Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 7591–7606
Tetrahedron

Synthesis of enantiomerically pure α-amino-β-hydroxy-cyclobutanone derivatives and their transformations into polyfunctional three- and five-membered ring compounds

Léon Ghosez,[a,b,*] Gaoqiang Yang,[a] José Renato Cagnon,[a] Franck Le Bideau[a] and Jacqueline Marchand-Brynaert[a]

[a]*Department of Chemistry, University of Louvain, Place L. Pasteur 1, B-1348 Louvain-la-Neuve, Belgium*
[b]*Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac Cedex, France*

Received 17 May 2004; revised 8 June 2004; accepted 11 June 2004

Dedicated to Professor Dieter Seebach in recognition of his seminal contributions to organic chemistry

Abstract—Ketenes readily cycloadded to (*R*)-*tert*-butyldihydrooxazole **2a**–**d** to yield enantiomerically pure bicyclic cyclobutanones. The cycloadditions proceeded with unusual regiochemistry giving predominantly or exclusively protected α-amino-β-hydroxycyclobutanone derivatives. The adducts could be converted into a variety of interesting enantiopure intermediates equipped with many functional groups: α-amino-β-hydroxy cyclopropane carboxylic acid derivatives, α-amino-β-hydroxy succinic acid derivatives, α-amino-β-hydroxy lactones and lactams derivatives.

1. Introduction

The growing resistance of bacterial strains to antibiotics is a major concern of our society.[1] β-Lactam antibiotics are the most often prescribed class of antibacterial agents and, as a result, bacteria have developed efficient resistance mechanisms to these antibiotics. For instance the microorganisms produce β-lactamases which are able to cleave the ester linkage formed by acylation of D,D-peptidases by the antibiotics, thus regenerating the free enzyme which can again exercise its biological function.[2] For several years, we have been interested in the design, synthesis and biological evaluation of new inhibitors of penicillin binding proteins.[3–5] Our approach was to design molecules which would make an ether link with the serine protease, thus suppressing the regeneration of the free enzyme by a hydrolytic mechanism. In this context, the replacement of the acylating lactam function of penicillins or cephalosporins by a reactive hydroxyalkylating carbonyl group could lead to stable adducts with bacterial serine proteases. General structure **1** (Fig. 1) or its stereoisomers were regarded as potential alkylating inhibitors of these enzymes: (a) the carbonyl group is part of a strained ring and more

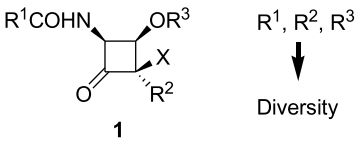
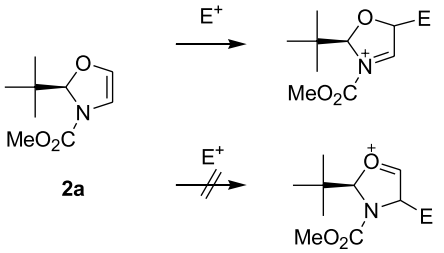


Figure 1.

susceptible to undergo addition reactions; (b) the X atom (H, F, Cl) could be used to modulate the electrophilic reactivity of the neighbouring carbonyl group; (c) the carboxyl and acylamino groups are properly placed to mimic the β-lactam antibiotics.

Clearly such an endeavour required an easy access to enantiomerically pure 2-aminocyclobutanones with appropriate functional groups at C-3 and C-4. Methyl (2*R*)-2-*tert*-butyldihydrooxazole **2a** first studied in Seebach's group[6]

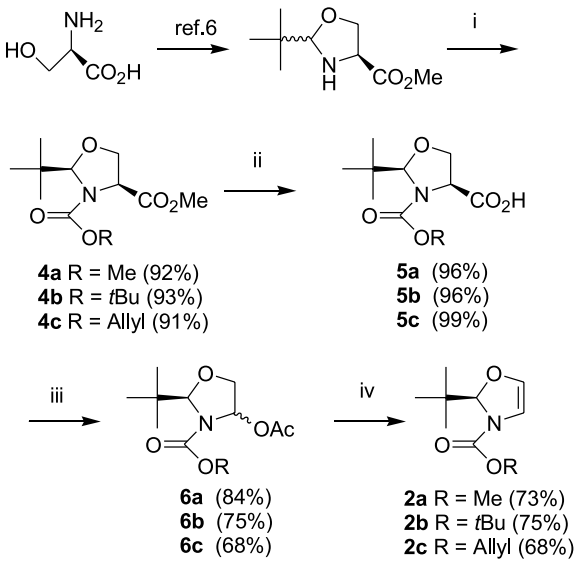


Scheme 1.

Keywords: Asymmetric synthesis; (2+2) Cycloaddition; Ketene; Cyclobutanone; Cyclopropane; Amino acid; Serine protease.
* Corresponding author. Tel: +33-5-4000-2217; fax: +33-5-4000-2222; e-mail address: l.ghosez@iecb.u-bordeaux.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.085

was regarded as an interesting olefinic building-block which should selectively cycloadd with ketenes from the face opposite to the *tert*-butyl substituent (Scheme 1). However Seebach et al. had shown that electrophilic additions to **2a** always occurred at C-5 as a result of the lower energy of an acyl iminium intermediate relative to that of an oxonium ion.[7] Thus ketenes were expected to react with **2** to yield an adduct with the carbonyl group α to the oxygen. Additional steps would then be needed to move the carbonyl group to the right position. Gratifyingly our initial studies showed that the theoretical predictions were not fulfilled: the cycloaddition of **2a** with diphenylketene led to the unpredicted, yet desired cycloadduct.[8] We now report the full details of the cycloaddition of ketenes to (2*H*)oxazoles as well as illustrative examples of the synthetic potential of the cycloadducts.



Scheme 2. Reagents and conditions: (i) MeOCOCl, Et_3N (**4a**), $(Boc)_2O$, $NaHCO_3$, MeOH (**4b**), AllylOCOCl, $NaHCO_3$, MeOH (**4c**); (ii) KOH, MeOH–H_2O, RT; (iii) $Pb(OAc)_4$, benzene, reflux, (iv) NH_4Br, 1,2-dichloroethane, reflux.

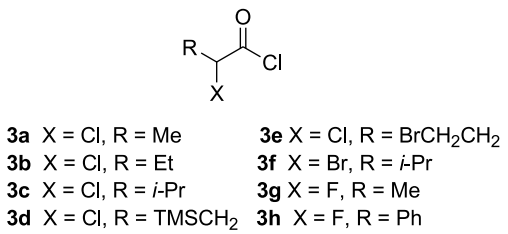


Figure 2.

2. Results and discussion

2.1. Synthesis of (2*H*)oxazoles

Methyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate **2a**,**b** were prepared from l-serine following the procedure described by Seebach[6] except for the electrochemical oxidative decarboxylation step (Scheme 2). We found that a thermal oxidative decarboxylation with lead tetraacetate was more practical and gave better yields (84 and 82%) than the described electrochemical method (33%). The new (2*H*)oxazoles **2c** and **2d** (enantiomer of **2b**, prepared from d-serine) were also synthesized by this modified procedure. These optimized sequences of reactions allowed us to prepare up to 50 g of enantiopure (2*H*)oxazoles in 35–45% overall yield.

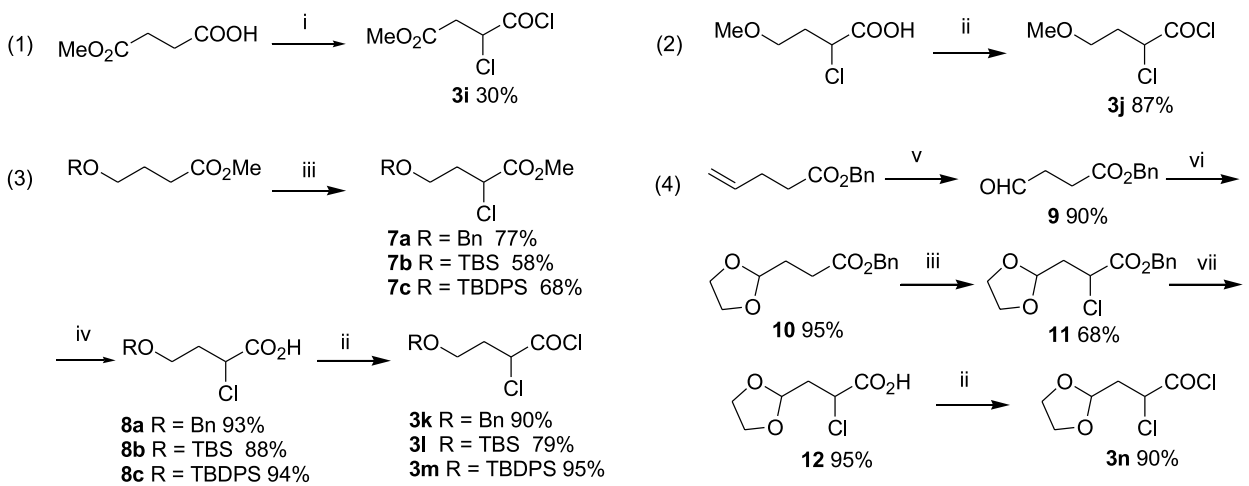
2.2. Synthesis of acyl chlorides

Ketenes were conveniently generated by dehydrochlorination of the corresponding acid chlorides. α-Chloroacyl chlorides **3a**–**h** were readily prepared following literature procedures (Fig. 2).[9]

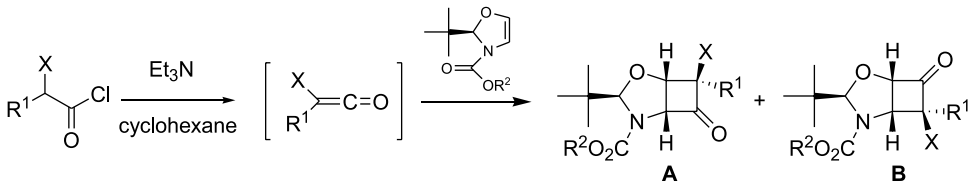
Acyl chlorides **3i**–**n** was synthesized by the sequences of reaction shown in Scheme 3.

2.3. Cycloaddition reactions

2.3.1. Cycloadditions to α-haloketenes. α-Haloketenes were generated in situ from the corresponding acid chlorides **3** and triethylamine. In most cases cycloadditions were performed in cyclohexane at 60 °C to give high yields of adducts (Scheme 4, Table 1). No cycloadduct was obtained



Scheme 3. Reagents and conditions: (i) $SOCl_2$, 70 °C, then NCS, $SOCl_2$, HCl, 85 °C; (ii) $(COCl)_2$, DMF, DCM; (iii) LDA, −78 °C, then CCl_4; (iv) LiOH, THF–H_2O, H_2O_2; (v) O_3, DCM; (vi) ethylene glycol, TsOH, benzene; (vii) H_2, Pd/C.



Scheme 4.

Table 1. Cycloadditions of oxazolines **2a–c** to haloketenes

Entry	R^1	R^2	X	Adduct	Yield (%)	**A/B**
1	Me	Me	Cl	**13**	80[a]	>98:2
2	*t*-Bu	Me	Cl	**14**	75[a]	>98:2
3	Allyl	Me	Cl	**15**	78	Only **A**
4	Me	Et	Cl	**16**	80	Only **A**
5	Me	*i*Pr	Cl	**17**	62[a]	10:1
6	*t*-Bu	*i*Pr	Cl	**18**	65[b]	4:1
7	Me	Ph	Cl	**19**	87[a]	10:1
8	*t*-Bu	Ph	Cl	**20**	60[a]	6:1
9	Me	CH_2TMS	Cl	**21**	86	Only **A**
10	*t*-Bu	CH_2TMS	Cl	**22**	82	Only **A**
11	Me	CH_2CH_2Br	Cl	**23**	80[b]	6:1
12	*t*-Bu	CH_2CH_2Br	Cl	**24**	72[b]	8:1
13	Allyl	CH_2CH_2Br	Cl	**25**	77[a]	20:1
14	Me	CH_2CH_2OMe	Cl	**26**	76[b]	8:1
15	Me	CH_2CH_2OSi*t*$BuMe_2$	Cl	**27**	54[a]	8/1
16	Me	CH_2CH_2OSi*t*$BuPh_2$	Cl	**28**	80[a]	19:1
17	*t*-Bu	CH_2CH_2OSi*t*$BuPh_2$	Cl	**29**	75[a]	20:1
18	Allyl	CH_2CH_2OSi*t*$BuPh_2$	Cl	**30**	77[b]	10:1
19	Me	CH_2CH_2OBn	Cl	**31**	72[b]	6:1
20	*t*-Bu	CH_2CH_2OBn	Cl	**32**	56	Only **A**
21	Me	$CH_2CH(OCH_2CH_2O)$	Cl	**33**	62[b]	10:1
22	Me	$CH_2CO_2CH_3$	Cl		0	
23	Me	*i*Pr	Br	**34**	74[b]	4:1
24	Me	Me	F		0	
25	Me	Ph	F		0	

[a] Pure isomer **A**.
[b] Purified mixture of **A** and **B**.

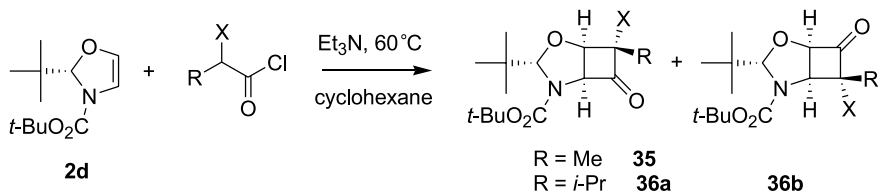
with the acid chloride derived from methyl monochlorosuccinate (entry 22). In this case, the ketene was probably not formed since a facile competitive β-elimination of HCl could occur. Also we did not get any adduct from the α-fluoroacyl chlorides (entries 24 and 25). It is also highly probable that the corresponding fluoroketenes were not formed. As in the model reaction with diphenylketene, the cycloaddition was regioselective, yielding predominantly or exclusively the isomer with the carbonyl group α to the nitrogen substituent.

The cycloadditions were remarkably stereoselective. In all cases, the addition took place from the face opposite to the *t*-butyl group and the halogen atom was always *exo*. Thus the reaction produced enantiomerically pure adducts. The configuration of the stereogenic centers of the adducts results from the selection of the serine enantiomer (here l-serine) and the stereochemical course of the reaction.

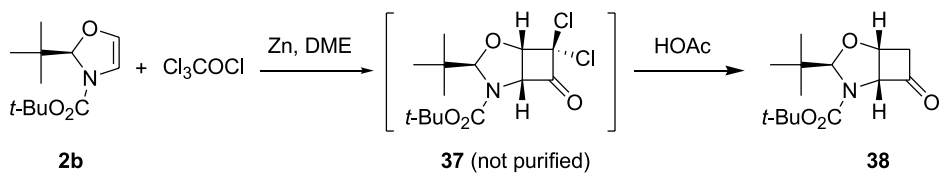
(2*H*)Oxazole **2d**, the enantiomer of **2b** was prepared from d-serine. It also reacted with ketenes derived from acid chlorides **3a** and **3c** to give good yields of adducts **35** and **36a-b** (Scheme 5).

