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Diels–Alder cycloaddition of electrophilic 2*H*-azirines with 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl) oxazolidin-2-ones. Treatment of the cycloadducts under acidic conditions

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Abstract—3-(3-(*tert*-Butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one was reacted with several electrophilic 2*H*-azirines to give the expected cycloadducts in moderate to good yields. Treatment of the cycloadducts under acidic conditions gave six-membered ring aminoenones and aziridine derivatives. In the case where anilinium fluoride was used an inversion at the C-2 stereogenic center was observed forming an isomer of the former cycloadduct. The chiral (*R*)-3-(3-(*tert*-butyldimethylsiloxy)buta-1,3-dienyl)-4-phenyloxazolidin-2-one was also reacted with an electrophilic 2*H*-azirine. The reaction showed no diastereoselectivity, but both diastereoisomers were fully isolated by chromatography.

1. Introduction

Diels–Alder cycloadditions of 3-(3-(trialkylsilyloxy)buta-1,3-dienyl)oxazolidin-2-ones in general have proved to be extremely interesting due to their high *endo* selectivity with a number of carbodienophiles, opening the possibility of generating cyclohexanones by hydrolysis of the cycloadducts.[1] Reactions with imines gave a no less interesting type of compounds: dihydro-4-pyridones, that are memory enhancers when functioning as ligands for acetylcholine receptors and are building blocks to a wide range of natural products of biological interest.[2,3] 2*H*-Azirines are special imines that have proved to be excellent partners in aza-Diels–Alder reactions that occur at rt when the C=N bond is activated with a conjugated oxo,[4] alkoxycarbonyl[5] or heteroaromatic group.[6]

2. Results and discussion

In order to exploit the potential of both 2*H*-azirines and the dienes quoted above, we combined the 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** with the azirines **2a–e** in toluene and left the solution stirring at rt for 4–5 days. Cycloadducts were obtained after dry flash chromatography in moderate to good yields. In cases where the 2*H*-azirine could not be isolated (**2a**, **2d**) the cycloaddition was preceded by the pyrolysis of the α-azido precursor **1a**, **1d**, then the reaction solution was cooled and the diene added (Scheme 1).

Products are assumed to be formed by an *endo* process, as generally occurs in reactions of electrophilic 2*H*-azirines with 1,3-conjugated dienes, in particular with Danishefsky's diene and other similar types of dienes.[5b,j,k] The chemical shift of H-7 has been recognized as indicative of the stereochemistry of the cycloadducts. Figure 1 shows a good equivalence for the chemical shifts of H-7 protons in compounds **6**[5b]**/5c**, and **7**[5c]**/5d**.

The exceptions to the *endo* rule in Diels–Alder cycloadditions envolving 2*H*-azirines occur with furan and its derivatives, where the easy retro Diels–Alder favors the thermodynamic product resulting from the *exo* approach.[5g]

After having succeeded with achiral reagents we chose to use the known chiral diene **4**[1] to test a possible diastereoselectivity in these reactions. It is well established that the carbonyl group on the imide nitrogen preferentially adopts the anti conformation, away from the dienyl moiety, as represented in structure **4**. Due to this fixed conformation

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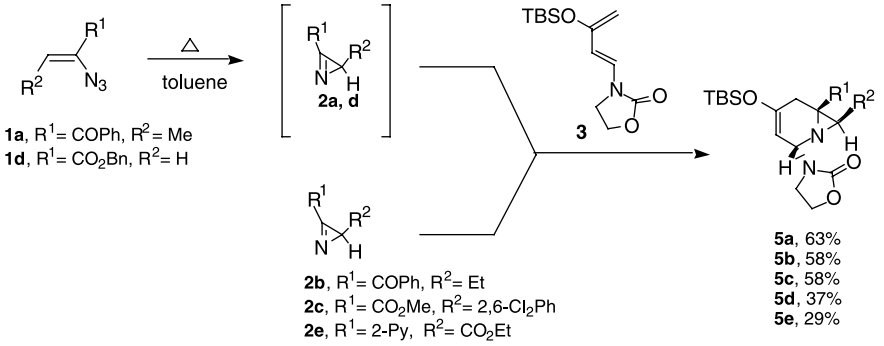


Scheme 1.

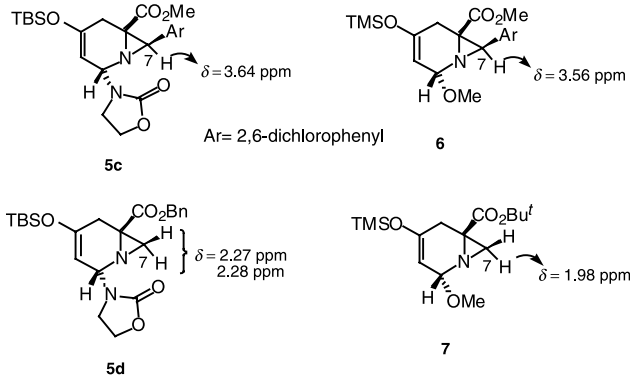


Figure 1.

the differentiation of the two faces of the diene made by the dienophile it is generally high. But this did not occur with the 2*H*-azirine **2d**. The small volume of the methylene group of the azirine is most probably responsible for the observed lack of selectivity. Figure 2 shows the two possible approaches of diene–azirine giving two diastereoisomers, compounds **8d** and **9d**.

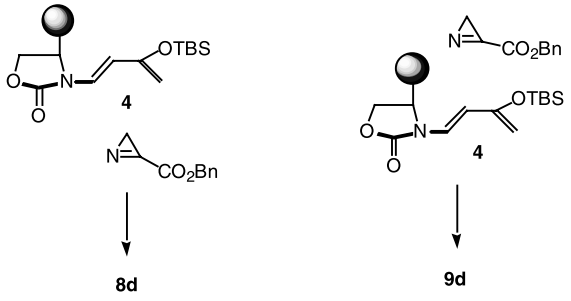
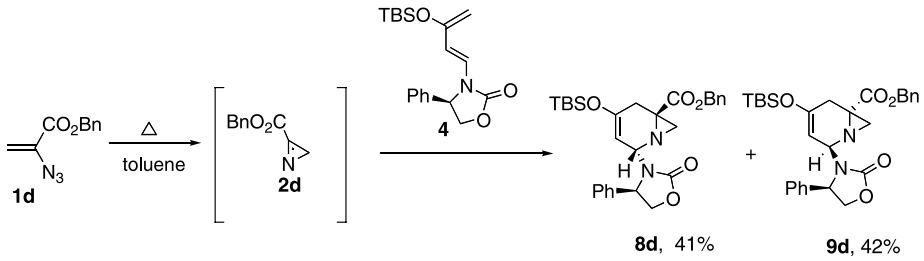


Figure 2.

