Pergamon

Tetrahedron 54 (1998) 11501–11516

TETRAHEDRON

Stereoselective Synthesis of Racemic α-Amino-Acid Derivatives with a β-Lactam Skeleton : Application of the Staudinger Reaction to Chiral Imines of Methyl Glyoxylate

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Received 21 April 1998; accepted 14 July 1998

Abstract: Selected imines of methyl glyoxylate act as good partners in the Staudinger cycloaddition reaction with a series of substituted ketenes. The *cis* stereoselectivity is almost complete with electron-donor substituted ketenes, but the asymmetric induction is low when imines derived from chiral 1-aryl-ethylamines are used.

INTRODUCTION

Linear oligopeptides are conformationally flexible in solution and only strictly adopt well defined three dimensional structures when they bind to their receptors or to the active site of enzymes.[1] The incorporation of peptidomimetic substitutes in bioactive molecules has been the subject of intensive research over the last fifteen years.[2] The replacement of the proteinogenic amide bond by a conformationally limited adequate mimic, does not only impose specific spacial orientations to the substituents and functionalities carried by the framework, but also enables the resulting pseudopeptides to resist to degradation by proteinases. Consequently, beyond a better information on active conformations of peptides, we can expect to increase affinities, metabolic stabilities and bioavailabilities.[3]

Freidinger and coll. were first to use γ-, δ- and ε-lactams as conformationally restricted dipeptide surrogates of glycyl-dipeptides.[4] Subsequent studies have demonstrated the potential uses of these lactams as conformational restraints in peptide mimetics.[5] However, the β-lactam skeleton has been exceptionally used in this context to mimic, for example, the unusual β-turn possessing a central *cis* amide bond.[6]

As part of our study on the use of *C*-alkoxycarbonyl-*N*-alkylimines as cycloaddition partners, we focused our interest on the utilization of the Staudinger reaction for the asymmetric synthesis of α-amino-acid derivatives bearing a β-lactam skeleton. We have previously shown that the aza-Diels-Alder strategy could be successfully applied to the asymmetric synthesis of six-membered ring α-amino-acid derivatives obtained from the chiral imine, resulting from the condensation of 1-phenylethylamine with methyl glyoxylate, and a series of dienes.[7]

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0040-4020/98/$ - see front matter
PII: S0040-4020(98)00683-8

The [2 + 2] cycloaddition reaction of ketenes to imines, known as the Staudinger reaction,[8] is essential for the synthesis of the azetidinone ring, both for basic research and industry. In recent years, various asymmetric adaptations of this reaction have been developed by using a combination of either chiral ketenes and achiral imines, achiral ketenes and chiral imines, or chiral ketenes and chiral imines.[9]

We report here our results obtained by opposing a series of ketenes substituted by electrodonating groups (such as chlorine atom and ethyl-, phenyl-, methoxy-, benzyloxy- or phthalimido-groups) to various imines of methyl glyoxylate possessing a chiral moiety such as an α-arylethyl group.

RESULTS AND DISCUSSION

Throughout our study on the asymmetric synthesis of α-amino-acids,[10] the choice of the imine was made upon two criteria : *i*) the nitrogen atom of the cycloadduct should carry an easily removable substituent to facilitate its later use in the construction of peptidic bonds, *ii*) the chirality of the imine should be borne by an atom close to the π-system involved in the cycloaddition reaction to obtain the best asymmetric induction during the reaction. We have studied successively the reactivity of four imines of methyl glyoxylate, derived from the following amines: 4-methoxyphenylamine [PMP-NH_2], *(±)*-1-phenylethylamine [Me(Ph)CH-NH_2], *(±)*-1-(naphthalen-1-yl)-ethylamine [Me(Naph)CH-NH_2], and *(R)*-1-(4-methoxyphenyl)-ethylamine [Me(PMP)CH-NH_2].

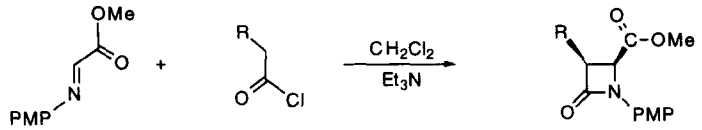
The 4-methoxyphenyl group (PMP) behaves towards the nitrogen atom as a protective group which can easily be removed. Thus, β-lactams synthesized from *p*-anisidine derived imines can be deprotected, without any ring alteration, under mild reaction conditions using either ammonium persulfate,[11] or cerium and ammonium nitrate [12] as oxidative agents. 1-Phenylethylamine is a chiral auxiliary and its two enantiomers are readily available. This advantage had been underlined by Thomas [13] and Teutsch [14] who suggested that it should be used in a straightforward process for β-lactam skeleton construction. 1-(Naphthalen-1-yl)-ethylamine, though less easily accessible than 1-phenylethylamine, is expected to induce a similar asymmetry. After formation of the β-lactam ring, α-phenylethyl and α-naphthylethyl groups should be cleavable either by oxidation using potassium persulfate[13-15] or by reduction using lithium[16] or sodium.[13] 1-(4-Methoxyphenyl)-ethylamine, the ether function of which increases oxidisability, is likely to improve the general yield of the deprotection reaction[17] and to retain the strengths of the previously described amines.

Consequently, for this study, we have chosen to use imines **1a-d** and ketenes obtained from acid chlorides **2a-h**. In each case, the ketenes were generated *in situ* by adding triethylamine to a solution of acid chloride **2** containing the preformed imine. The choice of the solvent, temperature and addition reaction time have been optimized. All these data are mentioned in Tables 1 and 2. The reaction is simple to implement. Indeed, it is possible to perform the successive chemical steps, imine synthesis and cycloaddition reaction, in the same solvent. As an example, the 2-methoxycarbonyl-3-chloro-azetidinone **3a** was prepared in methylene chloride, in the presence of 3-Å molecular sieves : 3 equiv of triethylamine then 3.5 equiv of chloroacetyl chloride were added successively, following the temperatures and the reaction times indicated in table 1, to equimolecular quantities of *p*-anisidine and methyl glyoxylate.[18]

Cycloaddition reactions with the imine **1a** *derived from p-anisidine.*

Chloroacetyl chloride **2a** (Table 1, entry 1) was added dropwise to a stirred solution of imine **1a** and triethylamine in methylene chloride at room temperature. The mixture was then refluxed for 17 h. *Cis* cycloadduct **3a** was obtained in 46% yield with total stereoselectivity. In a similar manner, phenylacetyl chloride **2b** (entry 2) gave *cis* **3b** in 45% yield, at room temperature. Starting from methoxyacetyl chloride **2c** (entry 3), the reaction was performed in refluxing benzene, over 15 h, and gave the expected cycloadducts **3c** (60% yield) as a 83:17 mixture of isolable *cis:trans* isomers. The relative stereochemistry of these compounds was

Table 1. Experimental Conditions and Results of [2+2] Cycloadditions Involving Achiral *C*-Methoxycarbonyl-imines.



1a **2a-c** **3a-c**

entry	2	R	Et_3N eq	2 eq	addition t_{min}/T°C	reaction t_{min}/T°C	3[a]	Yield %	*cis:trans*[b]
1	**2a**	Cl	3.5	3	15'/20°	17h/40°	**3a**	46	*cis*
2	**2b**	Ph	3.5	3	5'/20°	21h/20°	**3b**	45	*cis*
3[c]	**2c**	MeO	2	1.5	15'/20°	15h/80°	**3c**	60	*83:17*

a) Racemic compounds, only one diastereomer is depicted ; PMP = 4-methoxyphenyl.
b) Only the *cis* diastereomer is depicted.
c) Solvent: benzene.

established according to the coupling constant values (^{1}H-NMR) of vicinal protons C_2-H and C_3-H of the azetidinone ring ($J_{2,3}$ *cis* : 5-6 Hz, $J_{2,3}$ *trans* : 2-3 Hz).

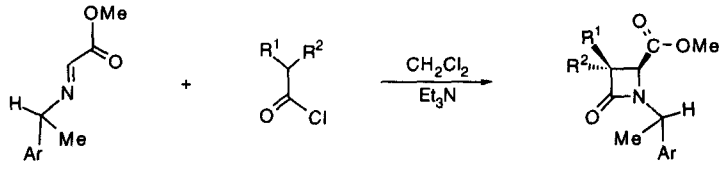
Cycloaddition reactions with the imine **1b** *derived from (±)-1-phenylethylamine.*

The reaction with dichloroacetyl chloride **2d** was used as a model for the optimization of the experimental conditions (Table 2, entries 5 to 8). The formation of two diastereomeric azetidinone derivatives **4d** was observed. A small amount of 2,2-dichloro-*N*-(1-phenylethyl)-acetamide, resulting from the condensation of imine **1b** and acid chloride **2d** followed by an hydrolysis reaction, was also observed. At 20°C (entry 5), the corresponding cycloadducts and amide were obtained in 70% and 4% yield respectively while at 40°C (entry 6) the yields increased to 80% and 6% respectively. It is worth noting that the yield increased slightly (83% *vs* 70%) when acid chloride **2d** was added slowly [30 min (entry 7) *vs* 5 min (entry 5)]. The yield raised from 50% up to 83%, when the excess of ketene precursor used was increased from 1.3 equiv to 3 equiv (entries 7 and 8). The duration of the reaction, generally of 4 h, was determined by following the disappearance of the imine GC signal. The best reaction conditions for the preparation of the 2-methoxycarbonyl-3,3-dichloro azetidinone **4d** are those specified in entry 7. The two diastereomeric *cis* β-lactam derivatives were formed in a 40:60 ratio under all the reaction conditions used (entries 5 to 8). All the other results are presented in Table 2 (entries 1 to 12). The relative *cis* and *trans* configurations of the cycloadducts were established as above but the relative configuration with respect to the configuration of the imine partner was not determined.

Cycloaddition reactions with imine **1d** *derived from (R)-1-(4-methoxyphenyl)ethylamine.*

All the cycloaddition reactions were done in dichloromethane, at room temperature (entries 14 to 21), except for those imploying the benzyloxyketene (entry 20) and the chlorophenylketene (entry 18), which were performed under reflux. The yields are generally good, and the *cis* selectivity is complete except for adducts **6e**. As for compounds **4a-h**, the attribution of *cis-trans* configuration were assigned on the basis of the $J_{2,3}$ coupling constant value observed in the ^{1}H NMR spectra of **6a-h** cycloadducts. The diastereoselectivity with respect to the configuration of the imine remains low ; in the best case a 37:63 ratio is obtained for lactam **6c** which is substituted in position the C_3 by a methoxy group.

Table 2. Experimental Conditions and Results of [2 + 2] Cycloadditions Involving Chiral *C*-Methoxycarbonyl-imines.