The cycloaddition of **2b** with dichloroketene was less successful as a result of the instability of the adduct **37** which was therefore dechlorinated in situ to give a modest 30% yield of **38**. The best conditions are described in Scheme 6.

The structure and configuration of adducts were established by a detailed analysis of their ^1H and ^{13}C NMR spectra and the use of NOE effects (Section 4). The assignments were confirmed by X-ray diffraction analyses of a 'minor' adduct **20B** and a 'major' adduct **29A**.[10] The regioselectivity of the cycloaddition excluded a two-step pathway involving a zwitterionic intermediate since an electrophilic addition to (2*H*)oxazoles should predominantly lead to isomer **B** in agreement with the earlier observations of Seebach's group.[6] Both the regio- and stereoselectivity of the cycloaddition can be accounted for by a concerted cycloaddition involving an orthogonal approach of the ketene to the less-hindered face (away from the *t*-butyl substituent) of the (2*H*)oxazole and with the larger



Scheme 5.



Scheme 6.

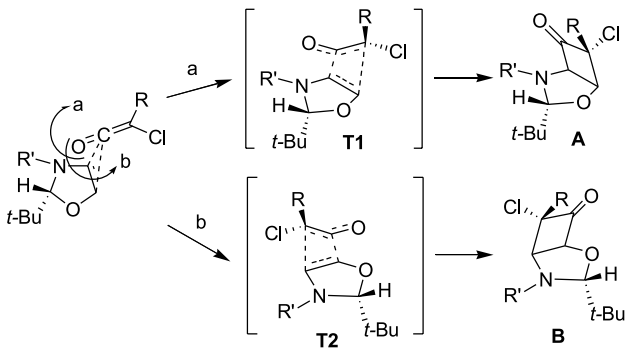
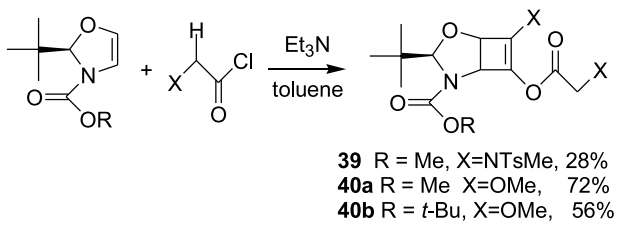


Figure 3.

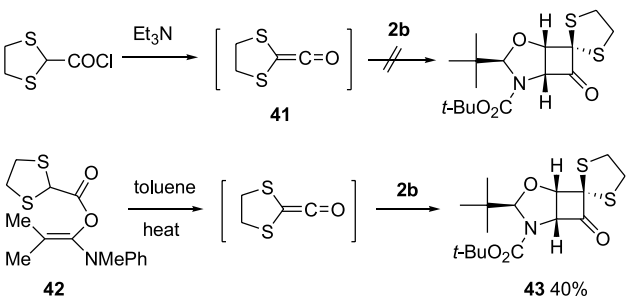
substituent R away from the double bond (Fig. 3). It can be readily seen that rotation *b* which is favoured by electronic factors would create an interaction between R and the nitrogen substituent. No such steric repulsion results from rotation *a* which places the carbonyl group α to the nitrogen atom. Thus, in all cases, steric effects superseded electronic effects.



39 R = Me, X=NTsMe, 28%
40a R = Me X=OMe, 72%
40b R = *t*-Bu, X=OMe, 56%

Scheme 7.

2.3.2. Cycloadditions to other ketenes. Scheme 7 describes the [2+2] cycloadditions of (2*H*)oxazoles **2a** and **2b** with *N*-methyl-*N*-tosyl- or methoxyketene.[11] Surprisingly we could not isolate the cyclobutanone adducts which were acylated in situ to give enol esters **39** and **40**. The high temperature (110 °C) required for these cycloadditions probably accounted for the acylation of the adducts. Of special interest to us was the cycloaddition of **2b** to dithiolanoketene **41**, a synthetic equivalent of the unknown dimer of CO (Scheme 8).[12] In this case, the cycloaddition did not occur when the ketene was generated from the acid chloride. However the thermolysis of **42** in refluxing toluene slowly generated ketene **41** which was trapped by olefin **2b** to give adduct **43** in moderate yields.

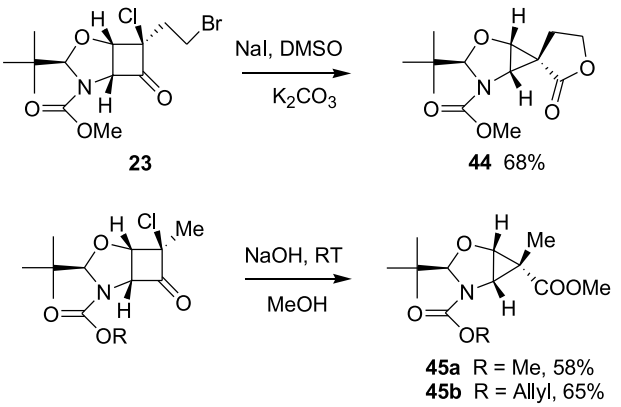


Scheme 8.

2.4. Selected transformations of the cycloadducts

The concatenation of many functional groups in these readily accessible cyclobutane derivatives make them interesting enantiopure synthetic intermediates. It was out of the scope of this work to investigate in detail the synthetic potential of these cyclobutanones. We just performed a selected number of transformations showing that the four-membered ring could readily be transformed into three- and five-membered rings or be cleaved to generate functionalized α-amino acid derivatives.

2.4.1. Synthesis of enantiopure α-aminocyclopropane carboxylic acid derivatives. In the course of our studies on the total synthesis of bacterial peptidase inhibitors, we observed that the treatment of cyclobutanone **23** with NaI in DMSO containing potassium carbonate did not yield the desired iodide but rather led to a cyclopropane carboxylic acid derivative **44** resulting from a Favorskii rearrangement (Scheme 9). The same ring contraction could be more classically effected by sodium hydroxide in methanol.[13]

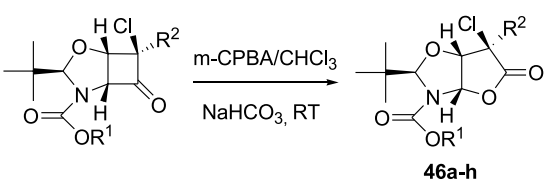


45a R = Me, 58%
45b R = Allyl, 65%

Scheme 9.

Thus the sequential cycloaddition-Favorskii rearrangement represents a potentially useful route towards highly functionalized enantiopure α-aminocyclopropane carboxylic acid derivatives.

2.4.2. Synthesis of enantiopure bicyclic γ-lactones and γ-lactams. A number of cyclobutanones could be readily oxidized to the corresponding γ-butyrolactones **46a–h** (Scheme 10, Table 2). The reaction was totally regiospecific giving the expected isomer resulting from the insertion of the oxygen atom into the carbon–carbon bond adjacent to the acylamino substituent. Yields were excellent.

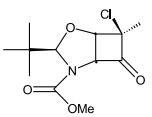
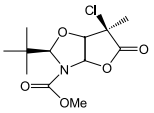
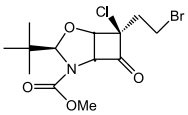
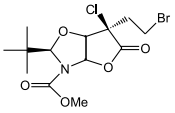
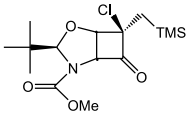
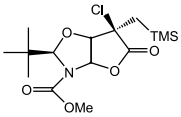
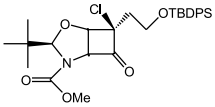
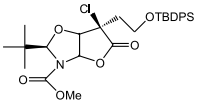
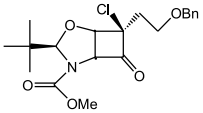
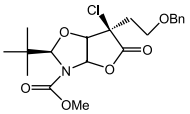
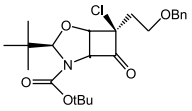
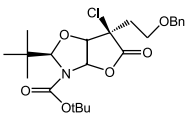
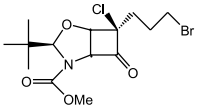
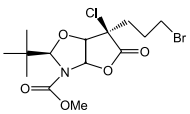
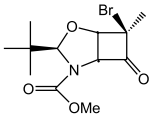
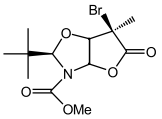


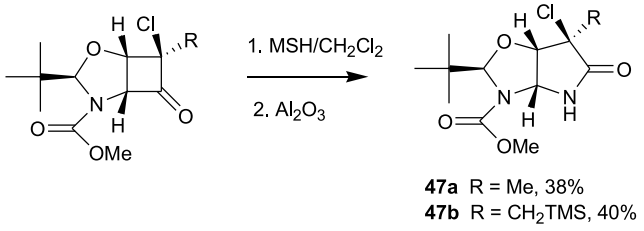
Scheme 10.

Similarly treatment of cyclobutanones **13** and **21** by an excess of *o*-mesitylsulfonylhydroxylamine,[14] followed by absorption on basic alumina and elution with methanol gave a moderate yield of bicyclic γ-lactam **47a–b** and but in moderate yields (Scheme 11).

2.4.3. Synthesis of enantiomerically pure α-amino-β-hydroxysuccinic acid derivatives. Based on previous

Table 2. Bayer–Villiger oxidations

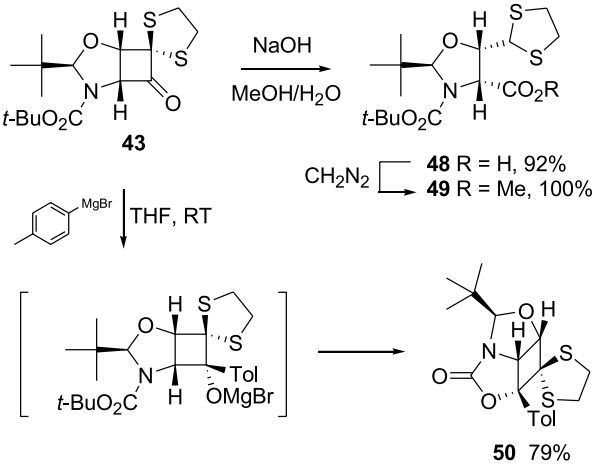
Substrates	Products		Yield (%)
		**46a**	90
		**46b**	85
		**46c**	92
		**46d**	90
		**46e**	88
		**46f**	86
		**46g**	85
		**46h**	80



Scheme 11.

observations, it was anticipated that cyclobutanone **43** should be readily cleaved by nucleophilic reagents. Indeed treatment of **43** with sodium hydroxide in methanol–water or with sodium methoxide at room temperature led to the selective cleavage of the four-membered ring in very high yield (Scheme 12). Compound **48** corresponds to a product of vicinal acylation of (2*H*)oxazole **2b**.

Interestingly the reaction of cyclobutanone **43** with tolyl magnesium bromide yielded the tricyclic structure **50** resulting from a stereoselective addition of the Grignard reagent from the *exo*-face of the bicyclic cyclobutanone



Scheme 12.

followed by nucleophilic attack of the resulting alkoxide ion on the carbamate group.

3. Conclusions

In conclusion, we have described the unique capacity of (2*H*)oxazole to react with ketenes to yield enantiopure α-amino-cyclobutanone derivatives. The stereochemistry of the cycloadditions is controlled by the large *t*-butyl group. Steric factors in an orthogonal transition state readily account for the unusual regiochemistry of these reactions. The rich functionality of the adducts should make them very useful for further transformations. These intermediates thus appeared to be well suited for the synthesis of our target inhibitors **1** of bacterial peptidases (Fig. 1). We have also shown in selected experiments that the four-membered ring could be contracted or expanded to generate enantiopure three- or five-membered ring derivatives. They could also be used for the preparation of new α-amino acids.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian Gemini 300BB (300 MHz for ^{1}H and 75 MHz for ^{13}C). High resolution spectra were recorded on a Brucker AM-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are given in ppm relative to the internal reference. Coupling constants (*J* values) are reported in Hertz (Hz), and multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). The MS spectra were recorded on a Varian MAT-44 or FINNIGAN MAT-TSQ 70 apparatus. Infrared spectra were recorded on a BIORAD FTS-135. The optical rotation values were measured on a PERKIN–ELMER 241 polarimeter. Concentrations are given in g/100 ml. Melting points were measured with a BUCHI apparatus (oil bath) and are uncorrected. Flash chromatography separations were performed using MERCK 60 40–63 μm silica and pre-distilled technical grade solvents. Triethylamine, CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled on CaH_2.

Cyclohexane and toluene were distilled on Na with benzophenone as indicator. DMF was dried over 3 Å MS.

4.1.1. 3-(*tert*-Butyl)4-methyl (2*R*,4*S*)-2-(*tert*-butyl)-1,3-oxazolane-3,4-dicarboxylate 4b. Into a 1 l three-necked flask equipped with a condenser, methyl (2*R*,4*S*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (38.0 g, 0.2 mol), sodium bicarbonate (41.72 g, 0.5 mol), di-*t*-butyl dicarbonate (44.7 g, 0.2 mol,) and methanol (550 ml) were added, the mixture was allowed to stay in an ultrasonic bath at 50 °C for 5 h. After cooling, the mixture was filtered, and the filtrate was concentrated under the reduced pressure. The resulting residue was diluted with diethyl ether, and washed with brine, dried over $MgSO_4$ and concentrated to give **4b** as a colourless oil (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H, NCHO), 4.70 (dd, J=8.3, 6.1 Hz, 1H, CH_2O), 4.30 (dd, J=8.4, 6.0 Hz, 1H, CH_2O), 4.12 (t, J=8.4 Hz, 1H, CHN), 3.75 (s, 3H, MeO), 1.47 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C=O), 155.2 (C=O), 97.8 (NCHO), 81.4 (O*t*Bu), 68.7 (CH_2O), 59.6 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 28.4 (O*t*Bu), 25.6 (*t*Bu). IR (neat) ν 2976, 1764, 1709. $[\alpha]_D^{20}=-33.1$ (*c* 1.14 $CHCl_3$). MS (CI) *m*/*z* 287 (M^+), 230, 174, 130, 57. Anal. Calcd for $C_{14}H_{25}NO_5$ C 58.52, H 8.76, N 4.87; found C 58.85, H 8.53, N 4.25.