Both products were effectively obtained from the reaction of the chiral diene **4** with 2*H*-azirine **2d**, prepared 'in situ' by pyrolysis of the α-azido compound **1d**. ^{1}H NMR of the crude product showed two diastereoisomers in approximately 1:1 ratio (Scheme 2). Compounds **8d** and **9d** were completely separated by dry flash chromatography (**8d**, 41% yield; **9d**, 42% yield).

Based on the ^{1}H NMR analysis both products **8d** and **9d** would be formed by an *endo* approach of reactants. The chemical shifts of the two H-7 protons are quite close to each other in both products (δ_H 2.10/2.27 ppm in compound **8d** and δ_H 2.00/2.48 ppm in compound **9d**) and in the other products obtained from *endo* approach, as those shown in Figure 1. The main spectroscopic difference between the two diastereoisomeric compounds **8d** and **9d**, is the chemical shift of H-2. Compound **8d** shows H-2 at δ_H 5.87 ppm, quite near the values of compounds **5a–e** (δ_H 5.67–5.90 ppm) and compound **9d** at δ_H 4.84 ppm, around 1 ppm upfield. This difference can be explained by the effect of the carbonyl of the oxazolidinone group over H-2 in one case that fails in the other. This is sustained by the chemical shift of H-2 in compound **7** at δ_H 4.91 ppm, also 1 ppm upfield. The methoxy group (in compound **7**) cannot display a similar effect to the carbonyl through space since the oxygen atom is away from H-2. ^{13}C spectrum shows that the inductive effect of the methoxy group (in compound **7**)[5c] is higher than the effect of the oxazolidinyl group (in compounds **5**, **8d** and **9d**). The C-2 chemical shift in compounds **5**, **8d** and **9d** are very near to each other ($\delta_C \sim 66$ ppm), but compound **7** shows C-2 around 20 ppm downfield, at δ_C 87.8 ppm. It is so clear that in compound **9d**, formed by approach of the azirine to the bulky face of the diene, the phenyl group in the oxazolidinone moiety will tend to move away from the methylene group of the aziridine to avoid a steric interaction between the two moieties of the molecule. The arrangement of groups in



Scheme 2.

conformer **I** is certainly less stable than in conformer **II**. Due to the absence of interaction between the carbonyl group and H-2 in conformer **II**, the effect disappears resulting in a drop of the chemical shift of H-2 in ca. 1 ppm (Fig. 3).

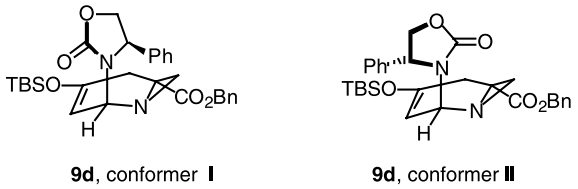


Figure 3.

Cycloadducts **5a–e** were then reacted under acidic conditions. The nature of the acid seems to play a decisive role in the outcome of reactions. It is to be expected that any reaction would begin with protonation either on the nitrogen atom of the aziridine ring, forming **5I**, or on the oxygen atom of the carbonyl group, forming **5II** (Fig. 4).

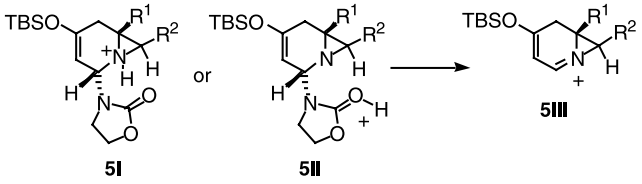


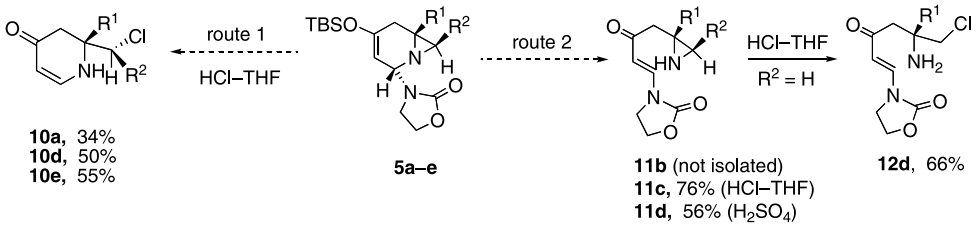
Figure 4.

Reaction of cycloadducts **5a**, **5d**, **5e** with 1 equiv of HCl in THF (15 min–1 h at rt) produced compounds **10a**, **10d**, **10e**. Either **5I**, **5II** or **5III** could have been the precursors in these reactions. The loss of the oxazolidinone from **5II** would form **5III**. Of course, the nucleophilic attack at C-7 is specially enhanced in structures **5I** and **5III**. After the three-membered ring opening, the oxazolidinone would be eliminated together with the silyl group. Reactions of cycloadducts **5b**, **5d** with 1 equiv of H_2SO_4/H_2O in THF formed a different type of product. The absence of a good nucleophilic species preserves the aziridine ring and the products are compounds **11b**, **11d** (Scheme 3). Since the oxazolidinone group is present in the molecule, the initial protonated species should be **5I** to avoid elimination of the oxazolidinone that would be converted into a very good leaving group if the carbonyl was protonated. And so it is reasonable to conclude that the same protonated species **5I**, could be the precursor of both compounds **10** and **11**.

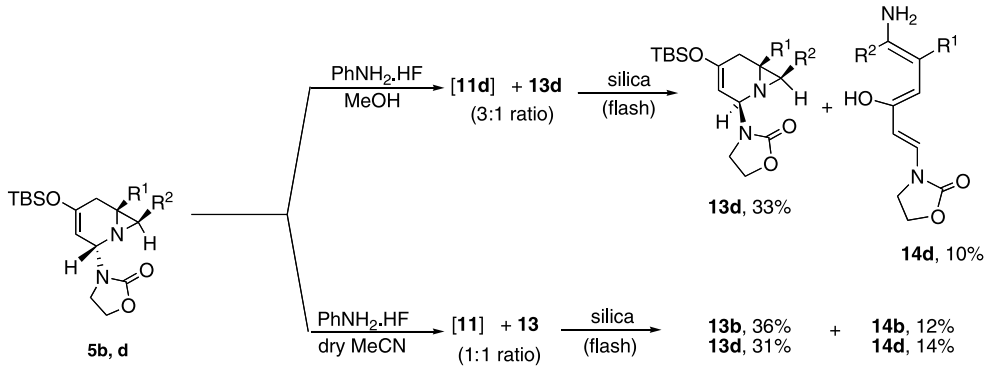
It was proved that compounds **11** are not intermediates in the formation of compounds **10**. When compound **11d** was re-dissolved in THF and treated with HCl in THF, under the same conditions used in route 1 in the formation of compounds **10**, a new compound was formed, isolated and identified as compound **12d**.

