine (25 mmol) was added fraction wise. When addition was finished, the mixture was stirred for 30 minutes and then was left until it rose to ambient temperature.

In a second flask containing dry ether (50 ml) was introduced under nitrogen sodium hydride (27 mmol) previously washed with dry ether; glycidol (25 mmol) was slowly added to the stirred and cooled suspension and the resulting mixture was stirred for 30 minutes. The content of the second flask was slowly siphoned into the first one using dry nitrogen flow and

keeping the temperature at 0 °C. The new mixture was then refluxed for 90 minutes and then was cooled to room temperature.

A 10% ammonium chloride aqueous solution was slowly added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 ml) and all organic layers were combined, washed with brine and dried over anhydrous calcium sulfate. After removal of solvent, the resulting residue was dissolved in dry ether and cooled at -18 °C. Triphenylphosphine oxide that separated was removed with suction and the procedure was repeated until no more triphenylphosphine oxide separated. This procedure was monitored by thin layer chromatography (TLC) using a mixture of petroleum ether (b.p. 40-60 °C) and dichloromethane (4:1). After removal of solvent, the final residue was purified on a silicagel column using the same mixture of solvents as for TLC. Removal of solvent from the filtrate afforded a white solid 98%, mp: 51 °C; $[\alpha]_D^{25}$ = - 26.5 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35(m, 1H, -N-C**H**-CH_2OH), 1.45(dd, *J* = 12.4 Hz, 6Hz, 1H, C**H** aziridine), 1.60(dd, *J* = 12.4 Hz, 7Hz, 1H, C**H** aziridine), 3.10(s, br, 1H, O**H**), 3.25(dd, *J* = 12.4 Hz, 0.5 Hz, 1H, C**H**$_2$OH), 3.40(dd, J = 12.4 Hz, 7 Hz, 1H, C**H**$_2$OH), 3.57(dd, *J* = 14 Hz, 7Hz, 1H, C**H**$_2$Ph), 3.70(dd, *J* = 14 Hz, 6.5 Hz, 1H, C**H**$_2$Ph), 5.10(dd, *J* = 7 HZ, 6.5 Hz, 1H, FtN-C**H**-CO), 7.15(m, 1H, Ph), 7.27(d, *J* = 4Hz, 2H, Ph), 7.36(d, *J* = 4Hz, 2H, Ph), 7.59(d, *J* = 5Hz, 2H, Ft), 7.72(d, *J* = 5Hz, 2H, Ft). ^{13}C NMR (75 MHz, $CDCl_3$): 28.92(**C**H_2, aziridine), 34.10(-N-**C**H-CH_2OH), 34.98(**C**H_2Ph), 59.97(-N-**C**H-CO), 123.65(**C**H, Ft), 124.88(Ph), 126.85(Ph), 127.68(Ph), 131.90(Ft), 168.00(**C**=O, Ft), 172.23(N-**C**=O). Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.70; H, 5.05; N, 8.25.

Methyl 2-(ethylideneamino)acetate 4

The compound was prepared in three steps

a) Methyl 2-aminoacetate hydrochloride.

To a solution of glycine (10g, 0.130mol) in methanol (100ml), thionyl chloride ($SOCl_2$) (23.32 g, 0.196 mol) was added dropwise with stirring at 0°C. The reaction mixture was heated under reflux for 2h. The mixture was cooled, then excess methanol and $SOCl_2$ were removed in vacuo to afford a white solid (77.77%); mp = 174°C. IR cm^{-1} KBr: 1743.95 (C=O), 1160.03 (C–O). The compound was stored in a dessiccator because it was moisture sensitive. IR cm^{-1} KBr: 1743.95 (C=O), 1160.03 (C–O).

b) The synthesis of imine 4.

Glycine methyl ester hydrochloride **(**3g, 23.89 mmol), acetaldehyde (1.2ml, 21.52 mmol) and $MgSO_4$ (4g, 8.31 mmol) were introduced under nitrogen in dry CH_2Cl_2. Anhydrous triethylamine (TEA) (4ml, 28.86 mmol) was slowly added at 0°C.When the addition was completed the reaction mixture was stirred for 12h. At the end, the mixture was diluted with ether, and then triethylammonium chloride was filtered off. The organic layer was dried over $CaSO_4$, filtered and concentrated in vacuo to afford oil (52.8%).