4.1.2. 3-Allyl 4-methyl (2*R*,4*S*)-2-(*tert*-butyl)-1,3-oxazolane-3,4-dicarboxylate 4c. Into a 500 ml three-necked flask equipped with an additional funnel, methyl (2*R*,4*S*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (38 g, 0.2 mol) and dichloromethane (250 ml) were added, the mixture was cooled to 0 °C, and then allyl chloroformate (25 g, 0.21 mol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. After filtration, the filtrate was washed with 1 N HCl and brine, then dried over $MgSO_4$ and concentrated to give the product as a colourless oil, yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 1H, =CH), 5.32 (ddd, J=17.2, 3.1, 1.5 Hz, 1H, CH_2=), 5.24 (ddd, J=10.4, 2.7, 1.3 Hz, 1H, CH_2=), 5.1 (s, 1H, NCHO), 4.77 (dd, J=8.0, 4.9 Hz, 1H, CH_2O), 4.64 (dd, J=5.4, 1.4 Hz, 2H, CH_2OCO), 4.35 (dd, J=8.6, 4.9 Hz, 1H, CH_2O), 4.12 (t, J=8.4 Hz, 1H, CHN), 3.72 (s, 3H, MeO), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C=O), 155.8 (C=O), 132.2 (CH=), 117.9 (CH_2=), 97.8 (NCHO), 68.2 (CH_2OCO), 66.7 (CH_2O), 59.6 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 25.6 (*t*Bu).

4.1.3. *tert*-Butyl (2*S*,4*R*)-4-methoxycarbonyl-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate (4d). Into a 250 ml flask equipped with a condenser, methyl (2*S*,4*R*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (15.7 g, 83.85 mmol), sodium bicarbonate (17.6 g, 209.6 mmol) and di-*t*-butyl dicarbonate (18.86 g, 83.85 mmol) in methanol (234 ml) were added. The mixture was stirred at 50 °C in an ultrasonic bath for 5 h. The solution was filtered and the MeOH was evaporated. The residue was diluted with ether and washed with brine, dried over $MgSO_4$ and concentrated to give the product (22.6 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H, NCHO), 4.7 (m, 1H, CH_2O), 4.28 (dd, J=8.6, 5.75 Hz, 1H, CH_2O), 4.14 (t, J=8.6 Hz, 1H, CHN), 3.76 (s, 3H, MeO), 1.48 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C=O), 155.9 (C=O), 97.5 (NCHO), 81.8 (O*t*Bu), 68.3 (CH_2O), 59.7 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 28.3 (O*t*Bu), 25.8 (*t*Bu).

4.2. General procedure for the preparation of 5a–5d

Into a 500 ml three-necked flask equipped with an additional funnel, **4a–4d** (1 equiv.) and methanol (2 ml/mmol) was added, the mixture was cooled to 0 °C and then 3 N KOH (1.5 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed, and the residue was diluted with ether, then acidified with 3 N HCl till pH 1–2, and then extracted with ether. The combined organic layers were washed with 2 N NaCl, dried and concentrated to give the product **5a–5d**.

4.2.1. (2*R*,4*S*)-4-(*tert*-Butoxycarbonyl)-2-(*tert*-butyl)-1,3-oxazolane-4-carboxylic acid 5b. White solid, yield 94%, mp 106–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (b, 1H, OH), 5.06 (s, 1H, NCHO), 4.69 (dd, J=9.0, 6.4 Hz, 1H, CH_2O), 4.40 (dd, J=9.0, 6.4 Hz, 1H, CH_2O), 4.23 (t, J=9.0 Hz, 1H, CHN), 1.49 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C=O), 155.8 (C=O), 97.6 (NCHO), 82.4 (O*t*Bu), 67.8 (CH_2O), 59.4 (CHN), 37.8 (*t*Bu), 28.2 (O*t*Bu), 25.6 (*t*Bu). IR (neat) ν (cm^{-1}) 3180, 2979, 1765, 1681. $[\alpha]_D^{20}=-64$ (*c* 1.0 $CHCl_3$). MS (CI) *m*/*z* 216 (M^+), 160, 116, 57. Anal. Calcd for $C_{14}H_{25}NO_5$ C 57.12, H 8.48, N 5.12; found C 57.56, H 8.20, N 5.68.

4.2.2. (2*R*,4*S*)-4-(Allyloxycarbonyl)-2-(*tert*-butyl)-1,3-oxazolane-4-carboxylic acid 5c. White solid, yield 96%, mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H, =CH), 5.34 (ddd, J=17.2, 3.0, 1.5 Hz, 1H, CH_2=), 5.25 (ddd, J=10.5, 2.7, 1.3 Hz, 1H, CH_2=), 5.12 (s, 1H, NCHO), 4.78 (dd, J=8.5, 5.5 Hz, 1H, CH_2O), 4.66 (ddd, J=15.7, 2.7, 1.4 Hz, 2H, CH_2OCO), 4.41 (dd, J=8.8, 5.5 Hz, 1H, CH_2O), 4.2 (t, J=8.6 Hz, 1H, CHN), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C=O), 156.5 (C=O), 131.8 (CH=), 118.6 (CH_2=), 97.9 (NCHO), 68.0 (CH_2OCO), 67.2 (CH_2O), 59.6 (CHN), 37.5 (*t*Bu), 25.6 (*t*Bu).

4.2.3. *tert*-Butyl (2*S*,4*R*)-4-hydroxycarbonyl-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate (5d). White solid, yield 89%, mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H, OH), 5.07 (s, 1H, NCHO), 4.65 (dd, J=8.7, 6.4 Hz, 1H, CH_2O), 4.47 (dd, J=8.7, 6.3 Hz, 1H, CH_2O), 4.24 (t, J=8.8 Hz, 1H, CHN), 1.50 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C=O), 155.9 (C=O), 97.4 (NCHO), 83.5 (O*t*Bu), 67.7 (CH_2O), 59.4 (CHN), 37.8 (*t*Bu), 28.1 (O*t*Bu), 26.7 (*t*Bu).

4.3. General procedure for the preparation of 6a–6d

Into a 1 l three-necked flask equipped with an additional funnel, lead tetraacetate (1.5 equiv.) and benzene (3 ml/mmol) were added. After stirring for 30 min, **5a–5d** (1 equiv.) in benzene (1 ml/mmol) was added dropwise. The mixture was allowed to heat to reflux for 8 h. After cooling, the mixture was filtered through a small column of 6–7 cm celite, washed with cyclohexane. The solvent was removed under the reduced pressure; the residue was diluted with

pentane, then filtered through a pad of silica gel. The filtrate was concentrated to give the product **6a–6d**.

4.3.1. *tert*-Butyl (2*R*,4*R*)-4-acetyloxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6b. Colorless oil, yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (dd, J=5.2, 2.2 Hz, 1H, CHOAc), 5.08 (s, 1H, NCHO), 4.15 (dd, J=10.2, 5.2 Hz, 1H, CH_2O), 3.98 (dd, J=10.0, 2.2 Hz, 1H, CH_2O), 2.08 (s, 3H, CH_3CO), 1.48 (s, 9H, O*t*Bu), 0.98 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 154.5 (C=O), 97.7 (NCHO), 82.9 (CHOAc), 81.4 (O*t*Bu), 66.8 (CH_2O), 38.0 (*t*Bu), 28.4 (O*t*Bu), 25.2 (*t*Bu), 21.2 (Me). IR (film) ν 2978, 1719, 1480, 1360. $[\alpha]_D^{20}$=+25.7 (*c* 1.07 $CHCl_3$). MS (EI) *m*/*z* 287 ($M^{+\cdot}$), 230 (M−*t*Bu)$^+$, 130. Anal. Calcd for $C_{14}H_{25}NO_5$ C 58.51, H 8.76, N 4.87; found C 58.75, H 8.87, N 4.97.

4.3.2. Allyl (2*R*,4*R*)-4-acetyloxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6c. Colourless oil, yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J=4.94, 1.92 Hz, 1H, CHOAc), 5.93 (m, 1H, =CH), 5.33 (ddd, J=17.2, 3.0, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.6, 2.7, 1.4 Hz, 1H, CH_2=), 5.12 (s, 1H, NCHO), 4.64 (dt, J=15.7, 1.4 Hz, 2H, CH_2OCO), 4.13 (dd, J=10.0, 5.0 Hz, 1H, CH_2O), 4.01 (dd, J=10.0, 1.9 Hz, 1H, CH_2O), 2.01 (s, 3H, CH_3CO), 0.98 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 154.5 (C=O), 131.8 (CH=), 118.4 (CH_2=), 97.7 (NCHO), 82.9 (CHOAc), 72.65 (CH_2OCO), 66.8 (CH_2O), 37.2 (*t*Bu), 25.6 (*t*Bu).

4.3.3. *tert*-Butyl (2*S*,4*R*)-4-acetoxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6d. Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (dd, J=5.3, 1.9 Hz, 1H, CHOCO), 5.08 (s, 1H, NCHO), 4.15 (dd, J=10.0, 5.3 Hz, 1H, CH_2O), 3.97 (dd, J=10.0, 2.4 Hz, 1H, CH_2O), 2.1 (s, 3H, Me), 1.48 (s, 9H, O*t*Bu), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C=O), 153.6 (C=O), 97.4 (NCHO), 83.3 (CHOCO), 81.8 (O*t*Bu), 72.7 (CH_2O), 37.1 (*t*Bu), 28.1 (O*t*Bu), 25.6 (*t*Bu), 21.0 (Me).

4.4. General procedure for the preparation of 2a–2d

Into a 500 ml three-necked flask equipped with an extractor connected with a condenser, **6a–6d** (1 equiv.), ammonium bromide (2.5 equiv.) and toluene (2 ml/mmol) were added. In the extractor toluene (150 ml) and 3 N KOH (150 ml) were added. The mixture was allowed to warm to reflux for 6 h. After cooling, the mixture was filtered and the filtrate was washed with a solution of saturated $NaHCO_3$ and brine, then dried and concentrated. The residue was flash chromatographied to give the product **2a–2d**.

4.4.1. *tert*-Butyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate 2b. White solid, yield 68%, mp 45–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J=13.7 Hz, 2H, CHO, CHN), 5.60 (s, 1H, NCHO), 1.44 (s, 9H, O*t*Bu), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 (C=O), 133.5 (CHO), 109.5 (CHN), 98.2 (NCHO), 81.2 (O*t*Bu), 38.3 (*t*Bu), 28.2 (O*t*Bu), 26.1 (*t*Bu). $[\alpha]_D^{20}$=+352 (*c* 1.01, $CHCl_3$). MS (CI) *m*/*z* 227 (M^+), 170, 114, 70. Anal. Calcd for $C_{12}H_{21}NO_3$ C 63.40, H 9.31, N 6.16; found C 63.10, H 9.22, N 5.91.

4.4.2. Allyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate 2c. White solid, yield 85%, mp 38–40 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J=13.7 Hz, 2H, CHO, CHN), 5.93 (m, 1H, =CH), 5.62 (s, 1H, NCHO), 5.33 (ddd, J=17.2, 3.1, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.4, 2.7, 1.4 Hz, 1H, CH_2=), 4.64 (dd, J=5.7, 1.4 Hz, 2H, CH_2), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C=O), 133.7 (CHO), 132.3 (CH=), 118.1 (CH_2=), 109.5 (CHN), 98.2 (NCHO), 66.4 (CH_2O), 38.3 (*t*Bu), 24.1 (*t*Bu). $[\alpha]_D^{20}$=+432 (*c* 1.05, $CHCl_3$). MS (EI) *m*/*z* (%) 211 (M+1, 74), 154 (M−*t*Bu, 100), 110 (74), 70 (19). Anal. Calcd for $C_{11}H_{17}NO_3$ C 62.86, H 8.08, N 6.42; found C 62.54, H 8.11, N 6.63.

4.4.3. *tert*-Butyl (2*S*)-2-(*tert*-butyl)-1,3-oxazole-3-carboxylate 2d. White solid, yield 74%, mp 45–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (se, 2H, NCHO, CH=), 5.56 (s, 1H, CH=), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C=O), 133.1 (CH=), 101.0 (CH=), 97.9 (NCHO), 81.0 (O*t*Bu), 38.2 (*t*Bu), 28.2 (O*t*Bu), 24.1 (*t*Bu). MS (APCI) *m*/*z* (%) 172 (M−*t*Bu, 10), 126 (M−Boc, 80). $[\alpha]_{20}^{D}$=−3.6 (*c* 1.3, $CHCl_3$), Anal. Calcd for $C_{12}H_{21}NO_3$ C 63.41, H 9.31, N 6.16; found C 63.72, H 9.08, N 6.29.

4.4.4. 2-Chloro-3-methoxycarbonylpropanoyl chloride 3i. Mono-methyl succinate (6.23 g, 44.79 mmol) and thionyl chloride (13.1 ml, 179.1 mmol) were placed in a 50 ml flask equipped with a magnetic bar and a condenser with a drying tube. The reaction mixture was stirred and heated in a 70 °C oil bath. After 0.5 h, the flask was removed from the oil bath and cooled to room temperature. The finely powdered *N*-chlorosuccinimide (12 g, 89.6 mmol), thionyl chloride (9 ml, 122.9 mmol) and hydrochloric acid (conc. 270 μl) were added consecutively. The flask was heated again to 85 °C for 3 h. The solvent was removed under the reduced pressure and the solid (succinimide) was washed with CCl_4. The filtrate was fractionally distilled to give the product (2.5 g, 30%), bp 30–32 °C/0.1 mm Hg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (dd, J=7.1, 6.5 Hz, 1H, CHCl), 3.76 (s, 3H, OCH_3), 3.04–3.29 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C=O), 167.8 (C=O), 66.4 (CHCl), 52.2 (OCH_3), 35.2 (CH_2).

4.5. General procedure for α-chlorination of ester

Methyl 4-benzyloxybutanoate (10 g, 48.0 mmol) in THF (25 ml) was added dropwise at −78 °C to a LDA solution that was prepared by adding *n*-butyllithium (2.4 M in hexane, 20 ml, 48.0 mmol) to diisopropylamine (7.1 ml, 50.4 mmol) in THF (250 ml) at 0 °C and stirring for 30 min. After stirring for a further 20 min, CCl_4 (5.0 ml, 52.8 mmol) was added rapidly and the resulting solution was stirred for 5 min at −78 °C, then a solution of saturated NH_4Cl (160 ml) was added and the mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give the product. Purification by flash chromatography gave pure product.

4.5.1. Methyl 4-benzyloxy-2-chlorobutanoate 7a. Colourless oil, yield 77%, R_f=0.3 (PE/AcOEt=9/1,) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5H, Ph), 4.55 (dd, J=8.35, 5.55 Hz, 1H, CHCl), 4.50 (s, 2H, $PhCH_2$), 3.71 (s,

3H, OMe), 3.65 (m, 2H, OCH_2), 2.16–2.37 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 138.0 (C_{arom}), 128.4, 128.3, 127.6 (CH_{arom}), 73.1 ($PhCH_2$), 65.7 (OCH_2), 54.3 (CHCl), 52.7 (OMe), 35.1 (CH_2). MS (APCI) *m/z* (%) 243 (M+1, 5), 91 (100). Anal. Calcd for $C_{12}H_{15}ClO_3$ C 59.39, H 6.23, Cl 14.60; found C 59.68, H 6.14, Cl 15.39.