1b-d **2a-h**

4a-h Ar = Ph
5a Ar = Naph
6a-h Ar = PMP

entry	1	Ar[a]	2	R^1	R^2	Et_3N eq	2 eq	addition t_{min}/T°C	reaction t_{min}/T°C	products[b]	Yield %	*cis:trans*[c]	d.r.[d]
1	(±)**1b**	Ph	**2a**	Cl	H	3.5	3	5'/20°	4h/20°	**4a**	95	*cis*	42:58
2	(±)**1b**	Ph	**2b**	Ph	H	4.5	4	5'/20°	4h/20°	**4b**	60	*cis*	48:52
3	(±)**1b**	Ph	**2c**	MeO	H	3.5	3	5'/20°	4h/20°	**4c**	51	*cis*	45:55
4[e]	(±)**1b**	Ph	**2c**	MeO	H	3.5	3	5'/20°	4h/80°	**4c**	57	*97:3*	47:53
5	(±)**1b**	Ph	**2d**	Cl	Cl	3.5	3	5'/20°	4h/20°	**4d**	70	-	40:60
6	(±)**1b**	Ph	**2d**	Cl	Cl	3.5	3	5'/40°	4h/40°	**4d**	80	-	40:60
7	(±)**1b**	Ph	**2d**	Cl	Cl	3.5	3	30'/20°	4h/20°	**4d**	83	-	40:60
8	(±)**1b**	Ph	**2d**	Cl	Cl	1.5	1.3	30'/40°	4h/40°	**4d**	50	-	40:60
9	(±)**1b**	Ph	**2e**	Ph	Cl	3.5	3	5'/20°	12h/20°	**4e**	70	*[16:22:26:36]*	
10	(±)**1b**	Ph	**2f**	Et	H	3.5	3	5'/20°	5h/40°	**4f**	74	*cis*	43:57
11	(±)**1b**	Ph	**2g**	$PhCH_2O$	H	3.5	3	5'/20°	14h/20°	**4g**	61	*96:4*	45:55
12	(±)**1b**	Ph	**2h**	Phthalim	H	1.5	1.3	15'/0°	3h/20°	**4h**	59	*cis*	47:53
13	(±)**1c**	Naph	**2a**	Cl	H	3.5	3	5'/20°	4h/20°	**5a**	74	*cis*	44:56
14	(*R*)**1d**	PMP	**2a**	Cl	H	2,5	2	5'/20°	4h/20°	**6a**	95	*cis*	45:55
15	(*R*)**1d**	PMP	**2b**	Ph	H	3,5	3	5'/20°	20h/40°	**6b**	71	*cis*	43:57
16	(*R*)**1d**	PMP	**2c**	MeO	H	3,5	3	5'/20°	19h/20°	**6c**	69	*cis*	37:63
17	(*R*)**1d**	PMP	**2d**	Cl	Cl	2,5	2	5'/15°	2h/15°	**6d**	94	-	42:58
18	(*R*)**1d**	PMP	**2e**	Ph	Cl	3,5	3	5'/20°	24h/40°	**6e**	98	*[1:14:46:39]*	
19	(*R*)**1d**	PMP	**2f**	Et	H	3,5	3	5'/20°	18h/20°	**6f**	99	*cis*	44:56
20	(*R*)**1d**	PMP	**2g**	$PhCH_2O$	H	3.5	3	5'/20°	4h/40°	**6g**	88	*cis*	44:56
21	(*R*)**1d**	PMP	**2h**	Phthalim	H	3,5	3	5'/20°	19h/20°	**6h**	95	*cis*	43:57

a) PMP = 4-methoxyphenyl, Naph = naphthalen-1-yl.
b) Only one diastereomer is depicted. The relative configuration with respect to the configuration of the carbon atom α to nitrogen has not been determined.
c) Only the *cis* diastereomer is depicted.
d) Diastereomeric ratio.
e) Solvent : benzene.

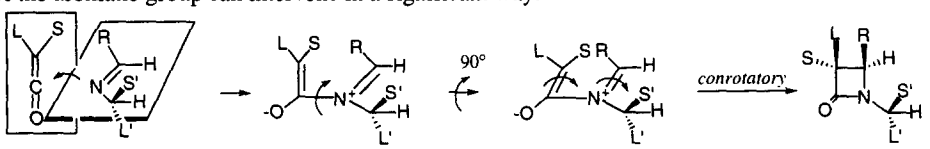
Asymmetric induction studies.

Palomo[19] has shown that imines derived from different chiral alkyl glyoxylates afford low diastereoselectivities in the Staudinger reaction using ethylketene (60:40 for menthyl or bornyl groups, and 66:33 for 8-phenylmenthyl group) ; in addition, this diastereoselectivity was only observed when imines of these chiral alkyl glyoxylates carried a bulky substituent, such as di-*p*-anisylmethyl (DAM), on the nitrogen atom and it disappeared completely with a less bulky group such as 4-methoxyphenyl (PMP). In this context, we have prepared the *tert*-butyl glyoxylate to know if the steric bulk increase of the glyoxylate alkyl group combined with the presence of a chiral center close to the nitrogen atom could have an impact on the stereochemical course of the reaction. Di-*tert*-butyl fumarate[20] was ozonolyzed in dichloromethane at -78°C to afford *tert*-butyl glyoxylate in 88% yield.[21] The cycloaddition of the imine, generated by condensation of *tert*-butyl glyoxylate and 1-phenylethylamine, with chloroketene at room temperature in dichloromethane afforded two *cis* disubstituted β-lactams in 54% yield. The diastereoselectivity of this cycloaddition was similar (40:60 ratio) to that observed with methyl glyoxylate.

Thereafter, the cycloaddition of methyl 1-naphthylethylamino acetate **1c** was performed with chloroketene (entry 13), at room temperature or at 0°C. Azetidinone **5a** was obtained in 74% yield with total *cis* selectivity. The ratio of diastereomers was 44:56. No diastereoselectivity variation was noticeable when the phenyl group of the chiral auxiliary was replaced by a naphthyl group. Similarly, Palomo obtained two *cis* diastereomeric cycloadducts in a 50:50 ratio through the condensation of the same imine **1c** with ethylketene in benzene solution.[22] With the imine derived from 1-naphthylethylamine and cinnamaldehyde, Georg obtained his best results using phenyloxyketene.[23] The higher induction (83:17) was obtained in benzene while in dimethylformamide the ratio of the two *cis* isomers was 60:40. In order to verify if such a solvent effect could be observed in our case, we have undertaken the cycloaddition of methyl 1-phenylethylimino acetate **1b** with methoxyketene in dichloromethane at room temperature and in refluxing benzene. The yields of these reactions are of similar magnitude (table 2, entries 3 and 4) and the *cis* selectivity is quantitative in the first case, and reaches 97% in the second. The *cis* diastereomers ratios are 45:55 in dichloromethane and 47:53 in benzene.

Origin of the facial differentiation

The *cis* selectivity, almost always observed in our study, can be accounted for[24] by the nucleophilic attack of the nitrogen of the imine on central carbon of the ketene according to the *exo* mode (scheme 1). In this mode, the smallest substituent (S) of the ketene and the smallest substituent (R=CO_2Me) of the imine approach in two orthogonal plans. The facial differentiation results from interactions between the ketene substituents and the substituents of the imine chiral center situated on either side of the plan. It is difficult to anticipate how aryl substituents such as phenyl and naphthyl, would behave, because their respective conformation may vary.[25] In addition, a stabilizing interaction between the S substituent (generally an hydrogen atom) of ketene and the π system of the aromatic group can intervene in a significant way.[26]



Scheme 1.

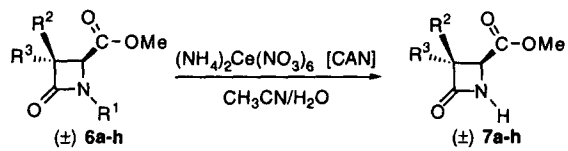
Deprotection of the nitrogen atom of β-lactam cycloadducts

The 4-methoxyphenyl group (PMP) was easily removed by oxidation with ammonium and cerium nitrate (CAN, 0°C, $MeCN/H_2O$).[12] With compounds **4a-h**, the 1-phenylethyl group was resistent to Pd-catalysed hydrogenolysis[27] and methods using dissolved metals in liquid ammonia (lithium[16] or sodium[13]) did not

succeed in selectively removing this group without substrate degradation. On the other hand, the oxidative debenzylation reaction using ammonium[28] or potassium[14] persulfate was not totally efficient. Thus, the yield of the transformation (potassium persulfate, 86-88°C, $AcOH/H_2O$) of the adduct **4f** bearing the ethyl group at the C_3 position was 36%. In addition, azetidinone **4f** was recovered in 38% yield.

Finally, the 1-(4-methoxyphenyl)ethyl group was selectively removed in satisfactory yields using CAN in $MeCN/H_2O$ (Table 3).[12c]

Table 3. *N*-Deprotection of Azetidinones **6a-h** [R'= Me(PMP)CH-]



Substrates **6**[a]	R^2	R^3	Products **7**[a]	Yields(%)
6a	Cl	H	**7a**	67
6b	Ph	H	**7b**	60
6c	MeO	H	**7c**	79
6d	Cl	Cl	**7d**	61
6e	Ph	Cl	**7e**	76
6f	Et	H	**7f**	65
6g	$PhCH_2O$	H	**7g**	89
6h	Phthalimido	H	**7h**	68

a) racemic compounds, only one diastereomer is depicted.

Deprotection of the carboxyl group of the cycloadducts

Several protocols for the saponification of an ester moiety in the presence of a β-lactam can be efficient.[22, 29] We have used a solution of 1.1 equiv of sodium hydroxide in an acetone/H_2O mixture.[30] The reaction was complete within 1 h, at room temperature. Under these reaction conditions, no β-lactam ring opening was observed.[30] The neutralization (pH 7) gave the corresponding sodium salt of azetidinone carboxylic acids.

CONCLUSION

The work described here shows that the imines of methyl glyoxylate represent efficient partners in cycloaddition reactions with variously substituted ketenes. The method allows the simple preparation, with good yields and total *cis* stereoselectivity, of a large series of α-amino acid derivatives with a β-lactam skeleton. The induction level resulting from the chirality borne by the carbon atom α to the imine nitrogen atom was low. This result is comparable to those generally obtained with imines derived from achiral aldehydes and chiral amines.[31] That is why the use of chiral ketenes, such as Evans-Sjögren ketenes,[16, 32] in the Staudinger reaction appears essential to reach optically pure cycloadducts, with imines of glyoxylates.[9d]

Acknowlegment. The authors are grateful to Professors Claudio Palomo and Reiner Sustmann for stimulating discussions. This work was part of the Bio Avenir program supported by Rhône-Poulenc with the participation of the Ministère de la Recherche and the Ministère de l'Industrie. One of us (D.M.) thanks the CNRS and Rhône-Poulenc Rorer for a grant.