IR cm^{-1} neat : 1744.58(C=O ester), 1631.22(C=N), 1199.66 (C–O).
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91(d, *J*=7.1Hz, 3H, NCHC**H**$_3$,), 2.43(s, 1H, NC**H**CO), 3.68(s, 3H, COOC**H**$_3$), 7.52(q, *J* = 6.2Hz, 1H, =NC**H**CH_3,). ^{13}C-RMN ($CDCl_3$, 500MHz) : 15.68(NCH**C**H_3), 51.62(COO**C**H_3), 58.63(N**C**HCO), 158,00(N**C**H), 170.34(**C**$OOCH_3$).

c) General procedure for the 1,3-dipolar cycloaddition:

To a solution of aziridine **1** (1equiv.) in a dry toluene (100ml) under dry nitrogen the dipolarophile (1equiv.) was added with magnetic stirring. The mixture was refluxed for various times and various temperature as described for each dipolarophile until no starting materials could be detected by thin layer chromatography (TLC). After drying and removal of solvent in vacuo, the reaction product was purified by column chromatography using the same mixture of solvents as for TLC. High vacuum removal of solvent left a residue that was analysed.

2-((*S*)-1-((*2S,5R*)-2-(hydroxymethyl)-5-phenyloxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione 3.

Experimental conditions: 50h; reflux toluene, yellow sticky paste, yield = 60.5%. TLC (Rf 0.52) and column chromatography: petroleum ether (b.p. 40-60 °C) and methanol (1:4).
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.24(dd, *J* = 16.5 Hz, *J* = 5.4 Hz, 1H, H_9), 3.50(dd, *J* = 16.5 Hz, *J* = 3.3 Hz, 1H, H_9), 3.55(dd, *J* = 8.7 Hz, *J* = 5.4 Hz, 1H, H_4), 3.64(dd, *J* = 8.7 Hz, *J* = 6.0 Hz, 1H, H_4), 3.70(s, 1H, O**H**), 3.79(dd, *J* = 8.7 Hz, *J* = 3.3 Hz, 1H, H_6), 4.04(dd, *J* = 8.7 Hz, *J* = 5.4 Hz, 1H, H_6), 4.20(dd, *J* = 6.0 Hz, *J* = 5.4 Hz, 1H, H_5), 5.13(dd, *J* = 5.4Hz, *J* = 3.3Hz, 1H, H_2), 5.24(dd, *J* = 5.4 Hz, *J* = 3.3Hz, 1H, H_8), 7.18(dd, *J* = 4.5Hz, *J* = 1.5 Hz 1H, Ph), 7.43(dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 2H, Ph), 7.46(dd, *J* = 7.5 H z, *J* = 4.5 Hz, 2H, Ph), 7.67(d, *J* = 6.9 Hz, 2H, Ft), 7.70(d, *J* = 6.9 Hz, 2H, Ft).
^{13}C NMR (75 MHz, $CDCl_3$): δ 35.03(**C**H_2Ph), 53.79(**C**HCH_2Ph), 62.36(**C**H_2CHCO), 77.17(**C**H_2OH), 77.59(Ph**C**OCH), 78.02(O**C**HN), 123.74(2C Ft), 132.37(2C Ft), 132.50(2C Ft), 169.16(2 **C**O Ft), 126.90(1C Ph), 127.17(2C Ph), 128.98(2C Ph), 134.17(1C Ph)], 128.81(1C Ph), 127.17(2C Ph), 128.98(2C Ph), 137.89(1C Ph)] , 170.56(**C**ON).
Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.25; H, 5.52; N, 6.30.

Methyl 2-((*2R,5S*)-3-(2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl)-2-(hydroxymethyl)-5-methylimidazolidin-1-yl)acetate 5.