4.5.2. Methyl 2-chloro-4-*tert*-butyldimethylsilyloxy butanoate 7b. Colorless oil, yield 58%, R_f=0.42 (PE/AcOEt=16/1) ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, *J*=9.0, 5.1 Hz, 1H, CHCl), 3.78 (s, 3H, OMe), 3.76 (m, 2H, OCH_2), 2.0–2.3 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 58.7 (OCH_2), 54.1 (CHCl), 52.9 (OMe), 37.5 (CH_2), 25.8 (*t*Bu), 18.2 (*t*Bu), −5.5 (SiMe).

4.5.3. Methyl 2-chloro-4-*tert*-butyldiphenylsilyloxy butanoate 7c. Yield 68%, R_f=0.3 (PE/Et_2O=16/1), ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.76 (m, 10H, 2Ph), 4.77 (dd, *J*=8.8, 4.94 Hz, 1H, CHCl), 3.9 (m, 2H, OCH_2), 3.8 (s, 3H, OMe), 2.15–2.45 (m, 2H, CH_2), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (C=O), 133.5 (C_{arom}), 135.5, 129.6, 127.6 (CH_{arom}), 59.7 (OCH_2), 54.1 (CHCl), 52.8 (OMe), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.2 (CH_2). MS (APCI) *m/z* (%) 391 (M+1, 5), 313 (M−Ph, 100). Anal. Calcd for $C_{21}H_{27}ClO_3Si$ C 64.51, H 6.96, Cl 9.07; found C 65.19, H 6.86, Cl 9.24.

4.5.4. General procedure for the hydrolysis of methyl esters. Into a 100 ml flask, methyl 2-chloro-4-benzyloxy-butanoate (3.65 g, 15.0 mmol) was dissloved in THF (90 ml), then a solution of lithium hydroxide monohydrate (947 mg, 22.55 mmol) in water (40 ml) was added at 0 °C. The mixture was stirred overnight, acidified with H_2SO_4 to pH 3, and then extracted with CH_2Cl_2. The combined dichloromethane was dried and evaporated to afford the product.

4.5.5. 4-Benzyloxy-2-chlorobutanoic acid 8a. Yield 93%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.7 (s, 1H, OH), 7.27–7.37 (m, 5H, Ph), 4.56 (dd, *J*=8.6, 5.2 Hz, 1H, CHCl), 4.51 (s, 2H, $PhCH_2$), 3.65 (m, 2H, OCH_2), 2.12–2.41 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C=O), 137.8 (C_{arom}), 128.4, 128.3, 127.6 (CH_{arom}), 73.1 ($PhCH_2$), 65.7 (OCH_2), 54.4 (CHCl), 34.8 (CH_2). MS (APCI) *m/z* (%) 229 (M+1, 45), 136 (10), 91 (100). Anal. Calcd for $C_{11}H_{13}ClO_3$ C 57.78, H 5.73, Cl 15.50; found C 58.10, H 5.89, Cl 16.75.

4.5.6. 2-Chloro-4-*tert*-butyldimethylsilyloxybutanoic acid 8b. Yield 88%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H, OH), 4.50 (dd, *J*=8.5, 5.1 Hz, 1H, CHCl), 3.80 (m, 2H, OCH_2), 2.0–2.3 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (C=O), 58.7 (OCH_2), 54.3 (CHCl), 37.5 (CH_2), 25.8 (*t*Bu), 18.3 (*t*Bu), −5.5 (SiMe).

4.5.7. 2-Chloro-4-*tert*-butyldiphenylsilyloxybutanoic acid 8c. White solid, yield 94%. ^1H NMR (300 MHz, $CDCl_3$) δ 10.45 (s, 1H, OH), 7.38–7.72 (m, 10H, 2Ph), 4.68 (dd, *J*=8.7, 5.0 Hz, 1H, CHCl), 3.8 (m, 2H, OCH_2), 2.07–2.36 (m, 2H, CH_2), 1.05 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (C=O), 133.2 (C_{arom}), 135.5, 129.6, 127.6 (CH_{arom}), 59.6 (OCH_2), 54.3 (CHCl), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.1 (CH_2). MS (APCI) *m/z* (%) 377 (M+1, 100), 299 (M−Ph, 30), 209 (30). Anal. Calcd for $C_{20}H_{25}ClO_3Si$ C 63.72, H 6.68, Cl 9.41; found C 63.02, H 6.69, Cl 9.62.

4.6. General procedure for the preparation 3j–n

Into a 100 ml flask, 4-methoxy-2-chloro-3-butanoic acid (1 equiv.), catalytical amount of DMF and CH_2Cl_2 (10 ml/mmol) were added, the mixture was cooled to 0 °C, then oxalyl chloride (5 equiv.) was added dropwise. The mixture was allowed to warm slowly to 15 °C for 30 min. The solvent was removed under the reduced pressure, and the residue was diluted with benzene and concentrated one more time to give the product.

4.6.1. 4-Methoxy-2-chloro-3-butanoyl chloride 3j. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (dd, *J*=8.0, 5.0 Hz, 1H, CH), 3.60 (m, 2H, OCH_2), 3.35 (s, 3H, OMe), 2.2–2.48 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C=O), 67.3 (OCH_2), 62.4 (CH), 58.8 (OMe), 34.7 (CH_2).

4.6.2. 4-Benzyloxy-2-chlorobutanoylchloride 3k. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.38 (m, 5H, Ph), 4.81 (dd, *J*=8.0, 5.2 Hz, 1H, CHCl), 4.50 (s, 2H, $PhCH_2$), 3.66 (m, 2H, OCH_2), 2.22–2.51 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 137.8 (C_{arom}), 128.4, 127.8, 127.6 (CH_{arom}), 73.3 ($PhCH_2$), 64.9 (OCH_2), 62.5 (CHCl), 34.9 (CH_2).

4.6.3. 2-Chloro-4-*tert*-butyldimethylsilyloxybutanoyl chloride 3l. Yield 79%, ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (dd, *J*=8.0, 4.9 Hz, 1H, CHCl), 3.84 (m, 2H, OCH_2), 2.17–2.46 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C=O), 62.5 (OCH_2), 58.0 (CHCl), 38.5 (CH_2), 25.9 (*t*Bu), 18.3 (*t*Bu), −5.5 (SiMe).

4.6.4. 2-Chloro-4-*tert*-butyldiphenylsilyloxybutanoyl chloride 3m. Yield 95%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.70 (m, 10H, 2Ph), 4.90 (dd, *J*=8.0, 4.9 Hz, 1H, CHCl), 3.84 (m, 2H, OCH_2), 2.17–2.46 (m, 2H, CH_2), 1.06 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C=O), 133.0 (C_{arom}), 135.5, 129.6, 127.7 (CH_{arom}), 62.5 (OCH_2), 59.0 (CHCl), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.2 (CH_2).

4.6.5. 2-Chloro-3-(1,3-dioxolan-2-yl)propanoyl chloride 3n. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 5.1 (dd, *J*=4.65, 3.3 Hz, 1H CHCl), 4.72 (dd, *J*=7.5, 6.15 Hz, 1H, OCHO), 3.89–4.04 (m, 4H, OCH_2CH_2O), 2.34–2.61 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 100.5 (OCHO), 65.1 (OCH_2CH_2O), 60.1 (CHCl), 38.7 (CH_2).

4.6.6. 4-Oxo-butyric acid benzyl ester 9. Ozone was passed through a solution of benzyl 4-pentenoate (21 g, 110.3 mmol) in dichloromethane (160 ml) in a 250 ml three-necked flask at −78 °C until the solution became blue. Then triethylamine (30.7 ml, 220.7 mmol) was added and the mixture was warmed gradually to room temperature. The mixture was washed with 1N HCl (100 ml), then 5% $NaHCO_3$ (50 ml). The organic layer was dried and evaporated. The residue was flash chromatographied (PE/

AcOEt=6/1) to give pure product as a colourless oil, yield 90%, R_f=0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H, CHO), 7.31–7.37 (m, 5H, Ph), 5.12 (s, 2H, OCH_2), 2.61–2.8 (m, 4H, CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5 (C=O), 171.6 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 127.9 (CH_{arom}), 68.6 (OCH_2), 37.5 (CH_2CHO), 26.5 (CH_2).

4.6.7. Benzyl 3-(1,3-dioxolan-2-yl)propanoate 10. Into a 500 ml flask equipped with a Dean-Stark dried with flame under argon, benzyl 4-oxobutanoate (23 g, 119.6 mmol), ethylene glycol (13.3 ml, 239.3 mmol), anhydrous *para*-toluenesulfonic acid (2.06 g, 11.96 mmol) and benzene (690 ml) were mixed and heated to reflux until 2 ml water was collected. After cooling, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$, then dried and evaporated to give the product which is pure enough for the next reaction, yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.37 (m, 5H, Ph), 5.12 (s, 2H, OCH_2), 4.95 (t, J=4.1 Hz, 1H, OCHO), 3.80–3.95 (m, 4H, OCH_2CH_2O), 2.49 (t, J=7.36 Hz, 2H, CH_2CO), 2.04 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 127.9 (CH_{arom}), 110.1 (OCHO), 68.2 (OCH_2), 367.5 (OCH_2CH_2O), 26.4 (CH_2CO), 25.9 (CH_2).

4.6.8. Benzyl 2-chloro-3-(1,3-dioxolan-2-yl)propanoate 11. Colourless oil, yield 68%, R_f=0.3 (PE/AcOEt=8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.37 (m, 5H, Ph), 5.21 (s, 2H, OCH_2), 5.04 (dd, J=5.22, 3.4 Hz, 1H CHCl), 4.51 (t, J=7.1 Hz, 1H, OCHO), 3.81–3.95 (m, 4H, OCH_2CH_2O), 2.27–2.50 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 128.0 (CH_{arom}), 110.1 (OCHO), 67.6 (OCH_2), 65.1 (OCH_2CH_2O), 52.4 (CHCl), 38.9 (CH_2).

4.6.9. 2-Chloro-3-(1,3-dioxolan-2-yl)propanoic acid 12. Benzyl 2-chloro-3-(1,3-dioxolan-2-yl) propanoate (3.65 g, 13.48 mmol), palladium on activated carbon (10% Pd, 1.3 g; 1.2 mmol) and ethyl acetate (110 ml) were added to a 250 ml flask at room temperature, then hydrogen was flushed through a balloon. After 12 h, the mixture was passed through a pad of celite, washed with ether, dried over $MgSO_4$ and evaporated to give the product as a white solid, yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.1 (s, 1H, OH), 5.1 (dd, J=5.2, 3.4 Hz, 1H CHCl), 4.51 (t, J=7.1 Hz, 1H, OCHO), 3.89–4.0 (m, 4H, OCH_2CH_2O), 2.29–2.51 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (C=O), 101.1 (OCHO), 65.1 (OCH_2CH_2O), 52.4 (CHCl), 38.7 (CH_2).

4.7. General procedure for the [2+2] cycloaddition of oxazolines to haloketenes

Into a 250 ml three-necked flask dried by flame under the argon, oxazoline **2** (1 equiv.), triethylamine (1.2 equiv.) and cyclohexane (5 ml/mmol) were added, then acyl chloride (1.0–1.2 equiv.) in cyclohexane (2 ml/mmol) was added dropwise by a syringe pump at 60 °C. After the addition, the mixture was stirred at 60 °C for another 4 h, then cooled to room temperature. The mixture was allowed to stay at room temperature overnight, then filtered. The filtrate was evaporated to give the crude cycloadduct, which was purified by flash chromatography.

4.7.1. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 13. White solid, yield 77%, mp 103–105 °C, R_f=0.27 (3% isopropanol in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.34 (d, J=5.5 Hz, 1H, CHN), 4.90 (d, J=5.5 Hz, 1H, CHO), 3.76 (s, 3H, OMe), 1.62 (s, 3H, Me), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9 (C=O), 154.6 (C=O), 102.1 (NCHO), 81.3 (CHO), 75.0 (CCl), 74.2 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.2 (*t*Bu), 17.3 (Me). $[\alpha]_D^{20}$=+0.97 (1.03, $CHCl_3$). IR (KBr) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (EI) m/z (%) 276 ($M^{+\cdot}$, 6), 248 (27), 246 (66), 220 (24), 218 (74), 164 (36), 162 (93), 128 (88), 126 (100). Anal. Calcd for $C_{12}H_{18}ClNO_4$ C 52.27, H 6.58, Cl 12.86, N 4.77; found C 51.87, H 6.46, Cl 13.03, N 4.77.

4.7.2. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 14. Yield 75%, R_f=0.28 (3% isopropanol in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (s, 1H, NCHO), 5.23 (d, J=5.5 Hz, 1H, CHN), 4.88 (d, J=5.5 Hz, 1H, CHO), 1.62 (s, 3H, Me), 1.47 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.0 (C=O), 153.2 (C=O), 101.8 (NCHO), 81.6 (O*t*Bu), 81.5 (CHO), 75.3 (CCl), 74.4 (CHN), 39.1 (*t*Bu), 28.1 (O*t*Bu), 25.3 (*t*Bu), 17.5 (Me). $[\alpha]_D^{20}$=+1.0 (c 1.1, $CHCl_3$). IR (KBr) ν 1803 (C=O), 1715 (C=$O_{carbamate}$). MS (EI) m/z (%) 318 ($M^{+\cdot}$, 7), 290 (24), 288 (60), 262 (20), 224 (69), 168 (100). Anal. Calcd for $C_{15}H_{24}ClNO_4$ C 56.7, H 7.61, Cl 11.16, N 4.40; found C 57.77, H 7.70, Cl 10.27, N 4.27.

4.7.3. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 15. Yield 78%, R_f=0.27 (petroleum ether/AcOEt=4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H, CH=), 5.39 (s, 1H, NCHO), 5.37 (d, J=5.5 Hz, 1H, CHN), 5.36 (ddd, J=17.2, 3.2, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.3, 2.8, 1.4 Hz, 1H, CH_2=), 4.92 (d, J=5.5 Hz, 1H, CHO), 4.63 (dt, J=5.8, 1.4 Hz, 2H, CH_2O), 1.64 (s, 3H, Me), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 154.1 (C=O), 132.2 (CH=), 118.5 (=CH_2), 102.1 (NCHO), 81.3 (CHO), 75.0 (CH_2O), 74.2 (CHN), 66.8 (CCl), 39.0 (*t*Bu), 25.3 (*t*Bu), 17.3 (Me). IR (film) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (CI) m/z (%) 302 (M+1, 5), 244 (M−*t*Bu, 69), 216 (M−Alloc, 44), 188 (100), 152 (88), 108 (71).

4.7.4. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 16. Yield 82%, R_f=0.29 (3% isopropanol in petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (s, 1H, NCHO), 5.31 (d, J=5.56 Hz, 1H, CHO), 4.90 (d, J=5.56 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 1.97 (q, J=7.3 Hz, 2H, CH_2), 1.10 (t, J=7.3 Hz, 3H, CH_3), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (C=O), 154.2 (C=O), 102.0 (NCHO), 81.1 (CHO), 80.0 (CCl), 73.6 (CHN), 62.8 (OMe), 39.0 (*t*Bu), 25.4 (*t*Bu), 23.5 (CH_2), 8.1 (Me). IR (KBr) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (APCI) m/z (%) 290 (M+1, 66), 251 (M−COOMe, 16), 222 (16), 186 (20), 144 (30). HRMS (ESI) Calcd for $C_{13}H_{20}ClNO_4$ 290.1159, found 290.1148.