Interestingly, reaction of compound **5c** with HCl–THF gives compound **11c** and not the expected structure **10**. The 2,6-dichlorophenyl group attached to C-7 makes the nucleophilic attack of the chloride ion difficult for steric reasons and so route 2 prevails over route 1 giving compound **11c** in 76% yield. Reaction of cycloadduct **5d** with anilinium fluoride in MeOH gave a 3:1 mixture of compounds **11d** and **13d**, according to the ^{1}H NMR spectrum. A long exposure (5–6 h) of this mixture to silica, during flash chromatography in order to separate the two products, showed decomposition of compound **11d**. Compound **13d** was obtained pure in 33% yield together with **14d** (10% yield) after flash chromatography. Compound **14d** is a decomposition product of **11d**. It was confirmed that **11d** is totally converted into **14d**, by treatment of a mixture of **11d** and **13d** with silica, giving **13d** and **14d**. A plausible explanation for the formation of compound **11d** is that being fluoride ion a much worst nucleophile than chloride ion, it fails to attack the aziridine and the alternative process of the six-membered ring opening prevails (route 2, Scheme 3). Product **13d** was formed by treatment of **5d** with anilinium fluoride either in methanol or acetonitrile. A conversion of **5d** into **13d** was also observed in the NMR tube. After 1 h at rt, a solution of **5d** in $CDCl_3$ showed **13d** together with traces of **5d**. Comparing the ^{1}H NMR spectra of crude products in reactions starting from **5d** in dry acetonitrile or **5d** in methanol, it is apparent that the silyl group was preserved to a larger extent in the case of acetonitrile as solvent. This is possibly due to the nucleophilic power of MeOH, towards silicon when used as solvent. Treatment of a solution of **5b** in acetonitrile with anilinium fluoride at rt gave **13b** and **14b** after dry flash chromatography (Scheme 4).

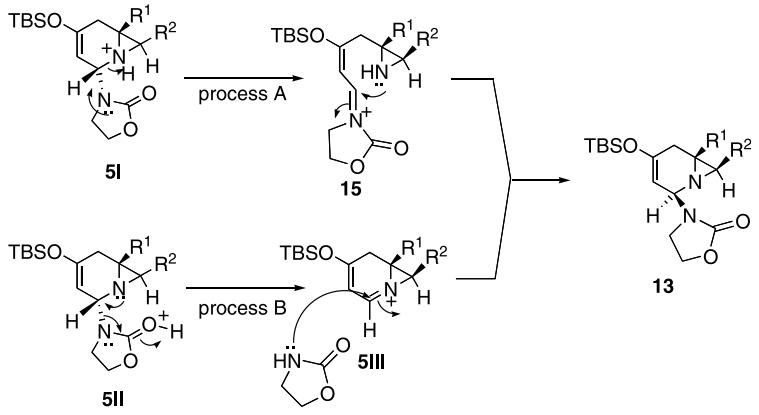
Two mechanistic processes can be envisaged for the inversion of the C-2 stereogenic center that occurred in formation of compounds **13** from adducts **5**: (1) the opening of the six-membered ring by conjugation of the electron pair on the nitrogen atom of the oxazolidinone ring, passing through the intermediate **15** (Scheme 5, process A), followed by an attack of the nitrogen lone pair of electrons in the aziridine to the other face to close the six-membered ring; (2) the elimination of the oxazolidinone followed by its attack from the other side of the six-membered ring (Scheme 5, process B). Indeed process A is more plausible considering either enthalpic (three-membered ring strain would be greater in intermediate **5III** than in **15**) and entropic factors.



Scheme 3.



Scheme 4.



Scheme 5.

An interesting mechanistic point that follows from these reactions is that the desilylation does not have to be concerted with the cleavage of C–N bond. In fact desilylation does not occur in the process of synthesis of compounds **13**. So in the mechanism that assists formation of compound **11** it is also possible that the cleavage of the silyl group occurs after cleavage of the C–N bond in the six-membered ring, being structure **15** the intermediate.

Major features of compounds **10** in ^{1}H NMR spectra are H-6 at $\delta_H \sim 7.0$ ppm and H-5 at $\delta_H \sim 5.0$ ppm with a geminal coupling of 7.2 or 7.8 Hz. The coupling of H-6 to NH is visible in the spectra of compounds **10a** and **10d** (6.9 Hz).

Compounds **11** showed the two ethylenic protons as doublets with a typical vicinal coupling (14.1 or 14.4 Hz), at δ 7.91–7.72 and 5.42–5.80 ppm. The two geminal protons of aziridine ring in compound **11d** are singlets at δ 1.79 and 2.22 ppm. ^{1}H NMR absorptions of compound **12d** are similar to those registered for compound **11d**, except for the new chloromethyl protons at δ 2.90 and 3.25 ppm with a coupling constant of 17.1 Hz that substituted the aziridine protons described as singlets.

^{1}H and ^{13}C NMR spectra of compounds **13** are virtually superimposable on those of their isomers **5**. The major difference is registered in the ^{1}H spectra: the coupling constant of H-2 to H-3 is 4.8–5.1 Hz in compounds **13** and 1.8–2.1 Hz in compounds **5**.

Compounds **14** showed a proton attached to the oxygen atom in the enol moiety at δ_H 10.00 ppm and a trans coupling of the vicinal ethylenic protons ($J=15$ Hz) at δ_H 5.50 and 7.44 ppm.

3. Conclusion

Methods of generating a new type of six-membered ring aminoenones and open chain aminoenones attached to aziridines have been devised. The chiral version of these compounds (both enantiomers) can be envisaged in the future once the parent cycloadducts have been formed and isolated. In reactions between the primary Diels–Alder cycloadducts and anilinium fluoride an interesting phenomenon has been observed: the inversion of C-2 stereogenic center with formation of a new isomer.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), quartets (q) and multiplets (m). J values are recorded in Hz. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Solid samples

were run as DCM mulls, and oils as thin films. Mass spectra were recorded on a VG Autospec M. spectrometer. Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mp) were determined on a Gallenkamp block. Dry flash chromatography was performed on silica gel 60<0.063 mm for column chromatography. Petroleum ether 40–60 °C was distilled before use. Toluene was distilled over sodium.