EXPERIMENTAL SECTION

Unless otherwise noted, materials were obtained from commercial suppliers (except for methyl glyoxylate[18]) and used without further purification. Methylene chloride (CH_2Cl_2) was dried over potassium carbonate, distilled and storred over 4-Å molecular sieves. Triethylamine was dried over KOH (pellets). Commercially available 3-Å and 4-Å molecular sieves (beads) were used without further activation. Reactions were carried out under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} analytical plates (0.2 mm thickness) visualized by using UV light, iodine vapor, or by means of a 5% ethanolic solution of molybdophosphoric acid. The retention factors (R_f) are measured on this support using as eluant the solvent indicated. Column chromatography was performed using Merck silica gel 60 (230-400 mesh). Gas chromatography (GC) was carried out on a Shimadzu GC-14A chromatograph with a J&W capillary column SE 30 (5%), 30 m length, 0,32 mm i. d., with 1 bar N_2 carrier gas pressure. The chromatograph was interfaced with a Shimadzu C-R6A chromatopac integrator. Retention times (t_R) are given for different oven programmed heating (injector at 250 °C) *i.e.* : *prog 1* = from 110°C (5 min) to 280°C (5 min) at 3°C/min rate, *prog 2* = from 110°C (5 min) to 230°C (5 min) at 3°C/min rate, *prog 3* = from 110°C (5 min) to 300°C (5 min) at 5°C/min rate, *prog 4* = from 110°C (5 min) to 350°C (5 min) at 5°/min rate. Distillations with Kugelrohr apparatus were performed on a Büchi GRK-51 instrument. Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AC 200 spectrometer, operating at 200 MHz for ^1H and 50 MHz for ^{13}C. Chemical shifts are reported as δ values in parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards respectively. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Coupling constants *J* are given in hertz. All structures were assigned after extensive 2D NMR studies (COSY H-H, COSY C-H) Infrared (IR) spectra were obtained using a IRTF Nicolet 20 SXB spectrophotometer. Resonances are reported in wavenumbers (cm^{-1}). GC-MS was carried out on a Ribermag R-10-10 C, at an ionizing voltage of 70 eV. The fused silica gel capillary column was 25 m length, 0,32 mm i. d., with 0.8 bar helium carrier gas pressure. The temperatures were 300°C (injector), 160°C (oven), 300°C (interface) and 150°C (source). Elemental analysis were performed at the University Department. Melting points were determined on a capillary Büchi apparatus and are uncorrected.

***Procedure for the Preparation of imines* 1a-d.**

(4-Methoxyphenyl-benzylidene)-carbamic acid methyl ester **1a**. To a stirred solution of methyl glyoxylate (210 mg, 2.38 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) at room temperature, under argon, were added the *p*-anisidine (250 mg, 2.03 mmol, 1 equiv) and 500 mg of 3-Å molecular sieves. The formation of the imine is followed by GC. The resulting yellow mixture was stirred for 1h and then filtered. The solvant was evaporated under reduced pressure to give the corresponding crude imine (0.38 g, 1.98 mmol, 97% yield), which was used as such in the cycloaddition step. GC (*prog 1*) t_R =16 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3H, *p*-OCH_3), 3.92 (s, 3H, $COOCH_3$), 6.92 & 7.35 (AA'BB', *J* = 8.8 Hz, 4H, CH arom), 7.93 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.69 (OCH_3), 55.44 (OCH_3), 114.55 & 123.67 (CH arom), 141.08 (C*ipso*-OCH_3), 147.35 (C=N), 160.60 (C *ipso* -N), 164.01 (C=O); MS (EI, rel int) *m/z* 194 (11), 193 (M^+, 89.8), 135 (23.5), 134 (100), 107 (70.9), 92 (41.9), 77 (56.8), 64 (33.1), 63 (20.7), 50 (13.2), 38 (11.2).

(2-Phenyl-propylidene)-carbamic acid methyl ester **1b**. From methyl glyoxylate (500 mg, 5.68 mmol, 1.05 equiv) in CH_2Cl_2 (15 mL), 1-phenylethylamine (680 µL, 5.41 mmol, 1 equiv) and 1.5 g of 3-Å molecular sieves. Stirring for 1 h at room temperature. 1 g (92% yield) of crude imine was obtained. GC (*progr 1*) t_R = 10 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 3.92 (s, 3H, OCH_3), 4.57 (q, *J* = 6.7 Hz, 1H, CH), 7.41 (m, 5H, Ph), 7.73 (d, *J*= 0.79 Hz, 1H, CH=N).

(2-Naphthalen-1-yl-propylidene)-carbamic acid methyl ester **1c**. From methyl glyoxylate (273 mg, 3.10 mmol, 1 equiv) in CH_2Cl_2 (15 mL), 1-(naphthalen-1-yl)-ethylamine (500 µL, 3.10 mmol, 1 equiv) and 1 g of 3-Å molecular sieves. 740 mg of crude imine were obtained (quantitative yield) . GC (*prog 4* with heating ramp of 2°C/min) t_R =15.7 min.

[2-(4-Methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d**. From methyl glyoxylate (183.5 mg, 2.08 mmol, 1.02 equiv) in CH_2Cl_2 (8 mL), 1*(R)*-(4-methoxyphenyl)-ethylamine (300 mg, 1.98 mmol, 1 equiv) and 500 mg of 3-Å molecular sieves. The mixture was stirred for 1 h at room temperature. The crude imine (400mg, 98%) was used as such in the cycloaddition step. GC (*prog 3*) t_R =16.0 min.

General Procedure for Cycloaddition Reactions:

A solution of the corresponding substituted acetyl chloride **2** in dry CH_2Cl_2 was added dropwise via syringe at the temperature and rate indicated in table 1 to a stirred solution containing the crude imine **1** and triethylamine in dry CH_2Cl_2, under argon. The resulting mixture was stirred at the temperature and during the time indicated in table 1. Then, the mixture was filtered, washed first with a saturated solution of $NaHCO_3$ then with a saturated solution of NaCl. The organic phase was dried over $MgSO_4$, then filtered. The solvent was evaporated under reduced pressure to give the crude β-lactam. A sample of the crude product was used to measure the isomers ratio either by GC and ^1H NMR. The product was further purified by column chromatography then conveniently caracterized.

3-Chloro-1-(4-methoxyphenyl)-4-oxo-azetidine-2-carboxylic acid methyl ester **3a**. CH_2Cl_2 20 mL, (4-methoxyphenyl-benzylidene)-carbamic acid methyl ester **1a** (1 equiv, 3.1 mmol, 600 mg), triethylamine (3.5 equiv, 10.88 mmol, 1.55 mL), addition in 15 min at 20°C of chloroacetyl chloride **2a** (3 equiv, 9.32 mmol, 742 µL), reaction for 17h at 40°C. The diastereomer **3a** was purified by column chromatography (CH_2Cl_2) (384 mg, 46%). TLC (CH_2Cl_2) R_f = 0.45. GC (*prog 1*) t_R = 32 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3H, OCH_3 ether), 3.85 (s, 3H, OCH_3 ester), 4.86 (d, *J* = 5.6 Hz, 1H, **CH**COOMe), 5.17 (d, *J* = 5.6 Hz, 1H, CHCl), 6.87 (d, *J* = 9.1 Hz, 2H, cyclic CH β-OMe); 7.26 (d, *J* = 9.1 Hz, cyclic CH β-N); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.93 (**O**CH_3 ether), 55.50 ($COOCH_3$), 57.06 (CHCl), 58.50 (**C**HCOOCH_3), 114.52 (arom β-OMe **C**H); 118.45 (arom β-N **C**H); 129.88 (*Cipso*-OCH_3); 157.11 (*Cipso*-N), 158.96 (β-lactam C=O), 166.81 (ester C=O). The by-product *2-chloro-N-(4-methoxyphenyl)-acetamide:* (161 mg, 26% yield) was also isolated. GC (*prog 1*) t_R =18 min; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2Cl), 6.88 & 7.44 (AA'BB', 4H, CH arom), 8.20 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.88 ($ClCH_2$), 55.47 (OCH_3), 114.26 (CH arom), 122.08 (CH arom), 129.76 (C *ipso*-OCH_3), 157.05 (C *ipso*-N), 163.78 (C=O). HRMS (DCI+) *m/z* Calcd for $C_{12}H_{13}ClNO_4$ (MH^+) 270.0533, found 270.0539.

1-(4-Methoxyphenyl)-3-phenyl-4-oxo-azetidine-2-carboxylic acid methyl ester **3b.** CH_2Cl_2 7 mL, (4-methoxyphenyl-benzylidene)-carbamic acid methyl ester **1a** (1 equiv, 6.09 mmol, 1.17g), triethylamine (3.5 equiv, 21.31 mmol, 3 mL), phenylacetyl chloride **2b** (3 equiv, 18.27 mmol, 2.4 mL), addition in 5 min at 20°C, reaction in 21h at 20°C. The diastereomer *cis* **3b** was purified by column chromatography (CH_2Cl_2) (860 mg, 45%); GC (*prog 3*) t_R = 29.5 min. ^1H NMR (C_6D_6, 200 MHz) δ 2.85 (s, 3H, $COOCH_3$), 3.25 (s, 3H, OCH_3 ether), 4.84 (d, *J* = 6.2 Hz, 1H, CH), 4.35 (d, *J* = 6.2 Hz, 1H, CH), 6.88 & 7.30 (m, 9H, Ph); ^{13}C NMR (C_6D_6, 50 MHz) δ 51.95, 55.44, 58.01, 58.21, 114.38, 118.10, 128.5, 131.35, 156.50, 163.50, 168.23; SM (EI, rel int) *m/z* 311 (M^+, 16), 150 (11), 149 (100), 134 (34), 91 (11), 77 (13). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.39; H, 5.48; N, 4.47.

3-Methoxy-1-(4-methoxyphenyl)-4-oxo-azetidine-2-carboxylic acid methyl ester $\mathbf{3c_c}$ and $\mathbf{3c_t}$. Benzene 7 mL., (4-methoxyphenyl-benzylidene)-carbamic acid methyl ester **1a** (1 equiv, 2.03 mmol, 392 mg), triethylamine (2 equiv, 4.06 mmol, 0,57 mL), methoxyacetyl chloride **2c** (1.5 equiv, 3.04 mmol. 0.28 mL), addition in 15 min at 20°C, reaction in 15h at 80°C. By GC and ^1H NMR were detected 17% of cycloadduct *trans* $\mathbf{3c_t}$ and 83% of cycloadduct *cis* $\mathbf{3c_c}$. The mixture of *cis* and *trans* cycloadducts (360 mg, 60% yield) were purified by column chromatography (CH_2Cl_2/AcOEt, 10/1). Pure *trans* $\mathbf{3c_t}$ cycloadduct (20 mg) and pure *cis* $\mathbf{3c_c}$ cycloadduct (220 mg) were isolated.