4.7.5. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 17. Colorless oil, yield 68%, R_f=0.20 (PE/Et_2O=10/1). ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H, NCHO), 5.31 (d, J=5.26 Hz, 1H, CHO), 4.90 (d, J=5.26 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 2.50 (m, 1H, $CHMe_2$), 1.10 (d, J=6.75 Hz, 3H, CH_3), 1.0 (d, J=6.75 Hz, 3H, CH_3), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1 (C=O), 154.3 (C=O), 101.9 (NCHO), 84.3 (CCl), 81.3 (CHO), 73.3 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 28.1 ($CHMe_2$), 25.4 (*t*Bu), 16.8 (Me), 16.7 (Me). IR (KBr) ν 1800 (C=O), 1716 (C=$O_{carbamate}$). MS (ESI) *m*/*z* (%) 304 (M+1, 16).

4.7.6. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 18. White solid, yield 58%, mp 114–116 °C, R_f=0.30 (PE/Et_2O=20/1). ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H, NCHO), 5.20 (d, J=5.7 Hz, 1H, CHO), 4.86 (d, J=5.7 Hz, 1H, CHN), 2.50 (m, 1H, $CHMe_2$), 1.49 (s, 9H, O*t*Bu), 1.10 (d, J=6.6 Hz, 3H, CH_3), 1.0 (d, J=6.6 Hz, 3H, CH_3), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 154.3 (C=O), 101.6 (NCHO), 84.7 (O*t*Bu), 81.5 (CHO), 77.9 (CCl), 73.6 (CHN), 39.1 (*t*Bu), 28.6 (O*t*Bu), 28.1 ($CHMe_2$), 25.4 (*t*Bu), 16.9 (Me), 16.8 (Me). $[\alpha]_D^{20}$=+1.25 (*c* 0.62, $CHCl_3$). IR (KBr) ν 1800 (C=O), 1716 (C=$O_{carbamate}$). MS (APCI) *m*/*z* (%) 290 (M−*t*Bu, 60), 126 (100). Anal. Calcd for $C_{17}H_{28}ClNO_4$ C 59.04, H 8.15, Cl 10.25, N 4.05; found C 59.08, H 7.92, Cl 10.03, N 3.93.

4.7.7. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-phenyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 19A. White solid, yield 76%, mp 159–162 °C. R_f=0.27 (PE/Et_2O=95/5), ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5H, Ph), 5.41 (d, J=5.3 Hz, 1H, CHN), 5.23 (d, J=5.4 Hz, 1H, CHO), 5.08 (s, 1H, NCHO), 3.76 (s, 3H, OMe), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9 (C=O), 154.2 (C=O), 132.7 ($C_{arom.}$), 129.4, 128.7, 128.2 (CH_{arom}), 102.0 (NCHO), 82.0 (CHO), 81.0 (CCl), 74.1 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.4 (*t*Bu). $[\alpha]_{20}^{D}$=+1.90 (*c* 0.5, $CHCl_3$). IR (KBr) ν 2990, 1800 (C=O), 1720 (C=$O_{carbamate}$), 1360. MS (CI) *m*/*z* 337 (M+1), 306, 280, 188. Anal. Calcd for $C_{17}H_{20}ClNO_4$ C 60.44, H 5.96, N 4.14; found C 59.96, H 6.32, N 3.88.

4.7.8. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-phenyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 20A. White solid, yield 76%, mp 101–103 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5H, Ph), 5.30 (d, J=5.2 Hz, 1H, CHN), 5.21 (d, J=5.2 Hz, 1H, CHO), 5.01 (s, 1H, NCHO), 1.49 (s, 9H, O*t*Bu), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C=O), 153.2 (C=O), 133.0 (C_{arom}), 129.2, 128.5, 128.3 (CH_{arom}), 101.3 (NCHO), 82.0 (CHO), 81.5 (O*t*Bu), 77.6 (CCl), 74.3 (CHN), 39.0 (*t*Bu), 28.8 (O*t*Bu), 25.4 (*t*Bu). IR (neat) ν 2920, 1810 (C=O), 1720 (C=$O_{carbamate}$), 1364. MS (CI) *m*/*z* 351 (M^+−CO), 295, 251, 222, 164. Anal. Calcd for $C_{20}H_{26}ClNO_4$ C 63.23, H 6.89, N 3.68; found C 63.39, H 7.00, N 3.19.

4.7.9. *tert*-Butyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-phenyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 20B. White solid, yield 76%, mp 121–125 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.6–7.30 (m, 5H, Ph), 5.63 (d, J=6.1 Hz, 1H, CHN), 5.55 (d, J=5.9 Hz, 1H, CHN), 5.44 (s, 1H, NCHO), 5.17 (s, 1H, NCHO), 4.91 (d, J=5.9 Hz, 1H, CHO), 4.79 (d, J=6.1 Hz, 1H, CHO), 1.11 (s, 9H, O*t*Bu), 1.09 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 152.2 (C=O), 129.1, 128.8 (C_{arom}), 128.6, 128.4, 128.3, 128.2, 128.1, 127.9 (CH_{arom}), 102.1, 101.3 (NCHO), 91.9, 90.7, 66.5, 66.1, 40.0, 39.9, 27.7, 27.5, 25.7. 82.0 (CHO), 81.5 (O*t*Bu), 77.6 (CCl), 74.3 (CHN), 39.0 (*t*Bu), 28.8 (O*t*Bu), 25.4 (*t*Bu).

4.7.10. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-trimethylsilylmethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 21. White solid, yield 86%, mp 127–129 °C, R_f=0.30 (3% isopropanol in petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, J=5.5 Hz, 1H, CHO), 5.33 (s, 1H, NCHO), 4.87 (d, J=5.5 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 1.36 (d, J=1.5 Hz, 2H, CH_2), 0.93 (s, 9H, *t*Bu), 0.14 (s, 9H, 3Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7 (C=O), 154.8 (C=O), 102.0 (NCHO), 81.9 (CHO), 79.0 (CCl), 73.9 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.5 (*t*Bu), 18.6 (CH_2), −0.04 ($SiMe_3$). $[\alpha]_D^{20}$=+1.16 (*c* 1.09, $CHCl_3$). IR (KBr) ν 2959, 1804 (C=O), 1716 (C=$O_{carbamate}$), 1367, 844. MS (CI) *m*/*z* (%) 348 (M+1, 19), 312 (12), 262 (19), 240 (24), 208 (12), 144 (39), 112 (35), 73 (100). Anal. Calcd for $C_{15}H_{26}ClNO_4Si$ C 51.78, H 7.53, N 4.03; found C 51.26, H 7.66, N 4.64.

4.7.11. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-trimethylsilylmethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 22. Yield 82%, R_f=0.29 (PE/Et_2O/*i*PrOH=100/3/3), mp 135–138 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H, NCHO), 5.26 (d, J=5.5 Hz, 1H, CHO), 4.85 (d, J=5.5 Hz, 1H, CHN), 1.49 (s, 9H, O*t*Bu), 1.36 (d, J=1.5 Hz, 2H, CH_2), 0.93 (s, 9H, *t*Bu), 0.14 (s, 9H, 3Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7 (C=O), 153.4 (C=O), 101.6 (NCHO), 82.0 (CHO), 81.4 (O*t*Bu), 79.1 (CCl), 74.1 (CHN), 39.0 (*t*Bu), 28.3 (O*t*Bu), 25.7 (*t*Bu), 18.8 (CH_2), −0.05 ($SiMe_3$). IR (KBr) ν 2960, 1805 (C=O), 1715 (C=$O_{carbamate}$), 1367, 845.

4.7.12. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromo)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 23. Yield 80%, R_f=0.26 (PE/Et_2O/*i*PrOH=100/4/3). ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (d, J=5.5 Hz, 1H, CHO), 5.35 (s, 1H, NCHO), 4.92 (d, J=5.5 Hz, 1H, CHN), 3.72 (s, 3H, OMe), 3.51 (m, 2H, CH_2Br), 2.50 (m, 2H, CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4 (C=O), 154.3 (C=O), 102.2 (NCHO), 80.8 (CHO), 77.0 (CCl), 74.3 (CHN), 52.9 (OMe), 39.0 (*t*Bu), 33.1 (CH_2Br), 25.2 (*t*Bu), 25.2 (CH_2). IR (film) ν 2972, 1804 (C=O), 1715 (C=$O_{carbamate}$), 1366, 1223. MS (EI) *m*/*z* (%) 368 ($M^{+\cdot}$, 5), 254 (11), 144 (15), 87 (100). Anal. Calcd for $C_{13}H_{19}BrClNO_4$ C 42.35, H 5.19, N 3.79; found C 41.87, H 4.97, N 3.59.

4.7.13. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromoethyl)-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 24A. Yield 72%, two inseparable regioisomers with a ratio of 8/1. R_f=0.30 (PE/AcOEt/*i*PrOH=100/5/3). ^1H NMR (200 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.29 (d, J=5.46 Hz, 1H, CHO), 4.92 (d, J=5.46 Hz, 1H, CHN), 3.55 (m, 2H, CH_2Br), 2.52 (m, 2H, CH_2), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR

(50 MHz, $CDCl_3$) δ 195.8 (C═O), 153.1 (C═O), 101.2 (NCHO), 83.4 (CHO), 82.6 (O*t*Bu), 77.4 (CCl), 74.5 (CHN), 39.1 (*t*Bu), 37.5 (CH_2Br), 28.5 (O*t*Bu), 26.1 (CH_2), 25.6 (*t*Bu). IR (film) ν 2982, 1800 (C═O), 1698 (C═$O_{cabamate}$), 1362, 1172. MS (FAB) *m*/*z* (%) 412 (M+1, 4), 356 (27), 154 (89), 136 (64).

4.7.14. *tert*-Butyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-(2-bromoethyl)-7-oxo-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 24B. ^{1}H NMR (200 MHz, CDCl3) δ 5.36 (s, 1H, NCHO), 4.65 (d, *J*=6.7 Hz, 1H, CHN), 4.41 (d, *J*=6.7 Hz, 1H, CHO), 3.55 (m, 2H, CH_2Br), 2.52 (m, 2H, CH_2), 1.50 (s, 9H, O*t*Bu), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, CDCl3) δ 194.8 (C═O), 153.1 (C═O), 101.2 (NCHO), 90.3 (CHO), 82.2 (O*t*Bu), 77.4 (CCl), 63.5 (CHN), 39.1 (*t*Bu), 37.5 (CH_2Br), 28.5 (O*t*Bu), 26.1 (CH_2), 25.6 (*t*Bu).

4.7.15. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromo)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 25. Yield 77%, R_f=0.3 (PE/AcOEt/*i*PrOH=100/5/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H, CH═), 5.42 (d, *J*=5.4 Hz, 1H, CHN), 5.40 (s, 1H, NCHO), 5.37 (ddd, *J*=17.1, 3.1, 1.5 Hz, 1H, CH_2═), 5.26 (ddd, *J*=10.3, 2.9, 1.4 Hz, 1H, CH_2═), 4.96 (d, *J*=5.5 Hz, 1H, CHO), 4.63 (dt, *J*=5.8, 1.4 Hz, 2H, CH_2O), 3.57 (m, 2H, CH_2Br), 2.50 (m, 2H, CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6 (C═O), 154.0 (C═O), 132.2 (CH═), 118.6 (═CH_2), 102.2 (NCHO), 80.9 (CHO), 77.0 (CH_2O), 74.2 (CHN), 66.9 (CCl), 39.6 (CH_2Br), 39.0 (*t*Bu), 25.5 (*t*Bu), 25.3 (CH_2). IR (film) ν 2942, 1792 (C═O), 1711 (C═O), 1140. MS (APCI) *m*/*z* (%) 394 (M+1, 3), 338 (5), 282 (100). Anal. Calcd for $C_{15}H_{21}BrClNO_4$ C 45.64, H 5.36, N 3.55; found C 43.97, H 5.17, N 3.45.

4.7.16. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-methoxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 26A. Yield 76%, R_f=0.24 (3% isopropanol in petroleum ether), two regioisomers inseparable with a proportion of 6/1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H, NCHO), 5.35 (d, *J*=5.45 Hz, 1H, CHN), 4.90 (d, *J*=5.45 Hz, 1H, CHO), 3.75 (s, 3H, OMe), 3.62 (m, 2H, CH_2O), 3.32 (s, 3H, OMe), 2.25 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1 (C═O), 154.5 (C═O), 102.0 (NCHO), 81.3 (CHO), 77.2 (CCl), 74.4 (CHN), 67.5 (CH_2O), 58.6 (OMe), 52.8 (OMe), 39.0 (*t*Bu), 29.7 (CH_2), 25.4 (*t*Bu). IR (KBr) ν 1804 (C═O), 1715 (C═$O_{carbamate}$). MS (EI) *m*/*z* (%) 320 ($M^{+\cdot}$, 22), 284 (31), 210 (30), 208 (100), 176 (72), 88 (76). Anal. Calcd for $C_{14}H_{22}ClNO_5$ C 52.58, H 6.93, N 4.38; found C 49.34, H 6.84, N 4.29.

4.7.17. Methyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-(2-methoxy)ethyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 26B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H, NCHO), 5.0 (d, *J*=6.7 Hz, 1H, CHN), 4.95 (d, *J*=6.7 Hz, 1H, CHO), 3.75 (s, 3H, OMe), 3.62 (m, 2H, CH_2O), 3.32 (s, 3H, OMe), 2.25 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0 (C═O), 154.5 (C═O), 102.0 (NCHO), 94.0 (CHO), 77.3 (CCl), 67.1 (CH_2O), 65.2 (CHN), 58.6 (OMe), 52.8 (OMe), 39.0 (*t*Bu), 29.7 (CH_2), 25.4 (*t*Bu).

4.7.18. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldimethylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 27. Yield 54%, R_f=0.29 (PE/AcOEt/*i*PrOH=100/4/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (d, *J*=5.2 Hz, 1H, CHN), 5.35 (s, 1H, NCHO), 4.88 (d, *J*=5.2 Hz, 1H, CHO), 3.85 (m, 2H, CH_2O), 3.74 (s, 3H, OMe), 2.37 (m, 1H, 1/2CH_2), 1.96 (m, 1H, 1/2CH_2), 0.98 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (C═O), 154.2 (C═O), 102.0 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.7 (CHN), 66.3 (CH_2O), 52.9 (OMe), 38.9 (*t*Bu), 30.6 (CH_2), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu), −5.4 (SiMe). IR (film) ν 2959, 1803 (C═O), 1733 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 420 (M+1, 14), 384 (8), 280 (20), 154 (39), 73 (100). Anal. Calcd for $C_{19}H_{34}ClNO_5Si$ C 54.33, H 8.16, N 3.33; found C 52.63, H 8.14, N 2.87.