4.2. Synthesis of cycloadducts

4.2.1. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 5a. The α-azide **1a** (0.25 g; 1.33 mmol) was dissolved in toluene (10 mL) and the solution refluxed for 2.5 h. After cooling the solution to rt 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.34 g; 1.26 mmol) in toluene (10 mL) was added. The reaction mixture was stirred under N_2 at rt for 5 days. After that the solvent was evaporated leaving an oil that was subjected to dry flash chromatography (pet. ether/ether; 2:5). A white solid was obtained and recrystallized from ether/pet. ether (mp 152.5–154.0 °C) to give compound **5a**. Yield (304 mg; 0.71 mmol, 63%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.16 (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, 3×Me), 1.12 (d, *J*=5.7 Hz, 3H, Me), 2.44 (dm, *J*=17.7 Hz, 1H, H-5), 2.52 (q, *J*=5.7 Hz, 1H, H-7), 2.82 (d, *J*=17.7 Hz, 1H, H-5), 3.64 (t, *J*=8.1 Hz, 2H, ox), 4.63 (t, *J*=2.1 Hz, 1H, H-3), 4.37 (dt, *J*=8.1 Hz, 3.3, 2H, ox), 5.90 (br s, 1H, H-2), 7.46–7.63 (m, 3H, Ar), 7.98–8.06 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.4 (Me), 15.2 (Me), 17.8 (C), 25.4 (Me), 29.3 (C-5), 34.4 (C-7), 41.4 (ox), 47.3 (C-6), 62.1 (ox), 65.6 (C-2), 98.2 (C-3), 128.6, 129.4, 133.4, 135.2, 149.4 (C-4), 157.4 (CO, ox), 197.4 (CO). $C_{23}H_{32}N_2O_4Si$ (428.05): calcd C 64.47, H 7.47, N 6.54; found C 64.20, H 7.56, N 6.47.

4.2.2. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-ethyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 5b. To a solution of 2*H*-azirine **2b** (420 mg; 2.42 mmol) in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.45 g; 1.68 mmol) dissolved in toluene (10 mL). The reaction mixture was stirred under N_2 at rt for 4 days. After that the solvent was evaporated and the crude subjected to dry flash chromatography (pet. ether/diethyl ether; 1:2). A white solid **5b** was obtained (mp 141.0–143.5 °C). Yield (434 mg; 0.98 mmol; 58%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.18 (s, 3H, Me), 0.90 (s, 9H, 3×Me), 0.97 (t, *J*=7.2 Hz, 3H, Me), 1.17–1.30 (m, 1H, C*H*H), 1.37–1.48 (m, 1H, CH*H*), 2.36–2.44 (m, 2H, H-5+H-7), 2.84 (d, *J*=18.0 Hz, 1H, H-5), 3.70 (m, 2H, ox), 4.34 (t, *J*=7.5 Hz, 2H, ox), 4.69 (t, *J*=1.8 Hz, 1H, H-3), 5.79 (br s, 1H, H-2), 7.43–7.57 (m, 3H, Ar), 8.03 (d, *J*=7.2 Hz, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.5 (Me), 11.4 (Me), 17.8 (C), 23.5 (Me), 25.4 (Me), 29.3 (C-5), 40.9 (C-7), 42.1 (ox), 47.5 (C-6), 62.0 (ox), 65.7 (C-2), 98.2 (C-3), 128.5, 129.4, 133.3, 135.3, 149.0 (C-4), 157.3 (CO, ox), 197.7 (CO). $C_{24}H_{34}N_2O_4Si$ (442.62): calculated C 65.12, H 7.74, N 6.33; found C 64.78, H 7.63, N 6.39.

4.2.3. Methyl 4-(*tert*-butyldimethylsilyloxy)-7-(2,6-dichlorophenyl)-2-(2-oxooxazolidin-3-yl)-1-azabicyclo[4.1.0]hept-3-en-6-carboxylate 5c. To a solution of 2*H*-azirine **2c** (420 mg, 1.72 mmol) in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)-oxazolidin-2-one **3** (0.85 g; 3.16 mmol) dissolved in toluene (10 mL). The reaction mixture was stirred under N_2 at rt over 4 days. After that the solvent was evaporated and a white solid **5c** was formed (mp 190.5–191.0 °C). Yield (865 mg; 1.69 mmol, 58%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.22 (s, 3H, Me), 0.23 (s, 3H, Me), 0.96 (s, 9H, 3× Me), 2.85 (dt, *J*=18.6, 2.1 Hz, 1H, H-5), 3.00 (dd, *J*=18.6, 1.2 Hz, 1H, H-5), 3.38 (s, 3H, OMe), 3.64 (s, 1H, H-7), 3.77 (t, *J*=8.1 Hz, 2H, ox), 4.37 (m, 2H, ox), 4.61 (t, *J*=2.1 Hz, 1H, H-3), 5.80 (br s, 1H, H-2), 7.08–7.15 (m, 1H, Ar), 7.25–7.30 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.3 (Me), −4.4 (Me), 17.9 (C), 25.5 (Me), 27.7 (C-5), 41.9 (C-7), 42.3 (ox), 43.5 (C-6), 52.2 (Me), 61.9 (ox), 66.5 (C-2), 96.9 (C-3), 128.4, 128.9, 130.8, 135.6, 150.3 (C-4), 157.4 (CO, ox), 170.1 (CO). $C_{23}H_{28}Cl_2N_2O_5Si$ (511.09): calculated C 54.00, H 5.48, N 5.48; found C 53.80, H 5.85, N 5.66.