Cis cycloadduct $\mathbf{3c_c}$ TLC (CH_2Cl_2/AcOEt 10:1) R_f= 0.64. GC (*prog 3*) t_R = 25 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.55 (s, 3H, *p*-OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.73 (d, *J* = 5.2 Hz, 1H, **CH**COOMe), 4.84 (d, *J* = 5.2 Hz, 1H, **CH**OCH_3), 6.85 (AA'BB', 2H, CH arom β-OMe), 7.26 (AA'BB', 2H, CH arom β-N); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.38 (OCH_3), 55.18 (OCH_3), 58.74 (OCH_3), 59.34 (**CH**COOCH_3), 83.85 (**CH**OCH_3), 114.17 (CH arom β-OMe), 118.07 (CH arom β-N), 130.00 (*Cipso*-OCH_3), 156.46 (*Cipso*-N), 162.24 (C=O β-lactam), 167.74 (C=O ester). SM (EI, rel int) *m/z* 265 (M^+, 26.2), 179 (7.6), 178 (59.2), 163 (9.0), 150 (16.2), 149 (100), 135 (9.6), 134 (93.3), 121 (7.5), 107 (15.6), 106 (12.9), 104 (14.3), 92 (17.6), 85 (14.7), 78 (8.5), 77 (23.6), 75 (39.2), 63 (7.5), 51 (6.9), 45 (57.2), 29 (12.9); mp 108°C; white solid; Anal. Calcd.for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.82; H, 5.73; N:5.28.

Trans cycloadduct $\mathbf{3c_t}$ TLC (CH_2Cl_2/AcOEt 10:1) R_f = 0.68; GC (*prog 3*) t_R = 24.5 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.58 (s, 3H, *p*-OCH_3), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.44 (d, *J* = 1.7 Hz, 1H, CH β-lactam), 4.72 (d, *J* = 1,7 Hz, 1H, CH β-lactam), 6.85 (d, *J* = 9.1 Hz, 2H, arom CH β-OMe), 7.24 (d, *J* =

9.1 Hz, arom CH β-N); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.93 (OCH_3), 55.51 (OCH_3), 58.18 (OCH_3), 59.09 (**C**HCOOCH$_3$), 86.99 (**C**HOCH$_3$), 114.51 (arom CH β-OMe), 118.43 (arom CH β-N), 130.28 (*Cipso*-OCH_3), 156.88 (*Cipso*-N), 161.97 (C=O β-lactam), 169.37 (C=O ester); SM (EI, rel int) *m/z* 265 (M^+, 11.4), 178 (29.0), 150 (7.4), 149 (100), 134 (47.2), 106 (7.1), 92 (8.8), 85 (9.6), 77 (15.5), 75 (20.9), 64 (7.0), 45 (34.3), 29 (10.3).

3-Chloro-4-oxo-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4a**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 g), triethylamine (3.5 equiv, 18.93 mmol, 2.64 mL), chloroacetyl chloride **2a** (3 equiv, 16.23 mmol, 1.833 g), addition in 5 min at 20°C, reaction in 4h at 20°C. The crude product was purified by column chromatography (CH_2Cl_2) (1,37g, 95% yield). TLC (CH_2Cl_2) R_f = 0.3. The two *cis* diastereomers were formed in the ratio 42:58. GC *(prog 2)* t_R *minor* = 28.3 min, t_R *major* = 29.1 min; ^{1}H NMR ($CDCl_3$, 200 MHz) *minor* δ 1.81 (d, 3H, *J* = 7 Hz, CH_3), 3.77 (s, 3H, OCH_3), 4.26 (d, 1H, *J* = 5.5 Hz, **CH**COOMe), 4.63 (q, 1H, *J* = 7 Hz, **CH**PhMe), 4,94 (d, 1H, *J* = 5.5 Hz, CHCl), 7.32 (m, 5H, Ph); *major* δ 1.65 (d, 3H, *J* = 7 Hz, CH_3), 3.71 (s, 3H, OCH_3), 4.23 (d, 1H, *J* = 5.5 Hz, **CH**COOMe), 4.94 (d, 1H, *J* = 5.5 Hz, CHCl), 5.01 (q, 1H, *J* = 7 Hz, **CH**PhMe), 7.32 (m, 5H, Ph); MS (EI, rel int) *minor m/z* 232 (M^+, 4.9), 132 (8.1), 106 (12.5), 105 (100), 103 (6.1), 79 (5.6), 77 (8.5), 51 (4.6), 27 (3.5); *major m/z* 232 (M^+, 4.2), 106 (12.3), 105 (100), 103 (6.8), 79 (6.1), 77 (9.1), 51 (4.9), 27 (3.7). HRMS (DCI+) *m/z* Calcd for $C_{13}H_{15}ClNO_3$ (MH^+) 268.0740, found 268.0740.

4-Oxo-3-phenyl-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4b**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 g), triethylamine (4.5 equiv, 24.34 mmol, 3.47 mL), phenylacetyl chloride **2b** (4 equiv, 21.64 mmol, 3.17 g), addition in 5 min at 20°C, reaction in 4h at 20°C. In the crude product, 6% of imine **1b** was detected (GC). The two *cis* diastereomers (1.0 g, 60%) obtained in the 48:52 ratio, were purified by flash column chromatography (cyclohexane/AcOEt, 80:20); TLC (cyclohexane/AcOEt 80:20) R_f = 0.33; GC *(prog 2) minor* t_R = 38.4 min; *major* t_R = 38.9 min. ^{1}H NMR ($CDCl_3$, 200 MHz) *minor* δ 1.66 (d, 3H, *J* = 7.1 Hz, CH_3), 3.17 (s, 3H, OCH_3), 4.19 (d, 1H, *J* = 6.2 Hz, **CH**CO_2Me), 4.58 (d, 1H, *J* = 6.2 Hz, **CH**Ph), 5.12 (q, 1H, *J* = 7.1 Hz, **CH**MePh), 7.22-7.32 (m, 10H, Ph); *major* δ 1.86 (d, 3H, *J* = 7.1 Hz, CH_3), 3.13 (s, 3H, OCH_3), 4.25 (d, 1H, *J* = 6.2 Hz, **CH**CO_2Me), 4.54 (d, 1H, *J* = 6.2 Hz, **CH**Ph), 4.62 (q, 1H, *J* = 7.1 Hz, **CH**MePh), 7.22-7.32 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) 18.2 & 20.2 (CH_3), 51.3, 52.1, 55.8, 57.3, 57.8, 58.0 (OCH_3, CHPh, 2 CH β-lactam), 126.7 & 128.7 (CH arom), 131.8, 131.9, 139.1, 140.8 (*Cipso* 2Ph), 166.3, 166.5, 169.0, 169.2 (CO ester, β-lactam). MS (EI, rel int) *minor m/z* 163 (12.1), 162 (92.2), 161 (23.9), 132 (9.3), 131 (60.5), 118 (7.9), 117 (5), 106 (9.5), 105 (100), 104 (76), 103 (22.7), 90 (8.3), 89 (5.9), 79 (9.2), 77 (20.5), 51 (8),27 (5.1); *major m/z* 163 (9.8), 162 (73.7), 161 (19.3), 131 (46), 118 (8.8), 106 (9.1), 105 (100), 104 (6.5), 103 (17.2), 90 (7.7), 89 (5.2), 79 (8.7), 77 (16.2), 51 (6.2). HRMS (DCI+) *m/z* Calcd for $C_{19}H_{20}NO_3$ (MH^+) 310.1443, found 310.1443.

3-Methoxy-4-oxo-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4c**. Benzene 9 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 2.70 mmol, 516 mg), triethylamine (3.5 equiv, 9.45 mmol, 1.32 mL), methoxyacetyl chloride **2c** (3 equiv, 8.11 mmol, 0.75 mL), addition in 5 min at 20°C, reaction in 4h at 80°C. *Cis* (97%) and *trans* (3%) cycloadducts were present. The two *cis* cycloadducts were formed in a 53:47 ratio. Column chromatography purification (CH_2Cl_2/AcOEt 9:1) afforded 380 mg of pure *cis* cycloadducts (54% yield). TLC (CH_2Cl_2/AcOEt 9:1) R_f = 0.33; GC *(prog 1)* t_R *major* = 24.9 min, t_R *minor* = 25.5 min; ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers δ 1.63 & 1.80 (d, *J* = 7.1 Hz, 3H, **CH**$_3$CHPh); 3.47 & 3.49 (s, 3H, CHO**Me**); 3.68 & 3.76 (s, 3H, COOMe); 4.06 & 4.10 (d, *J* = 5.1 Hz, 1H, **CH**COOMe); 4.57 & 4.60 (d, *J* = 5.1 Hz, **CH**OMe); 4.60 & 5.04 (q, *J* = 7.1 Hz, 1H, **CH**PhMe); 7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.63, 20.21 (**C**H$_3$CH); 51.81, 52.21, 55.49, 58.47, 59.29 (OCH_3, OCH_3, **C**HPh, **C**HCOOMe); 83.99, 83.81 (**C**HOCH$_3$); 126.8 à 128.7 (CH phenyl); 139.01, 140.36 (*Cipso*); 165.59, 165.82 (CO β-lactam); 168.75, 169.15 (CO ester); MS (EI, rel int) *major m/z* 176 (5.7), 132 (40.2), 118 (5.5), 117 (100), 116 (37.3), 106 (5.1), 105 (62.1), 104 (6.9), 103 (9.8), 87 (64), 85 (90), 84 (8.0), 79 (9.4), 77 (18.2), 59 (9.0), 51 (8.3), 42 (8.0), 29 (11.3), 27 (9.9). *minor m/z* 176 (6.1), 132 (40.5), 130 (6.9), 118 (6.4), 117 (100), 116 (34.4), 106 (6.7), 105 (78.6), 104 (7.8), 103 (11.5), 99 (5.9), 87 (70.4), 85 (89.6), 84 (7.7), 79 (11), 77 (19.9), 59 (9.9), 51 (9.0), 42 (8.1), 29 (13.4), 27 (11.2); IR 3074, 2846, 2341, 1787, 1350, 1301, 1202, 1026, 760, 698; Anal Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.37. Found: C, 63.79; H, 6.51; N, 5.25.