4.7.19. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 28. Yield 80%, R_f=0.28 (PE/AcOEt/*i*PrOH=100/4/3), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.71 (m, 10H, 2Ph), 5.41 (d, *J*=5.2 Hz, 1H, CHN), 5.32 (s, 1H, NCHO), 4.92 (d, *J*=5.2 Hz, 1H, CHO), 3.78–3.97 (m, 2H, CH_2O), 3.73 (s, 3H, OMe), 2.42 (ddd, *J*=15.0, 7.3, 7.3 Hz, 1H, 1/2CH_2), 2.0 (ddd, *J*=15.0, 6.4, 4.6 Hz, 1H, 1/2CH_2), 1.04 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9 (C═O), 154.2 (C═O), 133.3 (C_{arom}), 135.6, 130.0, 129.7, 127.8, 127.7 (CH_{arom}), 102.1 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.8 (CHN), 59.2 (CH_2O), 52.9 (OMe), 38.9 (*t*Bu), 30.6 (CH_2), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu). IR (film) ν 2958, 1803 (C═O), 1733 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 544 (M+1, 6), 486 (10), 217 (15), 197 (41), 135 (100). Anal. Calcd for $C_{29}H_{38}ClNO_5Si$ C 64.01, H 7.04, N 2.43; found C 63.85, H 7.05, N 2.43.

4.7.20. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 29. Yield 80%, R_f=0.25, (PE/Et_2O/*i*PrOH=100/3/3), mp129–131 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.72 (m, 10H, 2Ph), 5.34 (d, *J*=5.1 Hz, 1H, CHN), 5.32 (s, 1H, NCHO), 4.91 (d, *J*=5.1 Hz, 1H, CHO), 3.78–3.97 (m, 2H, CH_2O), 2.45 (ddd, *J*=14.8, 8.2, 6.3 Hz, 1H, 1/2CH_2), 1.97 (ddd, *J*=14.8, 6.3, 3.6 Hz, 1H, 1/2CH_2), 1.49 (s, 9H, O*t*Bu), 1.06 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3 (C═O), 153.2 (C═O), 133.4 (C_{arom}), 135.6, 130.0, 129.7, 127.8, 127.7 (CH_{arom}), 101.7 (NCHO), 81.7 (CHO), 81.4 (O*t*Bu), 75.0 (CHN), 74.5 (CCl), 59.2 (CH_2O), 39.0 (*t*Bu), 30.8 (CH_2), 28.0 (O*t*Bu), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu). IR (KBr) ν 2959, 1804 (C═O), 1726 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 586 (M+1). Anal. Calcd for $C_{32}H_{44}BrClNO_5S$ C 65.56, H 7.57, N 2.38, Cl 6.04; found C 65.85, H 7.68, N 2.31, Cl 5.70. $[\alpha]_{20}^{D}$=+0.99 (*c* 1.06, $CHCl_3$), X-Ray diffraction analysis wavelength: 0.71069 Å, Crystal system: orthorhombic unit cell dimensions, *a*=9.738 (3) Å, α=90°, *b*=10.205 (4) Å, β=90°, *c*=33.446 (8) Å, γ=90°.

4.7.21. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 30. Yield 77%, two inseparable regioisomers with a ratio of 10/1. R_f=0.27 (3%

isopropanol in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.69 (m, 10H, 2Ph), 5.98 (m, 1H, CH═), 5.43 (d, J=5.5 Hz, 1H, CHN), 5.37 (s, 1H, NCHO), 5.35 (ddd, J=17.4, 3.0, 1.5 Hz, 1H, CH_2═), 5.25 (ddd, J=10.3, 3.0, 1.5 Hz, 1H, CH_2═), 4.93 (d, J=5.5 Hz, 1H, CHO), 4.64 (dt, J=6.1, 1.5 Hz, 2H, CH_2OCO), 3.95 (ddd, J=10.1, 8.2, 6.7 Hz, 1H, CH_2OSi), 3.87 (ddd, J=10.1, 7.6, 4.0 Hz, 1H, CH_2OSi), 2.43 (ddd, J=14.6, 8.2, 7.6 Hz, 1H, CH_2), 2.03 (ddd, J=14.6, 6.7, 4.0 Hz, 1H, CH_2), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, CDCl3) δ 195.3 (C═O), 156.1 (C═O), 133.6 (C_{arom}), 132.3 (CH═), 135.5, 129.5, 127.7 (CH_{arom}), 118.3 (═CH2), 102.1 (NCHO), 81.5 (CHO), 77.3 (CH_2OCO), 74.8 (CHN), 66.7 (CCl), 59.3 (CH_2OSi), 39.0 (*t*Bu), 31.2 (CH_2), 25.3 (*t*Bu). IR (film) ν 2962, 1800 (C═O), 1709 (C═O). MS (APCI) *m*/*z* (%) 570 (M+1, 18), 534 (80), 492 (62), 314 (24). Anal. Calcd for $C_{31}H_{40}ClNO_4Si$ C 65.30, H 7.07, N 2.45; found C 63.95, H 7.49, N 2.20.

4.7.22. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-6-chloro-7-oxo-6-(2-{[*tert*-butyl (diphenyl)silyl]oxy}ethyl)-2-oxa-4-aza-bicyclo[3.2.0]heptane-4-carboxylate 30B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.7 (m, 10H, 2Ph), 5.98 (m, 1H, CH═), 5.37 (s, 1H, NCHO), 5.38 (ddd, J=17.5, 3.0, 1.5 Hz, 1H, CH_2═), 5.22 (ddd, J=10.3, 3.0, 1.5 Hz, 1H, CH_2═), 4.68 (dt, J=6.1, 1.5 Hz, 2H, CH_2OCO), 4.64 (d, J=6.1 Hz, 1H, CHN), 4.48 (d, J=6.1 Hz, 1H, CHO), 3.65–3.97 (m, 2H, CH_2OSi), 1.70–2.79 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C═O), 156.1 (C═O), 133.6 (C_{arom}), 132.3 (CH═), 135.5, 129.5, 127.7 (CH_{arom}), 118.3 (═CH_2), 102.1 (NCHO), 81.5 (CHO), 77.3 (CH_2OCO), 74.8 (CHN), 66.7 (CCl), 59.3 (CH_2OSi), 39.0 (*t*Bu), 31.2 (CH_2), 25.3 (*t*Bu).

4.7.23. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-benzyloxyethyl)-2-oxa-4-aza bicycle[3.2.0]heptane-4-carboxylate 31. Yield 72%, two inseparable regioisomers with a ratio of 6/1. R_f=0.26 (PE/Et_2O/*i*PrOH=100/3/3). ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C) δ 7.2–7.4 (m, 5H, Ph), 5.36 (s, 1H, NCHO), 5.35 (d, J=5.2 Hz, 1H, CHN), 4.90 (d, J=5.2 Hz, 1H, CHO), 4.45–4.55 (ab, J=12.2 Hz, 2H, CH_2Ph), 3.75 (m, 2H, CH_2O), 3.73 (s, 3H, OMe), 2.42 (ddd, J=15.0, 7.3, 7.3 Hz, 1H, 1/2CH_2), 2.14 (ddd, J=15.0, 6.4, 4.6 Hz, 1H, 1/2CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C) δ 195.1 (C═O), 154.6 (C═O), 138.3 (C_{arom}), 128.2, 127.4, 127.3 (CH_{arom}), 102.0 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.6 (CHN), 72.8 (CH_2Ph), 65.1 (CH_2O), 52.7 (OMe), 38.9 (*t*Bu), 29.6 (CH_2), 25.2 (*t*Bu). IR (film) ν 1804 (C═O), 1715 (C═$O_{carbamate}$). MS (CI) *m*/*z* (%) 396 (M+1, 4), 362 (5), 306 (9), 288 (15), 254 (11), 211 (100), 184 (11), 91 (51).

4.7.24. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 32. Yield 56%, R_f=0.26 (PE/AcOEt/*i*PrOH=100/4/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5H, Ph), 5.33 (s, ^{1}H, NCHO), 5.29 (d, J=5.2 Hz, 1H, CHO), 4.87 (d, J=5.2 Hz, 1H, CHN), 4.47–4.59 (ab, J=12.2 Hz, 2H, CH_2Ph), 3.75 (m, 2H, CH_2O), 2.14–2.42 (m, 2H, CH_2), 1.48 (s, 9H, O*t*Bu), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C═O), 154.3 (C═O), 138.3 (C_{arom}), 128.2, 127.4, 127.3 (CH_{arom}), 102.0 (NCHO), 82.4 (O*t*Bu), 81.6 (CHO), 77.4 (CCl), 74.3 (CHN), 72.8 (CH_2Ph), 65.1 (CH_2O), 39.0 (*t*Bu), 29.6 (CH_2), 28.6 (O*t*Bu), 25.2 (*t*Bu). IR (film) ν 1792 (C═O), 1706 (C═$O_{carbamate}$), 1368. MS (APCI) *m*/*z* (%) 438 (M+1, 12), 380, 316, 184 (11), 91 (51).

4.7.25. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(1,3-dioxolan-2-ylmethyl)-2-oxa-4-azabicyclo-[3.2.0]heptane-4-carboxylate 33. Yield 62%, R_f=0.26 (PE/AcOEt/*i*PrOH=100/5/3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.32 (d, J=5.4 Hz, 1H, CHN), 4.95 (d, J=5.4 Hz, 1H, CHO), 4.45 (dd, J=5.9, 4.5 Hz, 1H, OCHO), 3.86–3.98 (m, 4H, OCH_2CH_2O), 3.76 (s, 3H, OMe), 2.32 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.2 (C═O), 153.6 (C═O), 101.9 (NCHO), 101.2 (OCHO), 81.6 (CHO), 75.8 (CCl), 74.5 (CHN), 65.0 (OCH_2CH_2O), 52.6 (OMe), 38.9 (*t*Bu), 34.5 (CH_2), 27.2 (*t*Bu). IR (film) ν 2960, 1803 (C═O), 1724 (C═$O_{carbamate}$), 1363, 1115. MS (APCI) *m*/*z* (%) 348 (M+1, 23), 312 (17).

4.7.26. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-bromo-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 34A. Yield 76%, R_f=0.27 (3% isopropanol in petroleum ether), two regioisomers inseparable with a ratio of 4/1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 5.31 (d, J=5.3 Hz, 1H, CHN), 5.0 (d, J=5.3 Hz, 1H, CHO), 2.24 (m, 1H, $CHMe_2$), 1.47 (s, 9H, O*t*Bu), 1.09 (d, J=6.6 Hz, 3H, Me), 0.99 (d, J=6.5 Hz, 3H, Me), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (C═O), 153.6 (C═O), 101.6 (NCHO), 81.4 (CHO), 80.7 (O*t*Bu), 77.3 (CBr), 73.3 (CHN), 39.1 (*t*Bu), 28.2 (O*t*Bu), 25.4 ($CHMe_2$), 25.2 (*t*Bu), 18.2 (Me). IR (film) ν 2942, 1793 (C═O), 1696 (C═$O_{carbamate}$), 1368. MS (CI) *m*/*z* (%) 390 (M+1, 5), 334 (100), 290 (51), 256 (24).

4.7.27. Methyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-bromo-6-isopropyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 34B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 4.84 (d, J=6.2 Hz, 1H, CHN), 4.1 (d, J=6.2 Hz, 1H, CHO), 2.25 (m, 1H, $CHMe_2$), 1.47 (s, 9H, O*t*Bu), 1.09 (d, J=6.6 Hz, 3H, Me), 0.99 (d, J=6.5 Hz, 3H, Me), 0.90 (s, 9H, *t*Bu).

4.7.28. *tert*-Butyl (1*R*,3*S*,5*S*,7*S*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 35. White solid, yield 72%, R_f=0.16 (EP/Et_2O=20/1), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H, NCHO), 5.23 (d, J=5.26 Hz, 1H, CHO), 4.88 (d, J=5.26 Hz, 1H, CHN), 1.63 (s, 3H, Me), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2 (C═O), 153.6 (C═O), 101.7 (NCHO), 82.2 (O*t*Bu), 81.2 (CCl), 81.0 (CHO), 74.4 (CHN), 39.1 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu), 24.2 (Me). $[\alpha]_D^{20}$=−0.95 (*c* 0.44, $CHCl_3$). MS (APCI) *m*/*z* (%) 318 (M+1, 7), 260 (M−*t*Bu, 6), 218 (100). Anal. Calcd for $C_{15}H_{24}ClNO_4$ C 56.68, H 7.61, N 4.41; found C 55.69, H 7.37, N 4.34.

4.7.29. *tert*-Butyl (1*R*,3*S*,5*S*,7*S*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 36A. White solid, yield 66%, mp 110–113 °C, R_f=0.40 (PE/Et_2O=20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 5.20 (d, J=5.5 Hz, 1H, CHO), 4.87 (d, J=5.5 Hz, 1H, CHN), 2.48 (m, 1H, $CHMe_2$), 1.49 (s, 9H,

O*t*Bu), 1.09 (d, *J*=6.7 Hz, 3H, CH_3), 1.0 (d, *J*=6.7 Hz, 3H, CH_3), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2 (C=O), 153.6 (C=O), 101.5 (NCHO), 84.2 (O*t*Bu), 81.0 (CHO), 76.9 (CCl), 73.5 (CHN), 39.1 (*t*Bu), 28.4 (O*t*Bu), 28.0 ($CHMe_2$), 25.3 (*t*Bu), 16.9 (Me), 16.8 (Me). $[\alpha]_D^{20}$=−1.14 (*c* 1.25, $CHCl_3$). MS (APCI) *m*/*z* (%) 290 (M−*t*Bu, 46), 246 (100). Anal. Calcd for $C_{17}H_{28}ClNO_4$ C 59.03, H 8.16, Cl 10.25, N 4.05; found C 58.77, H 8.00, Cl 9.46, N 4.28.

4.7.30. *tert*-Butyl (1*R*,3*S*,5*S*,6*R*)-3-(*tert*-butyl)-6-chloro-6-isopropyl-7-oxo-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 36b. R_f=0.34 (PE/E_2O=20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (d, *J*=6.0 Hz, 1H, CHO), 5.29 (s, 1H, NCHO), 4.66 (d, *J*=6.0 Hz, 1H, CHN), 2.32 (m, 1H, $CHMe_2$), 1.50 (s, 9H, O*t*Bu), 1.15 (d, *J*=6.7 Hz, 3H, CH_3), 1.12 (d, *J*=6.7 Hz, 3H, CH_3), 0.94 (s, 9H, *t*Bu).