4.2.4. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 5d. The α-azide **1d** (1.80 g; 8.86 mmol) was dissolved in toluene (200 mL) and heated under reflux for 5 h. After cooling the solution to rt 3-(3-(*tert*-butyldimethylsilyloxy)-buta-1,3-dienyl)oxazolidin-2-one **3** (1.25 g; 4.64 mmol) was added, dissolved in toluene (15 mL). The reaction mixture was stirred under N_2 at rt, for 4.5 days. After that the solvent was evaporated to give a brown oil that was purified by dry flash chromatography (pet. ether/ether; gradient polarity). The product **5d** was obtained as an oil. Yield (768 mg; 1.73 mmol; 37%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.19 (s, 6H, 2×Me); 0.94 (s, 9H, 3×Me); 2.27 (s, 1H, H-7); 2.28 (s, 1H, H-7); 2.60 (d, *J*=18.0 Hz, 1H, H-5); 2.85 (br d, *J*=18.0 Hz, 1H, H-5), 3.60 (q, *J*=8.4 Hz, 1H, ox), 3.75 (q, *J*=8.4 Hz, 1H, ox), 4.35–4.42 (m, 2H, ox), 4.50 (t, *J*=2.1 Hz, 1H, H-3), 5.14 (d, *J*=12.3 Hz, 1H, OCH_2), 5.31 (d, *J*=12.3 Hz, 1H, OCH_2), 5.67 (br s, 1H, H-2), 7.39 (br s, 5H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.4 (Me), 17.8 (C), 25.4 (Me), 27.3 (C-5), 29.5 (C-7), 36.7 (C-6), 41.1 (ox), 62.0 (ox), 65.8 (C-2), 67.2 (CH_2), 96.7 (C-3), 128.3, 128.32, 128.5, 135.5, 150.1 (C-4), 157.3 (CO, ox), 171.2 (CO). HRMS (FAB): calcd 445.2159 [M+1]; found 445.2158.

4.2.5. Ethyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-6-(pyridin-2-yl)-1-aza-bicyclo[4.1.0]hept-3-en-7-carboxylate 5e. To the 2*H*-azirine **2e** (0.36 g; 1.87 mmol) solubilized in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.35 g; 1.87 mmol) solubilized in toluene (10 mL). The reaction mixture was stirred under N_2 at 75–80 °C for 2.5 days. After that the solvent was evaporated and the crude obtained was purified by dry flash-cromatography (pet. ether/diethyl ether; gradient polarity), to give compound **5e** as an oil. Yield (248 mg; 0.54 mmol; 29%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, 3×Me), 2.46 (dt, *J*=18.0, 2.4 Hz, 1H, H-5), 3.27 (dd, *J*=18.0, 0.9 Hz, 1H, H-5), 3.27 (s, 1H, H-7), 3.60–3.75 (m, 2H, ox), 3.88–4.00 (m, 2H, CH_2), 4.33–4.41 (m, 2H, ox), 4.58 (t, *J*=2.1 Hz, 1H, H-3), 5.82 (br s, 1H, H-2), 7.14–7.19 (m, 1H, Ar), 7.62–7.66 (m, 2H, Ar), 8.48–8.51 (m, 1H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.7 (Me), −4.4 (Me), 13.8 (Me), 17.8 (C), 25.4 (Me), 31.2 (C-5), 40.1

(C-7), 40.9 (ox), 47.2 (C-6), 60.9 (CH_2), 62.2 (ox), 65.9 (C-2), 97.1 (C-3), 122.4, 122.5, 136.3, 148.7, 150.5 (C-4), 157.4, 157.8, 168.1 (CO). HRMS (FAB): calcd 440.2268 [M+1]; found 440.2279.

4.2.6. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 8d and 9d. The α-azide **1d** (0.71 g; 3.46 mmol) was dissolved in toluene (100 mL) and heated under reflux for 5 h. (*R*)-3-(3-(*tert*-Butyldimethylsiloxy)-buta-1,3-dienyl)-4-phenyloxazolidin-2-one **4** (0.60 g; 1.73 mmol) was added after cooling the solution to rt. The reaction mixture was stirred under N_2 at rt, for 5 days. After that the solvent was evaporated to give a brown oil that was purified by dry flash chromatography (pet. ether/ether; gradient polarity). A first fraction was obtained as a thick oil identified as compound **8d**. Yield (370 mg; 0.71 mmol; 41%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=-0.27$ (s, 3H, Me), −0.12 (s, 3H, Me), 0.78 (s, 9H, 3×Me), 2.10 (s, 1H, H-7), 2.27 (s, 1H, H-7), 2.42 (dd, $J=17.7$, 0.6 Hz, 1H, H-5), 2.71 (dd, $J=17.7$, 1.2 Hz, 1H, H-5), 4.07 (t, $J=2.2$ Hz, 1H, H-3), 4.10 (dd, $J=8.7$, 6.3 Hz, 1H, ox), 4.67 (t, $J=8.7$ Hz, 1H, ox), 5.06 (dd, $J=8.7$, 6.3 Hz, 1H, ox), 5.12 (d, $J=12.6$ Hz, 1H, OCH_2), 5.28 (d, $J=12.6$ Hz, 1H, OCH_2), 5.78 (br s, 1H, H-2), 7.36 (br s, 10H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-5.0$ (Me), −4.8 (Me), 17.6 (C), 25.3 (Me), 27.4 (C-5), 29.6 (C-7), 36.6 (C-6), 57.4 (ox), 67.0 (C-2), 67.2 (OCH_2), 70.9 (ox), 97.4 (C-3), 126.9, 128.2, 128.3, 128.5, 129.0, 129.2, 135.4, 139.6, 148.4 (C-4), 158.4 (CO, ox), 171.1 (CO). HRMS (FAB): calcd 521.24717 [M+1]; found 521.24812.

A second fraction was obtained pure, as thick oil identified as compound **9d**. Yield (0.375 g; 0.72 mmol; 42%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=0.18$ (s, 3H, Me), 0.19 (s, 3H, Me), 0.92 (s, 9H, 3×Me), 2.00 (s, 1H, H-7), 2.48 (s, 1H, H-7), 2.52 (d, $J=17.7$ Hz, 1H, H-5), 2.70 (d, $J=17.7$ Hz, 1H, H-5), 4.10 (t, $J=8.4$ Hz, 1H, ox), 4.65 (t, $J=8.4$ Hz, 1H, ox), 4.79 (t, $J=2.1$ Hz, 1H, H-3), 4.84 (br s, 1H, H-2), 5.27 (t, $J=8.4$ Hz, 1H, ox), 5.13 (d, $J=12.6$ Hz, 1H, OCH_2), 5.20 (d, $J=12.6$ Hz, 1H, OCH_2), 7.30–7.41 (m, 10H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-4.7$ (Me), −4.4 (Me), 17.8 (C), 25.5 (Me), 27.4 (C-5), 30.4 (C-7), 37.7 (C-6), 60.0 (ox), 66.6 (C-2), 66.9 (OCH_2), 70.0 (ox), 98.2 (C-3), 127.2, 127.9, 128.1, 128.2, 128.5, 128.6, 129.0, 129.2, 135.6, 138.3, 148.0 (C-4), 157.5 (CO, ox), 171.6 (CO). HRMS (ESI): calcd 543.2291 [M+Na]; found 543.2292.