3,3-Dichloro-4-oxo-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4d**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 mg), triethylamine (3.5 equiv, 18.93 mmol, 2.65 mL), dichloroacetyl chloride **2d** (3 equiv, 16.23 mmol, 2.74g); addition in 5 min at 40°C, reaction in 4h at 40°C. The crude reaction mixture, analyzed by GC, was composed of imine **1b** (2.5%), amide $Cl_2CHCONHCH(Ph)CH_3$ (6%) and cycloadducts (80%). The mixture was purified by column chromatography using pentane, then CH_2Cl_2 and finally AcOEt. Pure cycloadducts **4d** were isolated (1.230 g, 75% yield). GC [*prog* from 110°C (5 min) to 150°C (5 min) at 3°C/min rate, then to 230°C (5 min) at 3°C/min rate] t_R = 28.1 min (40%), t_R = 28.9 min (60%). ^{1}H NMR ($CDCl_3$, 200 MHz) *minor* δ 1.86 (d, 3H, *J* = 7.1 Hz, CH_3), 3.79 (s, 3H, OCH_3), 4.30 (s, 1H, **CH**COOMe), 4.65 (q, 1H, *J* = 7.1 Hz, **CH**Ph), 7.32 (m, 5H, Ph); *major* δ 1.69 (d, 3H, *J* = 7.1 Hz, CH_3), 3.80 (s, 3H, OCH_3), 4.26 (s, 1H, **CH**COOMe), 5.1 (q, 1H, *J* = 7.1 Hz, **CH**Ph), 7.32 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.20 & 20.36 (CH_3), 52.92 & 53.11 (**CH**Ph), 56.69 (OCH_3), 69.32 & 69.80 (**CH**COOMe), 80.05 (CCl_2), 126.5 & 127.18 (C *para*), 128.40 & 128.57 (C *ortho*), 128.97 & 129.10 (C *meta*), 137.15 & 139.14 (C *ipso*), 159.78 & 165.73 & 166.10 (CO β-lactam & ester). MS (EI, rel int) *minor m/z* 132 (18.1), 106 (26.7), 105 (100), 104 (5.9), 103 (11), 79 (10.9), 77 (18.9), 51 (9.3), 27 (6.1); *major m/z* 132 (14.3), 106 (21), 105 (100), 104 (5.2), 103 (9.4), 79 (10), 77 (15.6), 51 (7.9), 27 (5.9). HRMS (DCI+) *m/z* Calcd for $C_{13}H_{14}Cl_2NO_3$ (MH^+) 302.0350, found 302.0341.

3-Chloro-4-oxo-3-phenyl-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4e**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 g), triethylamine (3.5 equiv, 18.93 mmol, 2.64 mL), phenylchloroacetyl chloride **2e** (3 equiv, 16.23 mmol, 3.7 mL); addition in 5 min at 20°C, reaction in 12h at 20°C. Four diastereomerss **A**, **B**, **C** and **D** were formed in the ratios 16:22:26:36 and in 70% total yield; GC (*prog 2*) t_{RA} = 39.6 min, t_{RB} = 40.0 min, t_{RC} = 40.4 min, t_{RD} = 40.9 min. MS (EI, rel int) (**A**) *m/z* 198 (8.6), 197 (10.1), 196 (24.6), 195 (13.3), 165 (9.6), 106 (8.9), 105 (100), 103 (6.4), 79 (5.6),77 (8.3); (**B**) *m/e* 198 (7.0), 197 (8.4), 195 (11.0), 196 (20.6), 165 (8.1), 106 (9.1), 105 (100), 103 (6.8), 79 (5.8), 77 (8.7); (**C**) *m/e* 198 (9.3), 197 (13.7), 196 (27.5), 195 (15.7), 165 (10.8), 106 (8.6), 105 (100), 103 (6.2), 79 (5.0), 77 (7.8); (**D**) *m/z* 198 (9.7), 197 (12.2), 196 (25.7), 195 (13.4), 165 (9.6), 106 (9.0), 105 (100), 103 (5.6), 79 (5.0), 77 (6.8). From the oily mixture dissolved in ether, the major **D** isomer cristallized; ^{1}H NMR ($CDCl_3$, 200 MHz) *major* (**D**) δ 1.72 (d, 3H, *J* = 7.1 Hz, CH_3); 3.86 (s, 3H, OCH_3); 4.31 (s, 1H, **CH**COOMe); 5.09 (q, 1H, *J* = 7.1 Hz, **CH**Ph); 7.40 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) *major* (**D**) δ 18.6 (CH_3), 45.9 (CCl), 52.9, 65.8, 72.6 (**CH**COOMe, OCH_3, **CH**Me), 126.8-129.4 (CH arom), 136.2, 138.1 (C*ipso* 2Ph), 163.6, 167.8 (CO ester, β-lactam). HRMS (DCI+) *m/z* Calcd for $C_{19}H_{19}ClNO_3$ (MH^+) 344.1053, found 344.1057.

3-Ethyl-4-oxo-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4f**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 g), triethylamine (3.5 equiv, 18.93 mmol, 2.64 mL), butyryl chloride **2f** (3 equiv, 16.23 mmol, 1.68 mL), addition in 5 min at 20°C, reaction in 5h at 40°C. GC (*prog 1*) t_R *minor* = 24 min (43%), t_R *major* = 25 min (57%). The obtained orange oil were purified by distillation with Kugelrhor apparatus. *Cis* cycloadducts **4f** were isolated (1.045 g, 74% yield); ^{1}H NMR ($CDCl_3$, 200 MHz) *major* δ 0.9 (m, 3H, CH_3-CH_2), 1.51 (d, *J* = 7.1 Hz, 3H, CH_3-CH), 1.52 (m, 2H, CH_2), 3.13 (m, 1H, CH-CH_2), 3.61 (s, 3H, $COOCH_3$), 3.87 (d, 1H, *J* = 5.8 Hz, **CH**COOMe), 4.90 (q, *J* = 7.1 Hz, 1H, **CH**Ph), 7.2 (m, 5H, Ph); *minor* δ 0.9 (m, 3H, CH_3-CH_2), 1.48 (m, 2H, CH_2), 1.69 (d, *J* = 7.1 Hz, 3H, CH_3-CH), 3.13 (m, 1H, CH-CH_2), 3.5 (s, 3H, $COOCH_3$), 3.93 (d, 1H, *J* = 5.8 Hz, **CH**COOMe), 4.48 (q, *J* = 7.1 Hz, 1H, **CH**Ph), 7.2 (m, 5H, Ph), ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 11.52, 18.32, 18.76, 18.97, 20.09, 21.63 (CH_3CH, CH_3CH_2, CH_2CH_3), 51.66, 51.74, 53.98, 54.23, 54.54, 54.64, 55.30 (OCH_3, $CHCH_3$, 2 CH β-lactam), 125.99-128.51 (CH phenyl), 139.19, 140.76 (C*ipso*), 168.66, 168.83, 170.10, 170.46 (CO); MS (EI, rel int) *minor m/z* 147 (7.3), 132 (48.6), 120 (7.4), 115 (37.4), 106 (17.3), 105 (100), 104 (11), 103 (12), 79 (11.3), 77(15), 27 (7.8); *major m/z* 191 (26.2), 147 (11.9), 132 (76.8), 115 (56.4), 106 (27), 105 (100), 104 (16.8), 103 (20.7), 79 (19.4), 77 (28.8), 55 (10.7), 39 (10.3), 27 (15). HRMS (DCI+) *m/z* Calcd for $C_{15}H_{20}NO_3$ (MH^+) 262.1443, found 262.1443.

3-Benzyloxy-4-oxo-1-(1-phenylethyl)-azetidine-2-carboxylic acid methyl ester **4g**. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol, 1.033 g), triethylamine (1 equiv, 18.93 mmol, 2.64 mL), benzyloxyacetyl chloride **2g** (3 equiv, 16.23 mmol, 2.99 g), addition in 5 min at 20°C; reaction in 14h at 20°C. GC (*prog 2*) t_R (**A**) = 42,9 min (1,5%), t_R (**B**) = 43,3 min (2,5%), t_R (**C**) = 43,8 min (52,7%), t_R (**D**)= 44,3 min (43.3%). From the mixture of the four diastereomers (1,12g, 61% yield) the *cis* and *trans* were separated by column chromatography (CH_2Cl_2). R_f = 0.3; GC (*prog 1*) t_R (**C**) = 44.08 min, t_R (**D**)=

44.68 min; ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers **C** & **D** δ 1.63 & 1.80 (d, *J* = 7.1 Hz, 3H, CH_3CH), 3.63 & 3.70 (s, 3H, OCH_3), 4.06 & 4.11 (d, *J* = 5.1 Hz, CHCOOMe), 4.64 & 5.03 (q, *J* = 7.1 Hz, 1H, $CHCH_3$), 4.67 & 4.69 (s, 2H, OCH_2), 4.73 & 4.77 (d, *J* = 5.1 Hz, 1H, $CHOCH_2Ph$), 7.30 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.52, 20.0 (CH_3CH), 51.77, 52.11, 52.19, 55.39, 58.46 (CHCOOMe, OCH_3, $CHCH_3$), 72.87-72.92 (OCH_2), 81.39, 81.59 ($CHOCH_2$), 126.7, 128.71 (CH arom), 136.4, 136.5, 138.9, 140.2 (*Cipso*), 165.57, 165.79, 168.73, 169.15 (CO), MS (EI rel int) **C** isomer *m/z* 192 (3.3), 174 (9.0), 106 (2.9), 105 (34.7), 103 (2.6), 92 (9.8), 91 (100), 79 (2.9), 77 (4.5), 65 (4.8), 39 (2.2); **D** isomer *m/z* 174 (12.1), 106 (4.8), 105 (45.8), 104 (2.5), 103 (3.9), 92 (12.9), 91 (100), 79 (4.3), 77 (5.6), 65 (6.4), 51 (2.7), 39 (3.2); IR 3072, 3036, 2990, 2958, 1785, 1457, 1439, 1346, 1301, 1202, 1073, 1022, 759, 698. HRMS (DCI+) *m/z* Calcd for $C_{20}H_{22}NO_4$ (MH^+) 340.1548, found 340.1553.