4.7.31. (1*R*,3*R*,5*R*)-4-(*tert*-Butoxycarbonyl)-6-(*tert*-butyl)-2-oxa-4-azabicyclo[3.2.0]heptane-6-one 38. Mp 90–91 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.07 (ddd, *J*=5.0, 5.0, 2.3 Hz, 1H), 4.92–4.85 (m, 1H), 3.18 (ddd, *J*=17.5, 5.0, 3.5 Hz, 1H), 3.08 (ddd, *J*=17.5, 2.3, 2.3 Hz), 1H), 1.48 (s, 9H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 153.1, 101.1, 81.2, 76.2, 71.3, 52.6, 39.0, 28.0, 25.5; $[\alpha]_D^{20}$=+116 (*c* 1.00, $CHCl_3$). IR (KBr) ν 2960, 1790, 1700. MS (CI) *m*/*z* (%) 227, 170, 57. Anal. Calcd for $C_{14}H_{23}NO_4$ C 62.03, H 8.60, N 5.2; found C 61.72, H 8.57, N 4.95.

4.8. General procedure for the [2+2] cycloaddition of oxazolines to methoxyketene and *N*-methyl-*N*-tosyl-aminoketene

Into a 25 ml three-necked flask dried by flame under the argon, (2*H*)oxazole **2** (1 equiv.), triethylamine (1.2–2.2 equiv.) and toluene (10 ml/mmol) were added, then acetyl chloride (1.2–2.2 equiv.) in toluene (2 ml/mmol) was added dropwise by a syringe pump at 110 °C. After the addition (2 h), the mixture was stirred at 110 °C for 8 h then 10 h at room temperature and filtered. The filtrate was evaporated to give crude product. Flash chromatography gave the pure product.

4.8.1. Methyl (3*R*)-3-(*tert*-butyl)-7-{methyl[(4-methylphenyl) sulfonyl]amino}-6-[(2-{methyl[(4-methylphenyl) sulfonyl]amino}acetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]-hept-6ene-4-carboxylate 39. White solid, yield 29%, mp 127–129 °C, R_f=0.35 (hexane/*i*PrOH/AcOEt=100/8/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.81 (m, 8H, 2Ph), 5.35 (s, 1H, NCHO), 5.31 (d, *J*=4.12 Hz, 1H, CHN), 5.03 (d, *J*=4.12 Hz, 1H, CHO), 4.05 (d, *J*=4.67 Hz, 2H, CH_2), 3.67 (s, 3H, OMe), 3.05 (s, 3H, NMe), 2.89 (s, 3H, NMe), 2.45 (s, 3H, Me), 2.43 (s, 3H, Me), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (C=O), 155.3 (C=O), 144.3, 143.8, 134.9, 134.7 (C_{arom}), 129.8, 129.7, 127.8, 127.7, 127.4 (CH_{arom}), 128.3 (OC=), 127.7 (=CN), 104.0 (NCHO), 74.3 (CHO), 61.5 (CHN), 52.7 (OMe), 50.6 (CH_2), 38.8 (*t*Bu), 35.5 (NMe), 34.7 (NMe), 25.0 (*t*Bu), 21.6 (Me), 21.5 (Me). $[\alpha]_D^{20}$=+0.98 (*c* 0.62, $CHCl_3$). IR (KBr) ν 2959, 1726 (C=O), 1710 (C=$O_{carbamate}$), 1654, 1259, 1172. MS (CI) *m*/*z* (%) 635 (M−Me, 17), 480 (18), 410 (36), 298 (20), 242 (59), 190 (86), 155 (100). Anal. Calcd for $C_{30}H_{39}N_3O_9S_2$ C 55.45, H 6.04, N 6.46; found C 53.85, H 5.69, N 6.37.

4.8.2. Methyl (3*R*)-3-(*tert*-butyl)-7-methoxy-6-[(2-methoxy acetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]hept-6ene-4-carboxylate 40a. Yield 72%, R_f=0.33 (hexane/MeOH/AcOEt=100/7/20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H, NCHO), 5.07 (d, *J*=4.4 Hz, 1H, CHO), 4.96 (d, *J*=4.4 Hz, 1H, CHN), 4.11 (s, 2H, CH_2), 3.79 (s, 3H, OMe), 3.64 (s, 3H, $OMe_{carbamate}$), 3.48 (s, 3H, $MeOCH_2$), 0.86 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C=O), 155.3 (C=O), 142.4 (OC=), 120.7 (=COMe), 104.5 (NCHO), 77.7 (CHO), 69.0 (OCH_2), 59.6 (CHN), 59.4 ($MeOCH_2$), 58.0 (OCH_3), 52.3 ($OMe_{carbamate}$), 38.7 (*t*Bu), 24.8 (*t*Bu). IR (KBr) ν 2959, 2931, 1780 (C=O), 1716 (C=$O_{carbamate}$), 1447, 1367, 1117. MS (CI) *m*/*z* (%) 330 (M+1, 16), 272 (M−*t*Bu, 32), 240 (M−$OCOCH_2OCH_3$, 54), 216 (38), 202 (22), 172 (100), 144 (75). Anal. Calcd for $C_{15}H_{23}NO_7$ C 54.7, H 7.03, N 4.25; found C 54.29, H 6.77, N 4.35.

4.8.3. *tert*-Butyl (3*R*)-3-(*tert*-butyl)-7-methoxy-6-[(2-methoxyacetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]hept-6ene-4-carboxylate 40b. Yield 56%, R_f=0.27 (hexane/*i*PrOH/AcOEt=100/8/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H, NCHO), 5.41 (d, *J*=4.12 Hz, 1H, CHN), 4.63 (d, *J*=4.12 Hz, 1H, CHO), 4.13 (s, 2H, CH_2), 3.83 (s, 3H, OMe), 3.48 (s, 3H, $MeOCH_2$), 1.46 (s, 9H, O*t*Bu), 0.88 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C=O), 153.8 (C=O), 142.4 (OC=), 120.8 (=COMe), 103.1 (NCHO), 80.2 (CHO), 79.3 (O*t*Bu), 69.2 (OCH_2), 59.8 (CHN), 59.5 ($MeOCH_2$), 58.0 (OCH_3), 39.0 (*t*Bu), 28.2 (O*t*Bu), 25.1 (*t*Bu). IR (KBr) ν 2959, 2931, 1780 (C=O), 1716 (C=$O_{carbamate}$), 1447, 1367, 1117. MS (CI) *m*/*z* (%) 372 (M+1, 12), 314 (M−*t*Bu, 25), 282 (M−$OCOCH_2OCH_3$, 23), 270 (M−CO_2*t*Bu, 5), 258 (15), 187 (67), 83 (100). HRMS (CI) Calcd for $C_{18}H_{29}NO_7$ 372.20235, found 372.20223.

4.8.4. *tert*-Butyl (1*S*,3*R*,5*R*)-3-(*tert*-butyl)-6-oxo-7,7-(ethylene dithio)-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 43. Into a 25 ml three-necked flask dried by flame under the argon, oxazoline **2b** (0.37 g, 1.6 mmol) and toluene (3 ml) were added and heated to reflux. 2,2-dimethyl-1-(*N*-methylphenylanilino)vinyl-1,3-dithiolane-2-carboxylate (1.34 g, 4.3 mmol) in toluene (2 ml) was added dropwise by a syringe pump during a period of 6 h. After the addition, the mixture was stirred for another 1 h. The solvent was evaporated, and the resulting residue was flash chromatographied to give product 0.23 g, 40%, R_f=0.47 (cyclohexane/AcOEt=4/1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.28 (s, 1H, NCHO), 5.03 (d, *J*=5.4 Hz, 1H, CHO), 4.96 (d, *J*=5.4 Hz, 1H, CHN), 3.38 (m, 4H, CH_2CH_2), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.8 (C=O), 153.02 (C=O), 101.5 (NCHO), 81.4 (CHO), 80.9 (O*t*Bu), 78.6 (CS), 74.4 (CHN), 39.7 (CH_2), 39.4 (CH_2), 28.1 (O*t*Bu), 25.3 (*t*Bu). IR (KBr) ν 1796 (C=O), 1714 (C=$O_{cabamate}$). MS (EI) *m*/*z* (%) 359 (M^+), 331, 230, 174, 57. Anal. Calcd For $C_{16}H_{25}NO_4S_2$ C 53.45, H 7.0, N 3.89, S 17.83; found C 53.45, H 7.01, N 3.82, S 18.08.

4.8.5. Favorskii rearrangement of 23. Into a 25 ml two-necked flask dried by flame under argon, sodium iodide

(56.9 mg, 0.38 mmol), potassium carbonate (53 mg, 0.38 mmol) and methyl sulfoxide (4 ml) were heated to 120 °C under argon, then methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromoethyl)-2-oxa-4-aza bicyclo [3.2.0]heptane-4carboxylate **23** (140 mg, 0.38 mmol) in DMSO (1 ml) was added. After stirring for an additional 1 h, the mixture was rapidly cooled and then poured into ice-cold brine (5 ml). The mixture was extracted with ether (2×5 ml). The combined extracts were washed with water, brine, 5% $NaHCO_3$ and brine, then dried and evaporated. The residue was chromatographied (PE/AcOEt=6/1, R_f=0.3) to give a Favorskii rearrangement product **44** (70 mg, 68%), mp 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 1H, NCHO), 4.49 (d, *J*=6.8 Hz, 1H, CHO), 4.46 (t, *J*=7.62 Hz, 2H, CH_2O), 3.78 (d, *J*=6.8 Hz, 1H, CHN), 3.77 (s, 3H, OMe), 2.12 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ 174.1 (C=O), 156.1 (C=O), 104.6 (NCHO), 66.3 (CH_2O), 66.0 (CHO), 53.2 (OMe), 42.4 (CHN), 38.0 (*t*Bu), 37.1 (CCO), 24.3 (*t*Bu), 20.8 (CH_2). IR (film) ν 2971, 1754 (C=O), 1718 (C=$O_{carbamate}$), 1351, 1021. MS (CI) *m*/*z* (%) 270 (M+1, 29), 211 (M−*t*Bu, 17), 144 (15), 184 (100), 144 (32), 89 (33). Anal. Calcd for $C_{13}H_{19}NO_5$ C 57.98, H 7.11, N 5.20; found C 57.74, 6.92, N 4.95.

4.8.6. Dimethyl (1*R*,3*R*,5*S*,6*R*)-3-(*tert*-butyl)-6-methyl-2-oxo-4-azabicyclo[3.1.0]hexane-4,6-dicarboxylate 45. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-[2-(benzyloxy)ethyl]-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate **13** (280 mg, 1.0 mmol) and sodium hydroxide (426 mg, 1.1 mmol) in MeOH/H_2O (5:1, 5 ml) were mixed and stirred at room temperature for 4 h, then solvent was removed under reduced pressure. The residue was diluted with ether (20 ml), washed with 1 N HCl (2 ml) and water (5 ml), dried over $MgSO_4$ and evaporated. Flash chromatography (PE/AcOEt/*i*PrOH=100/5/5, R_f=0.45) gave the product (0.16 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 1H, NCHO), 4.37 (d, *J*=5.8 Hz, 1H, CHO), 3.73 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.62 (d, *J*=5.8 Hz, 1H, CHN), 1.16 (s, 3H, CH_3), 0.95 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (C=O), 157.1 (C=O), 105.0 (NCHO), 67.8 (CHO), 53.0 (OMe), 52.0 (OMe), 44.5 (CHN), 38.0 (*t*Bu), 35.5 (CCO), 24.5 (*t*Bu), 6.3 (CH_3). IR (film) ν 2957, 1734 (C=O), 1708 (C=$O_{carbamate}$), 1361, 1121. MS (FAB+) *m*/*z* (%) 272 (M+1, 25), 214 (M−*t*Bu, 28), 154 (100), 136 (67), 89 (30).

4.9. General procedure for the Baeyer–Villiger oxidation

Into a 25 ml two-necked flask dried by flame under the argon, cyclobutanones (1 equiv.) and chloroform (5 ml/mmol) were added, then 3-chloroperoxybenzoic acid (1 equiv.) and sodium bicarbonate (1 equiv.) were added consecutively. The mixture was stirred at room temperature under argon overnight, then washed with sodium sulphite solution (10%) and saturated $NaHCO_3$ solution. The organic fraction was dried and evaporated. Flash chromatography (PE/Et_2O=8/1) gave pure product (**46a**–**h**).

4.9.1. Methyl (2*R*,6*R*)-6-methyl-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46a. 95% yield, R_f=0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J*=3.02 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.82 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.8 (s, 3H, CH_3), 0.96 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.7 (CHN), 85.0 (CHO), 66.0 (CCl), 53.5 (OMe), 38.9 (*t*Bu), 25.6 (*t*Bu), 18.9 (CH_3). IR (film) ν 2960, 1800 (C=$O_{lactone}$), 1740 (C=O), 1359, 1112. MS (APCI) *m*/*z* (%) 292 (M+1, 14).

4.9.2. Methyl (2*R*,6*R*)-6-(2-bromoethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46b. 85% yield, R_f=0.34. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, *J*=3.02 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 5.0 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 3.65 (m, 2H, CH_2Br), 2.67 (m, 2H, CH_2), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9 (C=O), 154.2 (C=O), 99.5 (NCHO), 89.2 (CHN), 83.6 (CHO), 66.0 (CCl), 53.5 (OMe), 39.1 (*t*Bu), 33.5 (CH_2Br), 25.7 (CH_2), 25.6 (*t*Bu). IR (film) ν 2958, 1799 (C=$O_{lactone}$), 1742 (C=O), 1365, 1124. MS (FAB) *m*/*z* (%) 384 (M+1, 8), 307 (21), 154 (100), 136 (82).

4.9.3. Methyl (2*R*,6*R*)-6-(trimethylsilyl)methyl-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46c. 96% yield, R_f=0.37. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (d, *J*=3.02 Hz, 1H, CHN), 5.28 (s, 1H, NCHO), 4.86 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.56 (ab, *J*=15.3 Hz, 2H, CH_2), 0.96 (s, 9H, *t*Bu), 0.18 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz) δ 171.6 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.4 (CHN), 84.7 (CHO), 67.3 (CCl), 53.5 (OMe), 39.1 (*t*Bu), 25.6 (*t*Bu), 20.2 (CH_2), −0.1 ($SiMe_3$). IR (film) ν 2959, 1798 (C=$O_{lactone}$), 1743 (C=O), 1360, 1160. MS (APCI) *m*/*z* (%) 364 (M+1, 32), 328 (44), 282 (88), 256 (100), 196 (19). Anal. Calcd for $C_{15}H_{26}ClNO_5Si$ C 49.51, H 7.20, N 3.82; found C 48.80, H 7.24, N 4.19.