4.3. Synthesis of hydrolysis products

4.3.1. 2-Benzoyl-2-(1-chloroethyl)-2,3-dihydropyridin-4-(1*H*)-one 10a. To a solution of the adduct **5a** (228 mg; 0.53 mmol) in THF (5 mL) was added dropwise a solution of HCl (45 μL; 0.53 mmol) in THF (3 mL) at 0 °C and left at rt for 15 min. The solvent was removed and the residue re-dissolved in DCM (25 mL). The solution was washed with water (25 mL) and the organic phase dried over $MgSO_4$ and evaporated. The crude material was subjected to dry flash chromatography (ether) to give a pale yellow oil identified as compound **10a**. Yield (68 mg; 0.18 mmol; 34%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.64$ (d, $J=6.6$ Hz, 3H, Me), 2.85 (d, $J=17.1$ Hz, 1H, H-3), 3.08 (d, $J=17.1$ Hz, 1H, H-3), 4.69 (q, $J=6.6$ Hz, 1H, H-1′), 5.07 (dd, $J=7.8$, 0.9 Hz, H-5), 5.95 (br d, $J=5.1$ Hz, 1H, NH), 7.32 (dd, $J=7.8$, 6.3 Hz, 1H, H-6), 7.40–7.80 (m, 5H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=19.7$ (Me), 41.6 (C-3), 61.9 (C-1′), 71.5 (C-2), 99.0 (C-5), 128.2, 128.5, 132.5, 135.5, 150.6 (C-6), 187.9 (CO), 200.3 (CO). HRMS (FAB): calcd 266.0762 [M+1]; found 266.0755.

4.3.2. Benzyl 2-(chloromethyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 10d. To a solution of the adduct **5d** (230 mg; 0.52 mmol) in THF (5 mL) was added dropwise a solution of HCl (43 μL; 0.52 mmol) in THF (3 mL) at 0 °C. Then the mixture was allowed to reach rt and was stirred for 1 h. After this time the solvent was partially evaporated, aqueous 10% $NaHCO_3$ (20 mL) was added and the mixture was stirred for 15 min at rt. The organic phase was separated and the aqueous phase washed with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$, and the solvent evaporated to give a brown oil. Dry flash chromatography (pet. ether/ether; polarity gradient) gave a white solid **10d** (mp 106–107 °C).Yield (67 mg; 25.5 mmol; 50%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.66$ (d, $J=16.5$ Hz, 1H, H-3), 2.94 (d, $J=16.5$ Hz, 1H, H-3), 3.81 (d, $J=11.1$ Hz, 1H, H-1′), 3.92 (d, $J=11.1$ Hz, 1H, H-1′), 5.08 (d, $J=7.8$ Hz, 1H, H-5), 5.23 (s, 2H, OCH_2), 5.85 (br s, 1H, NH), 7.21 (dd, $J=7.8$, 6.3 Hz, 1H, H-6), 7.34–7.37 (m, 5H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=42.1$ (C-3), 46.6 (C-1′), 64.2 (C-2), 68.4 (OCH_2), 99.9 (C-5), 128.3, 128.7, 128.72, 134.5, 149.3 (C-6), 169.76 (CO), 188.5 (CO). HRMS (FAB): calcd 280.0740 [M+1]; found 280.0745.

4.3.3. Ethyl 2′-chloro-2-(4-oxo-2-(pyridin-2-yl)-1,2,3,4-tetrahydropyridin-2-yl)acetate 10e. To a solution of **5e** (248 mg; 0.54 mmol) in THF (2 mL) was added dropwise at 0 °C HCl (45 μL; 0.54 mmol) dissolved in THF (3 mL). Then the mixture was allowed to reach rt and was stirred for 1 h. After this time the solvent was partially evaporated, 10% aqueous $NaHCO_3$ (20 mL) was added and stirred for 15 min at rt. The organic phase was separated and the aqueous phase washed with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$ and the solvent was evaporated to give a yellow oil that was purified by dry flash chromatography (ether) to afford an oil identified as compound **10e**. Yield (87 mg; 0.29 mmol; 55%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.22$ (t, $J=7.5$ Hz, 3H, Me), 3.10 (d, $J=16.5$ Hz, 1H, H-3), 3.22 (d, $J=16.5$ Hz, 1H, H-3), 4.15 (m, 2H, OCH_2), 5.09 (dd, $J=7.8$, 0.9 Hz, 1H, H-5), 5.09 (s, 1H, H-1′), 6.54 (br d, $J=6.0$ Hz, 1H, NH), 7.24–7.32 (m, 2H, Ar), 7.43 (dd, $J=7.8$, 0.9 Hz, 1H, H-6), 7.73 (dt, $J=7.5$, 1.8 Hz, 1H, Ar), 8.57 (dm, $J=4.5$ Hz, 1H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=13.8$ (Me), 43.2 (C-3), 61.6 (C-1′), 62.5 (OCH_2), 64.4 (C-2), 99.9 (C-5), 121.1 (CH), 123.3 (CH), 136.8 (CH), 149.0 (C), 149.1 (C-6), 156.6 (C), 166.8 (CO), 189.6 (CO). HRMS (FAB): calcd 295.0849 [M+1]; found 295.0853.

4.3.4. Attempt to the synthesis of (*E*)-3-(4-(2-benzoyl-3-ethylaziridin-2-yl)-3-oxobut-1-enyl)oxazolidin-2-one 11b. To a solution of the adduct **5b** (0.13 g; 0.29 mmol) in THF (5 mL) was added dropwise at 0 °C H_2SO_4 (16 μL; 0.29 mmol) and water (3 equiv; 25 μL). The mixture was

stirred for 30 min at 0 °C and another 30 min at rt. The solvent was removed, the residue re-dissolved in DCM, washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$ and the solvent evaporated to give a yellow solid. The crude product showed to be mainly compound **11b** by ^1H NMR. ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.03$ (t, $J=7.2$ Hz, 3H, Me), 1.25 (m, 1H, CH_2), 1.52 (m, 1H, CH_2), 1.95 (br s, 1H, NH), 2.33 (t, $J=5.7$ Hz, 1H, H-3), 2.75 (d, $J=16.8$ Hz, 1H, H-1′), 3.60 (d, $J=16.8$ Hz, 1H, H-1′), 3.70 (t, $J=7.2$ Hz, 2H, CH_2, ox), 4.50 (t, $J=7.2$ Hz, 2H, CH_2, ox), 5.37 (d, $J=14.1$ Hz, 1H, H-3′), 7.41–7.54 (m, 3H, Ar), 7.72 (d, $J=14.1$ Hz, 1H, H-4′), 7.89 (d, $J=6.9$ Hz, 2H, Ar). HRMS (FAB): calcd 328.1423 [M^+]; found 328.1434.