4-oxo-1-(1-phenylethyl)-3-phthalimido-azetidine-2-carboxiylic acid methyl ester **4h**. A mixture of phthaloylglycine (5.00 g, 0.024 mol, 1 equiv) and $SOCl_2$ (5.3 mL, 0.073 mol, 3 equiv) was refluxed for 18h. After cooling at room temperature, excess thionyl chloride was evaporated under reduced pressure. The residue was shaked in ether for 1h at 0°C. By filtration on Büchner, washing with cold ether and drying *in vacuo*, white cristals of acid chloride **2h**[33] were obtained (4.84 g, 89% yield) and used as such in the following cycloaddition. CH_2Cl_2 20 mL, (2-phenyl-propylidene)-carbamic acid methyl ester **1b** (1 equiv, 5.41 mmol. 1.033 g), triethylamine (1.5 equiv, 8.11 mmol, 1.15 mL), phthaloylglycine chloride **2h** (1.3 equiv, 7.03 mmol, 1.57 g), addition in 15 min at 0°C, reaction in 3h at 20°C. A gold yellow powder was obtained and purified by cold ether washing. Pure cycloadducts (1.20 g, 59% yield) were isolated as a white powder; GC (*prog 4*) t_R = 29.1 min (53%) et t_R = 29.3 min (47%). ^{1}H NMR ($CDCl_3$, 200 MHz) *minor* δ 1.78 (d, 3H, *J* = 7.1 Hz, CH_3), 3.47 (s, 3H, $COOCH_3$), 4.21 (d, 1H, *J* = 6 Hz, CHCOOMe), 5.13 (q, 1H, *J* = 7.1 Hz, CHPh), 5.43 (d, 1H, *J* = 6 Hz, CHN), 7.85-7.30 (m, 9H, Ph & phthalimido), *major* δ 1.92 (d, 3H, *J* = 7.1 Hz, CH_3); 3.52 (s, 3H, $COOCH_3$), 4.21 (d, 1H, *J* = 6 Hz, CHCOOMe), 4.87 (q, 1H, *J* = 7.1 Hz, CHPh), 5.49 (d, 1H, *J* = 6 Hz, CHN), 7.85-7.30 (m, 9H, H arom), ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.00, 20.27 (CH_3CH), 48.26, 52.38, 53.13, 55.42, 55.68, 55.93, 58.42, 58.87 (two β-lactams CH, $CHCH_3$, OCH_3), 123.76 (CH phthalimido), 126.20 à 128.95 (CH phenyl), 131.53 (C quaternary), 134.58 (CH phthalimido), 138.80 (C quaternary), 163.27-163.39-166.68-166.79-167.89-168.07 (CO); MS (EI, rel int) *major m/z* 232 (36.4), 231 (68.4), 201 (12.4), 200 (100), 172 (18.5), 132 (12) 105 (51.5), 104 (29.8), 103 (10.1), 77 (14.3) 76 (12.5); *minor m/z* 241 (11), 232 (36.7), 231 (70.8), 201 (12.5), 200 (100), 172 (1.8), 132 (13.7), 105 (58.3), 104 (31.3), 103 (10), 77 (14.4), 76 (12.7); IR 3073, 2911(CH arom), 1801, 1744 (C=O ester, β-lactam, phthalimido); 1379 (phthalimido), 1305, 1206, 1112, 716 (CH arom); mp= 169°C (mixture of two diastereomers). HRMS (DCI+) *m/z* Calcd for $C_{21}H_{19}N_2O_5$ (MH^+) 379.1293, found 379.1305

3-Chloro -1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6a**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 3.97 mmol, 882 mg), triethylamine (2.5 equiv, 9.92 mmol, 1.96 mL), chloroacetyl chloride **2a** (2 equiv, 7.94 mmol, 0.63 mL). Addition in 5 min at 20°C, reaction in 4h at 20°C. The cycloadducts (480 mg, 66% yield) were isolated by purification on column chromatography (CH_2Cl_2). GC (*prog 3*) t_R = 27.2 min (45%), t_R = 27.6 min (55%). ^{1}H NMR($CDCl_3$, 200 MHz) *major* δ 1.63 (d, *J* = 7.08 Hz, 3H, CH_3CH), 3.72 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.17 (d, *J* = 5.37 Hz, 1H, CHCOOMe), 4.90 (q, *J* = 7.08 Hz, 1H, $CHCH_3$), 4.88 (d, *J* = 5.37 Hz, 1H, CHCl), 7.0 (m, 4H, CH arom); *minor* δ 1.79 (d, *J* = 7.08 Hz, 3H, CH_3CH), 3.72 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.21 (d, *J* = 5.37 Hz, 1H, CHCOOMe), 4.59 (q, *J* = 7.08 Hz, 1H, $CHCH_3$), 4.88 (d, *J* = 5.37 Hz, 1H, CHCl), 7.0 (m, 4H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.41-19.97 (CH_3CH), 52.13, 52.34, 55.08, 56.32, 56.38, 57.62 (CHCOOMe, CHCl, OCH_3), 114.01, 128.37, 129.90 (CH), 159.24, 161,95, 167,47, 167,81 (CO ester & β-lactam). Calcd. for $C_{13}H_{14}ClNO_3$: C, 58.33; H, 5.27; N, 5.23; Cl, 13.24. Found: C,58.38; H, 5.15; N, 5.25; Cl, 13.26.

3-Phenyl-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6b**. CH_2Cl_2 10 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 2 mmol, 444 mg), triethylamine (3.5 equiv, 7 mmol, 0.98 mL), phenylacetyl chloride **2b** (3 equiv, 6 mmol, 880 mg). Addition in 5 min at 20°C, reaction in 20h at 40°C. The cycloadducts (482 mg, 71% yield) were isolated by purification on column chromatography (CH_2Cl_2). GC (*prog 3*) t_R = 32.3 min (43%), t_R = 32.6 min (57%). ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers δ 1.65 (d, *J* = 7.08 Hz, 3H, CH_3CH), 1.87 (d, *J* = 7.08 Hz, 3H, CH_3CH), 3.19 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.17 et 4.25 (d, *J* = 5.95 Hz, 1H, CHCOOMe or CHPh), 4.60 et 5.15 (q, *J* = 7.08 Hz, 1H, $CHCH_3$), 4,60 (d, *J* = 5.95 Hz, 1H, CHCOOMe or CHPh), 6.85-

7.35 (m, 9H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.51, 19.56 (**CH_3**CH), 51.38, 55.20, 57.15, 57.63 (**C**HCOOMe, CHPh, **OCH_3**), 113.57, 127.40-128.46 (CH), 130.66, 131.73, 132.75 (C quaternary), 159.06, 166.44, 169.06 (CO ester & β-lactam); Anal. Calcd.for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.83; H, 6.11; N, 4.15.

3-Methoxy-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6c**. CH_2Cl_2 (8 mL), [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 3.64 mmol, 808 mg), triethylamine (3.5 equiv, 12.6 mmol, 1.8 mL), methoxyacetyl chloride **2c** (3 equiv, 19.8 mmol, 1 mL). Addition in 5 min at 20°C, reaction in 19h at 20°C. The *cis* cycloadducts (740 mg, 69% yield) were isolated by purification on column chromatography (CH_2Cl_2 then 10% AcOEt). GC (*prog 3*) t_R = 25.11 min (63%), t_R = 25.50 min (37%); ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers δ 1.63 & 1.79 (d, *J* = 7.06 Hz, 3H, **CH_3**CH), 3.50 (s, 3H, **OCH_3**), 3.71 & 3.78 (s, 3H, **OCH_3**), 3.80 & 3.81 (s, 3H, **OCH_3**), 4.06 & 4.09 (d, *J* = 5.1 Hz, 1H, CH), 4.58 & 4.60 (q, *J* = 5.1 Hz, 1H, CH), 4.60 & 5.01 (q, *J* = 7.06 Hz, 1H, **CH**CH_3), 7.0 (m, 4H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 19.15, 20.61, 51.66, 52.62, 52.68, 55.26, 55.68, 58.77, 58.72, 84.13, 84.34, 114.56, 126.59, 128.87, 129.05, 131.37, 132.80, 159.73, 169.76, 169.28; SM (EI, rel int) *major m/z* 177 (40), 162 (54), 136 (10), 135 (100); *minor m/z* 177 (37), 162 (44), 136 (10), 135 (100); IR 3068, 2956, 2840, 1762, 1613, 1514, 1249, 213, 1179, 1028, 835; Anal. Calcd.for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.47; H, 6.55; N, 4.70.

3,3-Dichloro-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6d**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 4.83 mmol, 1.07 g), triethylamine (2.5 equiv, 12.07 mmol, 1.7 mL), dichloroacetyl chloride **2d** (2 equiv, 9.66 mmol, 0.93 mL). Addition in 5 min at 15°C, reaction in 2h at 15°C. The *cis* cycloadducts (1.54 g, 94% yield) were isolated by purification on column chromatography (CH_2Cl_2). GC (*prog 3*) t_R = 25.1 min (42%), t_R = 25.5 min (58%); ^{1}H NMR ($CDCl_3$, 200 MHz) *major* δ 1.67 (d, *J* = 7.06 Hz, 3H, **CH_3**CH), 3.80 (s, 1H, **OCH_3**), 4.21 (s, 1H, **CH**COOMe), 5.04 (q, *J* = 7.06 Hz, 1H, **CH**CH_3), 7.10 (m, 4H, CH arom), *minor* δ 1.84 (d, *J* =7.06 Hz, 3H, **CH_3**CH), 3.80 (s, 1H, **OCH_3**), 4.26 (s, 1H, **CH**COOMe), 4.63 (q, *J* = 7.06 Hz, 1H, **CH**CH_3), 7.10 (m, 4H, CH arom); ^{13}C NMR($CDCl_3$, 50 MHz) two diastereomers δ 18.39 & 20.44 (**CH_3**CH), 52.98, 55.29, 56.0 (**OCH_3**), 69.76 & 69.32 (**C**HCOOMe), 80.0 (CCl_2), 114.49 (CHN), 128 (CH arom), 131 (C), 159.67, 165.88, 166.26 (CO ester & β-lactam); MS (EI, rel int) *minor m/z* 162 (6.4), 136 (10), 135 (100), 105 (4.8), 103 (4.0), 91 (4.7), 79 (4.8), 77 (5.9), 65 (2.4), 59 (2.2), 39 (2.2); *major m/z* 331 (26) 296 (28), 162 (78), 147 (30), 136 (16), 135 (100), 120 (25), 105 (73), 103 (49), 92 (3.8), 91 (8.9), 79 (7.6), 78 (2.9), 77 (9.8), 65 (4.3), 59 (3.6), 51 (2.3), 39 (4); IR 3002, 2955, 2838, 1801, 1764, 1515, 1253, 1213, 1179, 837; Anal. Calcd. for $C_{14}H_{15}C_{12}NO_4$: C, 50.62; H, 4.55; N, 4.22; Cl, 21.35. Found: C, 50.32; H, 4.56; N, 4.07; Cl, 21.7.

3-Chloro-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-3-phenyl-azetidine-2-carboxylic acid methyl ester **6e**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 3.97 mmol, 882 mg), triethylamine (3.5 equiv, 13.9 mmol, 1.96 mL), 1-chloro-1-phenylacetyl chloride **2e** (3 equiv, 10.9 mmol, 1.9 mL). Addition in 5 min at 20°C, reaction in 24h at 40°C. The *cis* and *trans* cycloadducts (1.410 g, 95% yield) were isolated by purification on column chromatography (CH_2Cl_2). GC (*prog 3*) t_R = 32.6 min (1%), t_R = 32.8 min (14%), t_R = 33.1 min (46%), t_R = 33.4 min (39%). ^{1}H NMR ($CDCl_3$, 200 MHz) four diastereomers δ 1.69 & 1.87 (d, *J* = 7.06 Hz, 3H, **CH_3**CH), 3.26 (s, 3H, **OCH_3**), 3.74 & 3.84 (s, 3H, **OCH_3**), 4.29 (s, 1H, **CH**COOMe), 4.65, 5.05 & 5.15 (q, *J* = 7.06 Hz, 1H, **CH**CH_3), 6.83 à 7.54 (m, 9H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) four diastereomers δ 18.76, 20.56, 52.67, 55.18, 65.57, 68.38, 114.11, 126.79, 128.58, 131.79, 131.93, 136.20, 159.36, 163.52, 167.91; MS (EI rel int) isomer at 46% *m/z* 162 (12), 136 (10), 135 (100), 105 (4), 77 (4); isomer at 39% *m/z* 162 (10), 136 (10), 135 (100), 105 (3), 77 (3). IR 3068, 2956, 2840, 1774, 1613, 1515, 1251, 1180, 1034, 838; Anal. Calcd. for $C_{20}H_{20}ClNO_4$: C, 64.26; H, 5.39; N, 3.75; Cl, 9.48. Found: C, 64.20; H, 5.33; N, 3.64; Cl, 9.50.