Experimental conditions: 70h; reflux toluene; yellowish sticky paste; yield 52.8%. TLC (Rf 0.41) and column chromatography eluted with CH_2Cl_2-MeOH (4:1).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25(d, *J* = 7.2Hz, 3H, C_5-C**H$_3$**), 3.44(s, 2H, C**H$_2$**CO_2CH_3), 3.53(dd, *J* = 1.5Hz, *J* = 3.3Hz, 1H, $H_{5'}$), 3.53(dd, *J* = 8.7 Hz, 3.3 Hz, 1H, H_4), 3.55(dd, *J* = 13.8 Hz, *J* = 4.5 Hz, 1H, $H_{9'}$) 3.59(dd, *J* = 5.7Hz, *J* = 2.7Hz, 1H, H_5), 3.59(dd, *J* = 8.7 Hz, 5.7 Hz, 1H, H_4), 3.63(m, 1H, H_5), 3.65(s, 3H, CO_2C**H$_3$**), 3.70(dd, *J* = 13.8 Hz, *J* = 6 Hz, 1H, H_9), 3.75(s, O**H**), 3.77(dd, *J* = 11.8 Hz, *J* = 5.4 Hz 1H, C**H$_2$**OH), 4.01 (dd, *J* = 11.8Hz, *J* = 2.4Hz, 1H, C**H$_2$**OH), 4.29(dd, *J* = 5.4 Hz, *J* = 2.4 Hz, 1H, H_2), 5.15(dd, *J* = 6 Hz, *J* = 4.5 Hz, 1H, H_8), 7.16(dd, *J* = 5 Hz, *J* = 2 Hz, 1H, Ph), 7.46(dd, *J* = 6.7 Hz, *J* = 2 Hz, 2H, Ph), 7.48(d, *J* = 6.7 Hz, *J* = 5 Hz, 2H Ph), 7.63(d, *J* = 6.9 Hz, 2H, Ft), 7.70(d, *J* = 6.9Hz, 2H, Ft),
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.13(**C**H_3), 34.69(**C**H_2Ph), 53.46(CH_2CO_2**C**H_3), 53.80(**C**$H_2CO_2CH_3$), 62.04(CH**C**H_2N), 68.17(**C**HCON), 76.68(NCH_2**C**HN), 77.10(**C**H_2OH), 77.53(N**C**HN), 123.43(C Ft), 132.04(C Ft), 132.18(C Ft), 167.70(**C**O Ft), 126.82(1C Ph), 128.47(2C Ph), 128.63(2C Ph), 134.09(1C Ph)], 168.84(**C**ON), 170.80(**C**O_2CH_3).
Calcd for $C_{25}H_{27}N_3O_6$: C, 64.51; H, 5.85; N, 9.03. Found: C, 64.79; H, 6.18; N, 8.00

(*2S,3R*)-ethyl 1-((*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoyl)-2-(hydroxymethyl) pyrrolidine-3-carboxylate 6.

Experimental conditions: 48h; reflux toluene; brownish sticky paste, yield 66%. TLC (Rf 0.39) and column chromatography eluted with CH_2Cl_2-MeOH (9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22(t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 2.20(m, 2H, H_4), 2.58(ddd, *J* = 6 Hz, 3.6 Hz, 3.3 Hz, 1H, H_3), 3.24(dd, J = 8.7 Hz, 2.4 Hz, 1H, H_9), 3.35(dd, 2H, *J* =11.1 Hz, *J* = 5.1Hz, 1H, C**H₂**OH), 3.50(dd, *J* = 8.7 Hz, *J* = 5.4 Hz, 1H, H_9), 3.59(dd, *J* = 11.1 Hz, 1.8 Hz, 1H, C**H₂**OH), 3.63(m, 2H, H_5), 3.76(s, 1H, O**H**), 4.22(ddd, *J* = 5.1 Hz, *J* = 3.6 Hz, *J* = 1.8 Hz, 1H, H_2), 4.28(q, *J* = 7 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 5.17(dd, *J* = 5.4 Hz, *J* = 2.1Hz, 1H, H_8), 7.16(dd, *J* = 4.5Hz, *J* = 1.6 Hz 1H, Ph), 7.45(dd, *J* = 7.5 Hz, *J* = 1.6 Hz, 2H, Ph), 7.50(dd, *J* = 7.5 Hz, *J* = 4.5 Hz, 2H, Ph), 7.64(d, *J* = 7.2 Hz, 2H, Ft), 7.70(d, *J* = 7.2 Hz, 2H, Ft).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.15($CO_2CH_2\mathbf{C}H_3$), 29.69($NCH_2\mathbf{C}H_2$), 34.70(**C**H_2Ph), 53.45($CH_2\mathbf{C}HCO_2Et$), 53.64(N**C**H_2CH_2), 62.02(**C**HCH_2OH), 76.82(**C**H_2OH), 77.25($PhCH_2\mathbf{C}H$), 77.66($CO_2\mathbf{C}H_2CH_3$), 123.412(1C Ft), 132.02(2C Ft), 132.16(2C Ft), 167.47(2 **C**O Ft), 126.83(1C Ph), 128.48(2C Ph), 128.64(2C Ph), 134.13(1C Ph), 168.82(**C**ON), 170.18(**C**O_2Et).

Calcd for $C_{25}H_{26}N_2O_6$: C, 66.66; H, 5.82; N, 6.22. Found: C, 66.90; H, 6.01; N, 8.51

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