Dry flash chromatography (ether/DCM) gave a pure yellow solid, compound **14b** [mp 160 °C (dec)]. Yield (22 mg; 0.07 mmol; 23%). A second chromatography fraction was a mixture of at least three compounds, the original **5b**, compound **11b** and an unknown product. Re-dissolution of a portion of this fraction (20 mg) in DCM (5 mL) and treatment with silica for 1 h gave a mixture of compounds **11b** and **14b** as an oil after removal of silica and evaporation to dryness. Yield (15 mg). Compound **14b**: ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.31$ (3H, Me), 3.05 (q, 2H, $J=7.2$ Hz), 3.82 (t, 2H, $J=7.8$ Hz, ox), 4.53 (t, 2H, $J=8.4$ Hz, ox), 5.50 (d, 1H, $J=15.0$ Hz), 6.25 (d, 1H, $J=2.7$ Hz), 7.44 (d, 1H, $J=15.0$ Hz), 7.44–7.51 (m, 3H, Ar), 7.80 (m, 2H, Ar), 10.00 (br s, 1H, OH). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=13.9$ (Me), 20.9 (CH_2), 42.4 (CH_2), 62.6 (CH_2), 102.7 (CH), 111.6 (CH), 119.5 (C), 120.3 (CH), 125.9 (C), 127.9 (CH), 129.0 (CH), 131.0 (CH), 140.8 (C), 144.0 (C), 155.9 (CO, ox), 191.8 (CO).

4.3.5. (*E*)-Methyl 3-(2,6-dichlorophenyl)-2-(2-oxo-4-(2-oxooxazolidin-3-yl)but-3-enyl)aziridine-2-carboxylate 11c. To a solution of the adduct **5c** (250 mg; 0.53 mmol) in THF (5 mL) was added dropwise at 0 °C HCl (44 μL; 0.53 mmol) diluted in THF (3 mL). The mixture was allowed to reach rt and stirred for 1 h. The solvent was partially evaporated and 10% aqueous $NaHCO_3$ (20 mL) was added. The mixture was stirred for 15 min and then extracted with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$ and evaporated to give an oil that was purified recrystalization (DCM/pet. ether) to give a colorless solid (mp 162.5—164.5 °C) identified as compound **11c**. Yield (142 mg; 0.40 mmol; 76%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.65$ (d, $J=17.4$ Hz, 1H, H-1′), 2.95 (br s, 1H, NH), 3.16 (s, 1H, H-3), 3.51 (s, 3H, OMe), 3.82 (t, $J=7.8$ Hz, 2H, ox), 3.94 (d, $J=17.4$ Hz, 1H, H-1′), 4.56 (t, $J=7.8$ Hz, 2H, ox), 5.57 (d, $J=14.4$ Hz, 1H, H-3′), 7.17 (d, $J=8.1$ Hz, 1H, Ar), 7.28 (m, 2H, Ar), 7.92 (d, $J=14.4$ Hz, 1H, H-4′). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=42.1$ (ox), 42.8 (C-2), 43.4 (C-1′), 44.8 (C-3), 52.7 (OMe), 62.6 (ox), 109.6 (C-3′), 128.0, 129.3, 131.3 (C), 135.7 (C) 137.6 (C-4′), 154.7 (CO, ox), 170.9 (CO), 195.0 (CO). HRMS (FAB): calcd 399.0515 [M+1]; found 399.0514.

4.3.6. (*E*)-Benzyl 3-(2,6-dichlorophenyl)-2-(2-oxo-4-(2-oxooxazolidin-3-yl)but-3-enyl)aziridine-2-carboxylate 11d. To a solution of the adduct **5d** (0.25 g; 0.55 mmol) in THF (5 mL), H_2SO_4 (30 μL; 0.55 mmol) and water (3 equiv; 27 μL) were added dropwise at 0 °C. The mixture was stirred at rt for 1 h. The solvent was removed, the residue re-dissolved in DCM, washed with 10% aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$ and the solvent evaporated to give an oil. A fast dry flash chromatography (MeCN) gave a yellow oil identified as compound **11d**. Yield (101 mg; 0.31 mmol; 56%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.79$ (s, 1H, H-3), 2.22 (s, 1H, H-3), 2.75 (d, $J=17.1$ Hz, 1H, H-1′), 3.23 (d, $J=17.1$ Hz, 1H, H-1′), 3.66 (dt, 2H, $J=8.1$, 2.4 Hz, ox), 4.47 (t, $J=8.1$ Hz, 2H, ox), 5.12 (s, 2H, OCH_2), 5.45 (d, 1H, $J=14.1$ Hz, H-3′), 7.27–7.32 (m, 5H, Ar), 7.79 (d, $J=14.1$ Hz, 1H, H-4′). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=32.9$ (C-3), 35.1 (C-2), 41.9 (ox), 42.9 (C-1′), 62.5 (ox), 67.5 (OCH_2), 109.1 (C-3′), 128.1, 128.2, 128.4, 135.1 (C), 137.4 (C-4′), 154.5 (CO, ox), 172.7 (CO) 195.1 (CO). HRMS (FAB): calcd 331.1294 [M+1]; found 331.1298.

4.3.7. (*E*)-Benzyl 2-amino-2-(chloromethyl)-4-oxo-6-(2-oxooxazolidin-3-yl)hex-5-enoate 12d. To a solution of the adduct **11d** (45 mg; 0.14 mmol) in THF (2 mL) was added dropwise at 0 °C HCl (11.5 μL; 0.14 mmol) diluted in THF (1 mL). The mixture was allowed to reach rt and stirred for 1 h. The solvent was partially evaporated and 10% aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with DCM (3×5 mL). The organic extracts were combined and washed with water (10 mL), dried over $MgSO_4$ and evaporated to give a clean yellow oil that was identified as compound **12d**. Yield (33 mg; 0.90 mmol; 66%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.41$ (br s, 2H, NH_2), 2.91 (d, $J=17.1$ Hz, 1H, H-3), 3.26 (d, $J=17.1$ Hz, 1H, H-3), 3.67–3.75 (m, 4H, ox +H-1), 4.53 (t, $J=8.1$ Hz, 2H, ox), 5.17 (s, 2H, OCH_2), 5.44 (d, 1H, $J=14.1$ Hz, H-5), 7.31–7.36 (m, 5H, Ar), 7.84 (d, $J=14.1$ Hz, 1H, H-6). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=41.9$ (ox), 46.3 (C-3), 50.9 (CH_2Cl), 60.4 (C), 62.6 (ox), 67.6 (OCH_2), 109.1 (C-5), 128.3, 128.5, 128.6, 135.3 (C), 138.1 (C-6), 154.5 (CO, ox), 173.4 (CO) 195.3 (CO). HRMS (ESI): calcd 389.0889 [M+Na]; found 389.0875.