3-Ethyl-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6f**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 6.9 mmol, 1.532 g), triethylamine (3.5 equiv, 23.1 mmol, 3.3 mL), butyryl chloride **2f** (3 equiv, 19.8 mmol, 2.06 mL). Addition in 5 min at 20°C, reaction in 18h at 20°C. The *cis* cycloadducts (2.01 g, 99% yield) were isolated by purification on column chromatography (CH_2Cl_2). GC (*prog 3*): t_R = 25.36 min (44%), t_R = 25.88 min (56%); ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers δ 0.95 (t, *J* = 7.4 Hz, 3H, **CH_3CH_2**), 1.50 & 1.70 (d, *J* = 7.06 Hz, 3H, **CH_3**CH), 3.15 (m, 1H, **CH**CH_2), 3.63 & 3.66 (s, 3H, **OCH_3**), 3.74 (s, 3H, **OCH_3**), 3.85 et 3.95 (d, *J* = 6.1 Hz, 1H, **CH**COOMe), 4.48 & 4.90 (q, *J* = 7.06 Hz, 1H, **CH**CH_3), 7.10 (m, 4H, CH arom); ^{13}C NMR ($CDCl_3$, 50

MHz) two diastereomers δ 11.43, 18.35, 18.70, 20.03, 30.54, 51.04, 51.60, 51.66, 53.75, 54.00, 54.30, 54.47, 54.56, 54.92, 76.42, 77.06, 77.70, 112.76, 113.74, 127.89, 128.23, 131.07, 132.71, 158.87, 168.80, 170.13, 170.50; SM (EI, rel int) *minor m/z* 248 (5), 162 (15), 136 (10), 135 (100), 91 (6); *major m/z* 248 (7), 221 (6), 162 (16), 136 (10), 135 (100), 91 (6). IR 2953, 2938, 2887, 1758, 1613, 1514, 1250, 1202, 1178, 834. Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N:4.81. Found: C, 65.86; H, 7.23; N, 4.76.

3-Benzyloxy-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6g**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d** (1 equiv, 1.98 mmol, 439 mg), triethylamine (3.5 equiv, 6.93 mmol, 0.98 mL), benzyloxyacetyl chloride **2g** (3 equiv, 5.94 mmol, 0.72 mL). Addition in 5 min at 20°C, reaction in 4h at 40°C. The two *cis* cycloadducts in the ratio 56:44 (610 mg, 88% yield) were isolated by purification on column chromatography (CH_2Cl_2 than AcOEt). GC (*prog 3*) t_R *major* = 35.4 min, t_R *minor* = 35.7 min; ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers: δ 1.60 & 1.75 (d, *J* = 7.06 Hz, 3H, C**H**$_3$CH), 3.60 & 3.67 (s, 1H, OCH_3), 3.73 (s, 3H, OCH_3), 4.05 & 4.09 (d, *J* = 5.1 Hz, 1H, C**H**COOMe), 4.68 (s, 2H, OCH_2), 4.71 (d, *J* = 5.1 Hz, CHOBn), 5.03 (q, *J* = 7.06 Hz, 1H, CH_3C**H**), 6.85-7.27 (m, 9H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.51, 19.92, 51.92, 54.49, 54.95, 58.18, 58.24, 72.74, 81.17, 81.40, 113.15, 128.15, 130.7, 132.08, 136.32, 136.38, 159.02, 165.28, 165.48, 168.63; MS (EI, rel int) *major m/z* 177 (69), 162 (57), 136 (11), 135 (100), 91 (88); *minor m/z* 177 (60), 162 (46), 136 (11), 135 (100), 91 (65); IR 3067, 2953, 2837, 1764, 1514, 1250, 1205, 1178; Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.23; H, 6.20; N, 3.75.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6h**. CH_2Cl_2 8 mL, [2-(4-methoxyphenyl)-propylidene)-carbamic acid methyl ester **1d**[33] (1 equiv, 1.98 mmol, 439 mg), triethylamine (3.5 equiv, 6.80 mmol, 0.98 mL), phthaloylglycine chloride **2h**[33] (3 equiv, 5.94 mmol, 1.328 g). Addition in 5 min at 20°C, reaction in 19h at 20°C. The *cis* cycloadducts (767 mg, 95% yield) were isolated by purification on column chromatography (CH_2Cl_2 then AcOEt). GC (*prog 3*) t_R = 43,1 min (57%), t_R = 43,2 min (43%); ^{1}H NMR ($CDCl_3$, 200 MHz) two diastereomers δ 1.78 & 1.90 (d, *J* = 7.06 Hz, 3H, C**H**$_3$CH), 3.51 & 3.55 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.25 & 4.26 (d, *J* = 6 Hz, 1H, CH), 4.87 & 5.13 (q, *J* = 7.06 Hz, 1H, C**H**CH$_3$), 5.46 & 5.50 (d, *J* = 6 Hz, 1H, CH), 6.90 & 7.30 (m, 4H, CH arom); 7.79 (m, 4H, phthaloyl); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 18.87, 20.06, 52.22, 55.05, 55.34, 55.66, 56.50, 113.99, 123.52, 127.76, 131.23, 134.38, 158.98, 162.97, 167.73. MS (EI, rel int) *major m/z* 177 (22), 135 (100), 136 (10), 162 (30); *minor m/z* 177 (20), 162 (33), 136 (12), 135 (100). IR 3431, 2953, 2838, 1766, 1722, 1612, 1514, 1391, 1248, 1179, 720. Anal. Calcd. for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.76; H, 4.90; N, 6.93.

Transformation of the N-(4-methoxyphenyl) group into the N-H function by CAN oxidation: 3-Chloro-4-oxo-azetidine-2-carboxylic acid methyl ester **7a**. To a cold solution (0°C) of 3-chloro-1-(4-methoxy-phenyl)-4-oxo-azetidine-2-carboxylic acid methyl ester **3a** (1 equiv, 0.74 mmol, 200 mg) in acetonitrile (8 mL) was added dropwise the CAN (3 equiv, 2.23 mmol, 1, 22 g) aqueous solution (10 mL H_2O sat. NaCl). The mixture was stirred at 0°C for 25 min, then diluted with H_2O. The aqueous phase was extracted with ethyl acetate (x 3). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2) to give the desired product **7a** (0.06 g, 0.37 mmol, 50%). GC (*prog 1*) t_R = 8 min. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 1H, OCH_3), 4.58 (d, *J* = 5.4 Hz, 1H, C**H**COOMe), 5.11 (d, *J* = 5.4 Hz, CHCl), 7.14 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.92 (OCH_3), 55.47 (CHCl), 59.32 (**C**H-COOCH$_3$), 163.43 & 166.37 (C=O, ester & β-lactam); MS (EI, rel int) *m/z* 128 (1.9), 122 (14.1), 104 (21.6), 61 (10.4), 59 (9.9), 41 (12.7); Anal. Calcd. for $C_5H_6ClNO_3$: C, 36.72; H, 3.70; N, 8.56; Cl, 21.68. Found: C, 36.66; H, 3.70; N, 8.60; Cl, 21.60.

Transformation of the N-(1-phenyl-ethyl) group into the N-H function by potassium persulfate oxidation: 3-Ethyl-4-oxo-azetidine-2-carboxylic acid methyl ester **7f**. To a stirred solution of 3-ethyl-1-[1-(4-methoxy-phenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6f** (522 mg 2 mmol, 1 equiv) in a mixture of acetic acid (6.5 mL) and water (4.5 mL), heated at 88°C, was added $K_2S_2O_8$ (1.42 mg 5.2 mmol, 2.6 equiv). On TLC, the desired compound **7f** were not visualized by UV light or by means of a 5% ethanolic solution of molybdophosphoric acid. Thus, the reaction was monitored by GC. After 45 min at this temperature, the mixture was heated at 50°C and K_2HPO_4 (2 g) was added. Le solvent was removed under reduced pressure. The residue was dissolved in a mixture of water (10 mL) and ethyl acetate (6 mL) and solid $NaHCO_3$ was added until bubbling stoppped. The suspension was filtered on celite and rinsed with ethyl acetate. The aqueous phase

was extracted with ethyl acetate. The organic portions were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2) to give the starting material **6f** (70 mg) and the desired product **7f** (200 mg, 36%). GC (*prog 1*) t_R = 6.3 min; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (t, 3H, *J* = 7.2 Hz, CH_3-CH_2), 1.63 (m, 2H, CH_3-CH_2), 3.45 (m, 1H, CH-CH_2), 3.78 (s, 3H, OCH_3), 4.29 (d, 2H, *J* = 5.8 Hz, CHCOOMe), 6.7 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.5 (CH_3CH_2), 19.46 (CH_3CH_2), 52.27 (CH_3OCO), 52.38 (CHNH), 56.80 (CH-CH_2), 170.2 (CO β-lactam), 170.98 (CO ester); MS (EI, rel int) *m/z*, 114 (88.9), 98 (16.5), 83 (33.6), 82 (39.9), 70 (12.6), 59 (40.7), 55 (100), 54 (32.1), 53 (16.5), 43 (54.5), 42 (20.9), 41 (35.3), 39 (35.2), 29 (30.8), 27 (32.6); IR 3411, 2955, 1772, 1748, 1439, 1215; Anal. Calcd.for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.43; H, 7.05; N, 8.87.

Transformation of the N-(4-methoxyphenyl-ethyl) group into the N-H function by CAN oxidation.

To a cooled (0°C) acetonitrile solution of azetidinone, was added dropwise a NaCl saturated aqueous solution of CAN. The mixture was stirred at 0°C for the time indicated in each case then diluted with H_2O. The aqueous phase was extracted with ethyl acetate (x 3). The organic portions were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.

4-Oxo-3-phenyl-azetidine-2-carboxylic acid methyl ester **7b**. Acetonitrile (10 mL), 3-phenyl-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6b** (1 equiv, 0.97 mmol. 328 mg), CAN (3 equiv, 2.9 mmol, 1.5 g) in 12 mL H_2O (sat. NaCl). Reaction for 30 min. Column chromatography (CH_2Cl_2 then AcOEt). 121 mg, 60% yield. GC (*prog 3*) t_R = 15,5 min; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.30 (s, 3H, OCH_3); 4.56 (d, *J* = 6 Hz, 1H, CH), 4.81 (d, *J* = 6 Hz, 1H, CH), 6.46 (s br, 1H, NH), 7.28 (m, 5H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.77 (OCH_3), 54.94 (CH), 60.46 (CH), 127.81 (CH arom), 131.69 (C *ipso*), 167.5 & 169.78 (CO ester & β-lactam); MS (EI, rel int) *m/z* 162 (100), 161 (29), 131 (76), 118 (12), 103 (24), 91 (14), 90 (24), 89 (19), 77 (13); IR 3329, 3065, 2941, 2853, 1751, 1731, 1438, 1220, 1067, 695; Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 65.34; H, 5.52; N, 6.06.

3-Methoxy-4-oxo-azetidine-2-carboxylic acid methyl ester **7c**. Acetonitrile (9 mL), 3-methoxy-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6c** (1 equiv, 0.8 mmol. 240 mg), CAN (4 equiv, 3.2 mmol, 1.79 g) in 15 mL H_2O (sat. NaCl). Reaction for 1h. Column chromatography (CH_2Cl_2, R_f = 0.1 then AcOEt R_f = 0.8). 100 mg 79% yield. GC (*prog 3*) t_R = 8.95 min. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.53 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.42 (d, *J* = 5.1 Hz, 1H, $CHOCH_3$), 4.79 (m, 1H, CHCOOMe), 7,06 (m, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.60 (OCH_3), 55.86 (CH), 59.50 (OCH_3), 86.61 (CH), 167.29 & 169.66 (CO ester & β lactam); MS (EI, rel int) *m/z* 87 (49), 85 (100), 72 (20), 45 (14), 29 (19); IR 3412, 3068, 2956, 2843, 1790, 1752, 1439, 1216. Anal. Calcd. for $C_6H_9NO_4$: C, 45,28; H, 5,70; N, 8,80. Found: C, 45,27; H, 5,64; N, 8,73.

3,3-Dichloro-4-oxo-azetidine-2-carboxylic acid methyl ester **7d**. Acetonitrile (11 mL), 3,3-dichloro-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6d** (1 equiv, 1 mmol, 332 mg), CAN (4 equiv, 4 mmol, 2,19 g) in 18 mL H_2O (sat. NaCl). Reaction for 12h. Column chromatography (CH_2Cl_2 R_f = 0.1 then AcOEt R_f = 0.8), 120 mg, 61% yield. GC (*prog 3*) t_R = 11,1 min. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.90 (s, 3H, OCH_3), 4.70 (s, 1H, CH), 7.53 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.93 (OMe or CH), 67.82 (OMe or CH), 82.98 (CCl_2), 161.11 & 167.18 (CO ester & β-lactam); MS (EI, rel int) *m/z* 156 (24), 154 (35), 125 (66), 123 (100), 110 (14), 59 (12), 28 (31); IR 3403, 3068, 2958, 1818, 1761, 1440, 1250, 1224, 1158, 1039, 941; Anal. Calcd. for $C_5H_5Cl_2NO_3$: C, 30.33; H, 2.55; N, 7.07; Cl, 35.81.Found: C, 30.48; H, 2.48; N, 7.15; Cl, 35.50.

3-Chloro-4-oxo-3-phenyl-azetidine-2-carboxylic acid methyl ester **7e**. Acetonitrile (35 mL), 3-chloro-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-3-phenyl-azetidine-2-carboxylic acid methyl ester **6e** (1 equiv, 3.2 mmol, 1.2 g), CAN (4 equiv, 12.8 mmol, 7g) in 58 mL H_2O (sat. NaCl), reaction for 3h. Column chromatography (CH_2Cl_2, R_f = 0.4). 580 mg, 76% yield. GC (*progr 3*): t_R *minor* (42%) = 19.4 min, t_R *major* (58%) = 20.7 min. ^{1}H NMR ($CDCl_3$, 200 MHz) *major* δ 3.32 (s, 1H, NH), 3.90 (s, 3H, OCH_3), 4.68 (s, 1H, CH), 7.50 (m, 5H, CH arom); ^{13}C NMR ($CDCl_3$, 50 MHz) two diastereomers δ 53.01, 62.86, 66.15 (CH & OCH_3), 127.05, 129.01, 129.62 (CH arom), 132.91, 135.86 (C-*ipso*), 164.50, 164.79, 167.88, 168.34 (CO ester & β-lactam); MS (EI, rel int) *minor m/z*, 198 (18), 197 (21), 196 (58), 195 (49), 167 (30), 165 (100), 117 (13), 102 (21), 91 (52), 89 (49), 63 (18), 39 (15);*major m/z* 197 (20) 196 (63), 195 (50), 167 (33), 165 (100), 117 (16), 102

(23), 90 (17), 89 (41), 63 (15), 39 (14); IR 3406, 3068, 2956, 1799, 1757, 1439, 1247, 1218; Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84; Cl, 14.79. Found: C, 55.10; H, 4.36; N, 5.89; Cl, 14.90.

3-Ethyl-4-oxo-azetidine-2-carboxylic acid methyl ester **7f**. Acetonitrile (8 mL), 3-ethyl-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6f** (1 equiv, 0.69 mmol, 200 mg), CAN (4 equiv, 2.76 mmol, 1.51 g) in 12 mL H_2O (sat. NaCl). Reaction for 3h. Column chromatography CH_2Cl_2, R_f = 0.1 then AcOEt, R_f = 0.8), 70 mg, 65% yield. GC (*prog 3*) t_R = 8.85 min. ^1H, ^{13}C NMR and MS previously described.

3-Benzyloxy-4-oxo-azetidine-2-carboxylic acid methyl ester **7g**. Acetonitrile (10 mL), 3-benzyloxy-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo-azetidine-2-carboxylic acid methyl ester **6g** (1 equiv, 0.813 mmol. 300 mg), CAN (3 equiv, 2.4 mmol. 1.34 g) in 12 mL H_2O (sat. NaCl). Reaction for 1h. Column chromatography (CH_2Cl_2 then AcOEt). 170 mg, 89% yield; GC: (*prog 3*) t_R = 22.02 min. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 3H, OCH_3), 4.39 (d, J = 5 Hz, 1H, CHOBn), 4,71 (s, 2H, OCH_2), 4.93 (m, 1H, CHNH), 7.07 (m, 1H, NH), 7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.03 (OCH_3), 56.46 (CHCOOMe), 73.63 (OCH_2), 84.75 (OCH), 128.0-129.2 (CH arom), 136.97 (C *ipso*), 167.87 & 170.71 (CO ester & β lactam); MS (EI, rel int) *m/z* 174 (5), 92 (9), 91 (100), 65 (6); IR 3412, 3068, 2955, 2853, 1789, 1752, 1439, 1215, 1120, 688; Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.16; H, 5.56; N, 5.93.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-oxo-azetidine-2-carboxylic acid methyl ester **7h**. Acetonitrile (10 mL), 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1-[1-(4-methoxyphenyl)-ethyl]-4-oxo azetidine-2-carboxylic acid methyl ester **6h** (1 equiv, 0.96 mmol, 390 mg), CAN (4 equiv, 3.8 mmol, 2.09 g) in 17 mL H_2O (sat. NaCl). Reaction for 1h. From the crude product, the desired β-lactam **7h** was extracted with pentane in which the β-lactam **6h** was insoluble, 180 mg, 68% yield. GC (*prog 3*) t_R = 31.29 min. RMN ^1H ($CDCl_3$, 200 MHz) δ 3.46 (s, 3H, OCH_3), 4.65 (d, J = 5.86 Hz, 1H, CH), 5.67 (d, J = 5.86 Hz, 1H, CH), 7.90 (m, 4H, phthaloyl), 9.06 (s br, 1H, NH); MS (EI, rel int) *m/z* 231 (80), 200 (100), 172 (39), 104 (38),,76 (48); IR 3319, 2939, 1800, 1770, 1724, 1711, 1399, 1271, 724; Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.85; H, 3.62; N, 10.21.

Sodium salt of 3-chloro-4-oxo-azetidine-2-carboxylic acid. To a solution of 3-chloro-4-oxo-azetidine-2-carboxylic acid methyl ester **7a** (163.5 mg, 0.92 mmol, 1 equiv) in acetone (2.4 mL) was added a solution of NaOH (40 mg, 1.0 mmol, 1.1 equiv) in water (2 mL). The mixture was stirred at room temperature for 2h. Acetone was evaporated and the resulting solution was diluted with water, neutralised by addition of a 3N HCl solution. The aqueous solution was washed with CH_2Cl_2 (10 mL) and then evaporated under reduced pressure. The solid residue was shaked with methanol (2 mL) to precipitate the NaCl which was eliminated by filtration. After methanol evaporation, the sodium carboxylate of **7a** was obtained as a white solid (60 mg, 43 % yield). ^1H NMR (DMSO, 300 MHz) δ 4.0 (d, J = 5.3 Hz, 1H, CHCO), 5.1 (d, J = 5.3 Hz, 1H, CHCl), IR 3427, 1766, 1614, 1416, 1314. Anal. Too hygroscopic to allow an accurate weighting.

Sodium salt of 3-ethyl-4-oxo-azetidine-2-carboxylic acid. From 3-ethyl-4-oxo-azetidine-2-carboxylic acid methyl ester **7f** (120 mg, 0.76 mmol, 1 equiv) in acetone (2 mL) and NaOH (34 mg, 0.84 mmol, 1.1 equiv) in water (1.3 mL). White solid (80 mg, 64% yield).^1H NMR (D_2O, 200 MHz) δ 1.00 (t, J = 7.4 Hz, 3H, CH_3), 1.61 (m, 2H, CH_2), 3.40 (m, 1H, CHCH$_2$), 4.21 (d, J = 5.6 Hz, 1H, CHNH); ^{13}C NMR (D_2O, 50 MHz) δ 12.00 (CH_3), 19.94 (CH_2), 54.94 (CH), 55.02 (CH), 175.90 & 178.32 (CO ester & β-lactam); MS (EI, rel int) *m/z* 125 (48), 82 (42), 59 (35), 54 (100), 44 (72), 39 (50); IR 3427, 2968, 2940, 1744, 1597, 1420. Anal. Too hygroscopic to allow an accurate weighting.

Sodium salt of 3-benzyloxy-4-oxo-azetidine-2-carboxylic acid . From 3-benzyloxy-4-oxo-azetidine-2-carboxylic acid methyl ester **7g** (410 mg, 1.74 mmol, 1 equiv) in acetone (4.5 mL) and NaOH (77 mg, 1.9 mmol, 1.1 equiv) in water (3 mL). White hygroscopic solid (200 mg, 49 % yield).^1H NMR (DMSO, 200 MHz) δ 3.9 (d, J = 5.8 Hz, 1H, CHCOO), 4.5 (d, J = 11.5 Hz, 1H, benzylic), 4.7 (d, J = 5.8 Hz, 1H, CHCO), 4.8 (d, J = 11.5 Hz, 1H, benzylic), 7.3 (m, 5H, Ph); IR 3419, 1752, 1605, 1420, 1128, 697. Anal. Too hygroscopic to allow an accurate weighting.

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