4.3.8. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-ethyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 13b. To a solution of the adduct **5b** (260 mg, 0.59 mmol) in dry CH_3CN (10 mL) was added anilinium fluoride in one portion at 0 °C. The reaction mixture was stirred for 45 min at rt. The solvent was removed and the residue re-dissolved in DCM (30 mL). The organic phase was washed with 10% aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated to give a crude material. This product was subjected to dry flash chromatography (pet. ether/ether; 1:3) giving a pure solid (130.5–131.5 °C) identified as compound **13b**. Yield (95 mg; 0.21 mmol, 36%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=0.13$ (s, 3H, Me), 0.17 (s, 3H, Me), 0.89 (s, 9H, 3× Me), 0.98–1.06 (m, 4H, Me+C*H*H), 1.55–1.63 (m, 1H, CH*H*), 2.25 (dd, $J=8.4$, 3.0 Hz, 1H, H-7), 2.36 (dt, $J=18.0$, 2.1 Hz, 1H, H-5), 2.81 (dd, $J=18.0$, 2.1 Hz, 1H, H-5), 3.37 (q, $J=7.8$ Hz, 1H, ox), 4.05–4.14 (m, 1H, ox), 4.29–4.38 (m, 1H, ox), 4.43–4.52 (m, 1H, ox), 4.64–4.66 (m, 1H, H-3), 5.59–5.62 (m, 1H, H-2), 7.56–7.61 (m, 2H, Ar), 7.65–7.71 (m, 1H, Ar), 7.99–8.02 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-4.6$ (Me), −4.4 (Me), 11.7 (Me), 17.9 (C), 24.0 (Me), 25.4 (Me), 29.8 (C-5), 39.5 (ox), 44.2 (C-7), 51.5

(C-6), 62.3 (ox), 67.4 (C-2), 96.4 (C-3), 128.8, 129.2, 133.7, 134.9, 149.0 (C-4), 157.7 (CO, ox), 196.6 (CO). HRMS (FAB): calcd 443.2366 [M+1]; found 443.2361.

A second fraction (ether) gave a white solid (mp>160 °C (dec)) identified as compound **14b**. Yield (22 mg; 0.067 mmol; 12%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=1.31 (t, *J*=7.2 Hz, 3H, Me), 3.05 (q, *J*=7.2 Hz, 2H, CH_2), 3.82 (t, *J*=7.8 Hz, 2H, ox), 4.53 (t, *J*=8.4 Hz, 2H, ox), 5.50 (d, *J*=15.0 Hz, 1H), 6.25 (d, *J*=2.7 Hz, 1H), 7.44 (d, *J*=15.0 Hz, 1H), 7.44–7.51 (m, 3H, Ar), 7.80 (m, 2H, Ar), 10.00 (br s, 1H, OH). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=13.9 (Me), 20.9 (CH_2), 42.4 (CH_2 ox), 62.6 (CH_2 ox), 102.7 (CH), 11.6 (CH), 119.5 (C), 120.3 (CH), 125.9 (C), 127.9 (CH), 129.0 (CH), 131.0 (CH), 140.8 (C), 144.0 (C), 155.9 (CO, ox), 191.8 (CO). HRMS (FAB): calcd 329.1501 [M+1]; found 329.1492.

4.3.9. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 13d. *Method 1*. To a solution of the adduct **5d** (488 mg; 1.09 mmol) in dry MeCN (10 mL) was added anilinium fluoride (125 mg, 1.1 mmol) in one portion at 0 °C. The reaction mixture was stirred at rt for 45 min. The solvent was then removed and the residue re-dissolved in DCM (25 mL). The organic phase was washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated. A yellow solid was obtained and subjected to dry flash chromatography (ether) to give a pure solid (mp 104–106 °C), identified as compound **13d**. Yield (0.15 g; 0.34 mmol; 31%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.16 (s, 3H, Me), 0.92 (s, 9H, 3×Me), 1.91 (s, 1H, H-7), 2.40 (s, 1H, H-7), 2.56 (dd, *J*=18.3, 1.8 Hz, 1H, H-5), 2.94 (d, *J*=18.3 Hz, 1H, H-5), 3.40 (m, 2H, ox), 4.26 (t, *J*=7.8 Hz, 2H, ox), 4.60 (dd, *J*=5.1, 2.7 Hz, 1H, H-3), 5.13 (d, *J*=12.6 Hz, 1H, OCH_2), 5.51 (dt, *J*=5.1, 1.5 Hz, 1H, H-2), 5.62 (d, *J*=12.6 Hz, 1H, OCH_2), 7.35–7.55 (m, 5H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=−4.56 (Me), −4.58 (Me), 17.9 (C), 25.4 (Me), 26.8 (C-5), 31.1 (C-7), 49.8 (ox), 40.6 (C-6), 62.0 (ox), 67.0 (OCH_2), 67.2 (C-2), 95.0 (C-3), 128.0, 128.3, 128.5, 135.5 (C), 149.6 (C-4), 157.5 (CO, ox), 171.0 (CO). HRMS (FAB): calcd 445.2159 [M+1]; found 445.2158. An impure sample of compound **14d** was also obtained. Some peaks of its ^{1}H NMR spectrum are registered: ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=3.82 (t, 2H, *J*=8.4 Hz, ox), 4.53 (t, 2H, *J*=8.4 Hz, ox), 5.29 (s, 2H), 5.70 (d, 1H, *J*=15.0 Hz), 6.99 (s, 1H), 7.19 (d, 1H, *J*=15.0 Hz), 7.32–7.44 (m, 5H, Ar), 8.95 (br s, 1H, OH). HRMS (ESI): calcd 353.1114 [M+Na]; found 353.1115.

Method 2. To a solution of the adduct **5d** (100 mg; 0.23 mmol) in MeOH (5 mL), anilinium fluoride (26 mg; 0.23 mmol) was added in one portion at 0 °C. The reaction mixture was stirred at rt for 45 min. The solvent was then removed and the mixture re-dissolved in DCM (30 mL), washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated giving a yellow oil. Dry flash chromatography (ether) gave a pure solid, compound **13d**, by comparation with product obtained in method 1. Yield (33 mg; 0.08 mmol; 33%). A second fraction (ether/DCM; 9:1) was obtained and identified by ^{1}H NMR as compound **14d** (10 mg; 0.02 mmol; 10%).

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