4.9.4. Methyl (2*R*,6*R*)-6-(2-{[*tert*-butyl(diphenyl)silyl]-oxy}ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46d. 92% yield. R_f=0.3 (PE/Et_2O=10/1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.70 (m, 10H, 2Ph), 6.18 (d, *J*=3.0 Hz, 1H, CHN), 5.23 (s, 1H, NCHO), 4.82 (d, *J*=3.0 Hz, 1H, CHO), 3.98 (m, 2H, OCH_2), 3.80 (s, 3H, OMe), 2.44 (m, 2H, CH_2), 1.07 (s, 9H, Si*t*Bu), 0.86 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz) δ 170.6 (C=O), 154.3 (C=O), 133.4 (C_{arom}), 135.5, 129.8, 127.8 (CH_{arom}), 99.5 (NCHO), 89.3 (CHN), 84.1 (CHO), 65.4 (CCl), 59.7 (CH_2O), 53.5 (OMe), 39.0 (*t*Bu), 32.8 (Si*t*Bu), 26.9 (CH_2), 25.6 (*t*Bu), 19.2 (Si*t*Bu). IR (film) ν 2960, 1798 (C=$O_{lactone}$), 1735 (C=O), 1360, 1168, 760. MS (APCI) *m*/*z* (%) 560 (M+1, 12), 446 (17).

4.9.5. Methyl (2*R*,6*R*)-6-(2-[benzyloxy]ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46e. 88% yield, R_f=0.33. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.35 (m, 5H, Ph), 6.17 (d, *J*=2.8 Hz, 1H, CHN), 5.21 (s, 1H, NCHO), 4.88 (d, *J*=2.8 Hz, 1H, CHO), 4.52 (s, 2H, CH_2Ph), 3.82 (m, 2H, CH_2O), 3.79 (s, 3H, OMe), 2.23–2.54 (m, 2H, CH_2), 0.84 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8 (C=O), 154.3 (C=O), 137.8 (C_{arom}), 128.5, 128.2, 127.8 (CH_{arom}), 99.2 (NCHO), 89.3 (CHN), 84.4 (CHO), 73.4 (CH_2Ph), 66.2 (CCl), 65.1 (CH_2O), 53.3 (OMe), 38.8 (*t*Bu), 31.9 (CH_2), 25.5 (*t*Bu). IR (film) ν 2927, 1796 (C=$O_{lactone}$), 1738

(C=O), 1360, 1109. MS (APCI) *m/z* (%) 412 (M+1, 12), 394 (74), 326 (63), 304 (100), 246 (72).

4.9.6. *tert*-Butyl (2*R*,6*R*)-6-(2-[benzyloxy]ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46f. 89% yield, R_f=0.36. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.37 (m, 5H, Ph), 6.11 (d, *J*=2.8 Hz, 1H, CHN), 5.21 (s, 1H, NCHO), 4.84 (d, *J*=2.8 Hz, 1H, CHO), 4.54 (ab, *J*=15.4 Hz, 2H, CH_2Ph), 3.81 (m, 2H, CH_2O), 2.54 (ddd, *J*=15.1, 9.6, 6.1 Hz, 1H, CH_2), 2.23 (ddd, *J*=15.1, 4.7, 3.3 Hz, 1H, CH_2), 1.47 (s, 9H, O*t*Bu), 0.85 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6 (C=O), 156.0 (C=O), 137.5 (C_{arom}), 128.7, 128.2, 128.0 (CH_{arom}), 99.1 (NCHO), 90.2 (CHN), 84.7 (CHO), 82.2 (O*t*Bu), 73.6 (CH_2Ph), 69.2 (CCl), 65.5 (CH_2O), 39.2 (*t*Bu), 30.3 (CH_2), 28.4 (O*t*Bu), 25.9 (*t*Bu). IR (KBr) ν 2977, 1799 ($C=O_{lactone}$), 1734 (C=O), 1361, 1163. MS (APCI) *m/z* (%) 454 (M+1, 14), 282 (100), 144 (12). Anal. Calcd for $C_{23}H_{32}ClNO_6$ C 60.85, H 7.10, N 3.08, Cl 7.81; found C 60.68, H 6.95, N 2.97, Cl 8.01. X-ray diffraction analysis Wavelength: 0.71069 Å, Crystal system: orthorhombic; unit cell dimensions: *a*=9.560 (3) Å, α=90°; *b*=10.468 (3), β=90°; *c*=23.952 (9), γ=90°.

4.9.7. Methyl (2*R*,6*R*)-6-(3-bromopropyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46g. 90% yield, R_f=0.3. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, *J*=3.0 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.82 (d, *J*=3.0 Hz, 1H, CHO), 3.80 (s, 3H, OMe), 3.47 (m, 2H, CH_2Br), 2.21–2.33 (m, 4H, CH_2CH_2), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2 (C=O), 154.1 (C=O), 99.5 (NCHO), 88.9 (CHN), 83.9 (CHO), 66.4 (CCl), 53.5 (OMe), 39.0 (*t*Bu), 32.2 (CH_2Br), 30.2 (CH_2), 27.2 (CH_2), 25.6 (*t*Bu). IR (film) ν 2960, 1798 ($C=O_{lactone}$), 1738 (C=O), 1360, 1143. MS (APCI) *m/z* (%) 398 (M+1, 9), 282 (100), 220 (32), 144 (12). Anal. Calcd for $C_{14}H_{21}BrClNO_5$ C 42.17, H 5.31, N 3.51, Cl 8.89; found C 42.07, H 5.44, N 3.58, Cl 9.29.

4.9.8. Methyl (2*R*,6*R*)-6-methyl-2-(*tert*-butyl)-6-bromo-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46h. 91% yield, R_f=0.34. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21 (d, *J*=2.9 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.97 (d, *J*=2.9 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.94 (s, 3H, CH_3), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.6 (CHN), 85.2 (CHO), 62.8 (CBr), 53.5 (OMe), 39.0 (*t*Bu), 25.6 (*t*Bu), 19.8 (CH_3). IR (film) ν 2960, 1797 ($C=O_{lactone}$), 1739 (C=O), 1360, 1110. MS (APCI) *m/z* (%) 336 (M+1, 9), 282 (100).

4.10. General procedure for the Beckmann rearrangement

To a solution of cyclobutanones (1 equiv.) in dichloromethane (1 ml/mmol) was added with stirring O-mesitylenesulfonylhydroxylamine (1.2 equiv.) in dichloromethane (1 ml/mmol) dropwise at room temperature. After stirring for another 70 min, the solvent was removed under reduced pressure to yield a colourless oil which was then dissolved in benzene–methanol (3:1, 1 ml/mmol) and the resulting mixture was added dropwise to a stirring suspension of alumina (5 g/mmol) in methanol (5 ml/mmol). The mixture was stirred for 4 h and filtered. The alumina was washed with methanol. The combined methanolic solution was concentrated. The residue was dissloved in $CHCl_3$ (2 ml/mmol) and the insoluble material was removed. After evaporation of the solvent, the residue was chromatographied on silica gel to give the product (**47a–b**).

4.10.1. Methyl (2*R*,3a*R*,6*R*,6a*R*)-2-(*tert*-butyl)-6-chloro-6-methyl-5-oxotetrahydro-2*H*-pyrrolo[2,3-*d*][1,3]oxazole-3(3a*H*)-carboxylate 47a. 38% yield, R_f=0.25 (PE/Et_2O=5/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (s, 1H, NH), 6.21 (d, *J*=3.0 Hz, 1H, CHN), 5.28 (s, 1H, NCHO), 4.81 (d, *J*=3.0 Hz, 1H, CHN), 3.81 (s, 3H, OMe), 1.76 (s, 3H, CH_3), 0.96 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2 (C=O), 153.4 (C=O), 100.2 (NCHO), 85.7 (CHN), 75.9 (CHO), 69.5 (CCl), 54.6 (OMe), 39.1 (*t*Bu), 25.3 (*t*Bu), 17.6 (CH_3). IR (KBr) ν 2964, 1741 ($C=O_{lactam}$), 1728 (C=O), 1361, 1112. MS (CI) *m/z* (%) 291 (M+1, 12), 253 (10), 199 (86), 183 (100).

4.10.2. Methyl (2*R*,3a*R*,6*R*,6a*R*)-2-(*tert*-butyl)-6-chloro-6-(trimethylsilylmethyl)-5-oxotetrahydro-2*H*-pyrrolo[2,3-*d*][1,3]oxazole-3(3a*H*)-carboxylate 47b. 40% yield, R_f=0.25 (PE/Et_2O=6/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.76 (s, 1H, NH), 5.36 (d, *J*=4.8 Hz, 1H, CHN), 5.01 (s, 1H, NCHO), 4.48 (d, *J*=4.8 Hz, 1H, CHN), 3.66 (s, 3H, OMe), 0.86 (s, 9H, *t*Bu), 0.14 ($SiMe_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3 (C=O), 154.5 (C=O), 98.6 (NCHO), 84.7 (CHN), 69.3 (CCl), 68.5 (CHO), 53.2 (OMe), 39.2 (*t*Bu), 25.6 (*t*Bu), 19.6 (CH_2), 0.1 ($SiMe_3$). IR (film) ν 3237, 2942, 1744 (C=O), 1723 (C=O), 976. MS (CI+Q1MS) *m/z* (%): 363 (M+1, 35), 347 (100), 327 (32), 313 (14), 89 (10). MS (CI−Q1MS) *m/z* (%) 361 (M−1, 22), 240 (24), 168 (100). Anal. Calcd for $C_{15}H_{27}ClN_2O_4Si$ C 49.64, H 7.50, N 7.71; found C 50.27, H 7.60, N 6.76.

4.10.3. (2*R*,4*R*,5*S*)-2-*tert*-Butyl-5-[1,3]dithiolan-2-yl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 48. Into a suspension of **43** (0.3 g, 0.83 mmol) and NaOH (60 mg, 1.5 mmol) in H_2O (10 ml) was added acetone until a clear solution was formed. The mixture was stirred overnight, then diluted phosphoric acid was added to pH 1. The mixture was extracted with ether (4×10 ml). The combined ether was evaporated to give crude product which was recrystallized in *n*-hexane–CH_2Cl_2 to afford pure product 0.29 g, 92%, mp 148.7–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (s, 1H, NCHO), 4.48–4.35 (m, 3H), 3.22–3.19 (m, 4H), 1.43 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C=O), 154.5 (C=O), 97.1 (NCHO), 84.6 (CHN), 81.7 (O*t*Bu), 64.3 (CH_2O), 51.9 (SCHS), 39.1 (CH_2), 38.5 (CH_2), 28.1 (O*t*Bu), 26.5 (*t*Bu). IR (film) ν 3340, 2960, 1720 (C=O). MS (EI) *m/z* (%) 334 $(M-CO_2)^+$, 320 (M−*t*Bu), 264, 220, 175 (100). Anal. Calcd for $C_{16}H_{27}NO_5S_2$ C 50.80, H 7.20, N 3.71, S 16.98; found C 50.45, H 7.18, N 3.47, S 16.70.

4.10.4. (2*R*,4*R*,5*S*)-2-*tert*-Butyl-5-[1,3]dithiolan-2-yl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester 49. Into a solution of **48** (91 mg, 0.24 mmol) in ether (15 ml) was added CH_2N_2 in ether at 0 °C. After stirring for 15 min, acetic acid was added to neutralize excess CH_2N_2. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 ml), dried over $MgSO_4$ and concentrated. Recrystallization in *n*-hexane gave pure product 0.31 g,

94%, mp 118.9–119.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (s, 1H, NCHO), 4.56–4.37 (m, 2H), 4.15 (m, 1H), 3.77 (s, 3H), 3.27–3.12 (m, 4H), 1.40 (s, 9H, O*t*Bu), 0.96 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (C═O), 154.3 (C═O), 96.7 (NCHO), 84.6 (CHN), 81.4 (O*t*Bu), 64.4 (CH_2O), 52.1 (OMe), 51.9 (SCHS), 39.0 (CH_2), 38.8 (CH_2), 28.1 (O*t*Bu), 26.5 (*t*Bu). IR (film) ν 3055, 2987, 1747 (C═O), 1719 (C═O). MS (EI) *m*/*z* 335 $(M-C_4H_8)^+$, 278, 234, 189 (100%). Anal. Calcd for $C_{17}H_{29}NO_5S_2$ C 52.14, H 7.46, N 3.57, S 16.37; found C 51.99, H 7.48, N 3.36, S 15.74.

4.10.5. 5-*tert*-Butyl-1a-(*p*-tolyl)1a,6b-dihydrospiro{1*H*,3*H*,5*H*-cyclobuta[*gh*]oxazolo[3,4-*c*]oxazole-1,2′-[1,3]-dithiolan}-3-one 50. Into a solution of **43** (100 mg, 0.29 mmol) in THF (3 ml) was added 1 M para-tolylmagnesium bromide in ether at room temperature. After stirring for 2 h, saturated aqueous NH_4Cl (1 ml) was added. The mixture was extracted with ether (3×5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography (c-hexane/AcOEt=4/1) gave pure product 86 mg, 79%, mp 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 4H), 5.36 (s, 1H), 4.85 (d, 1H, *J*=4.6 Hz), 4.79 (d, 1H, *J*=4.6 Hz), 2.40 (s, 3H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 139.1, 131.8, 129.1, 125.8, 105.0, 87.9, 83.6, 77.4, 66.2, 39.9, 39.5, 36.3, 24.9, 21.3. IR (film) ν 2990, 1760 (C═O), 1610, 1486, 1455, 1320. MS (EI) *m*/*z* 377 $(M)^+$, 321, 277, 91, 57; HRMS Calcd for $C_{19}H_{23}NO_3S_2$ 377.111, found 377.113.

Acknowledgements

This work was generously supported by grants from CNPq and CAPES (Brazil), Services fédéraux des Affaires Scientifiques, Techniques et Culturelles (P.A.I. no 19), the Fonds National de la Recherche Scientifique and UCL. We would also like to thank Dr. B.Tinant and Prof. J. P. Declecq for X-ray structure determinations, Prof. E. De Hoffmann for the mass spectra and Dr. R. Touillaux for high field NMR studies

References and notes

1. Selected reviews: (a) Russel, A. D. *Prog. Med. Chem.* **1998**, *35*, 133. (b) Cuhna, B. A. *Drugs Today* **1998**, *34*, 691.
2. See for examples: (a) Frère, J. M.; Duez, C.; Dusart, J.; Coyette, J.; Leyh-Bouille, M.; Ghuysen, J. M.; Dideberg, O.; Knox, J. R. In *Enzyme Inhibitors as Drugs*; Sandler, M., Ed.; McMillan, London and Basingstoke, 1980. (b) Ghuysen, J. M.; Frère, J. M.; Dive, G.; Lamotte-Brasseur, J.; Dideberg, O.; Charlier, P. *Biochem. J.* **1991**, *279*, 213. (c) Page, M. I. *The Chemistry of β-Lactams*; Blackie Academic and Professional, Glasgow, 1992. (d) Page, M. I. *Curr. Pharm. Des.* **1999**, *5*, 895. (e) Caselli, E.; Shoichet, B. K. *Chem. Biol.* **2001**, *8*, 17.
3. Reviews (a) Marchand-Brynaert, J.; Bounkhala-Krouz, Z.; Carretero, J. C.; Davies, J.; Ferroud, D.; Van Keulen, B. J.; Serckx-Poncin, B.; Ghosez, L. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bentley, P. H., Southgate, R., Eds.; Chemical Society Special Publications, London, 1989; Vol. 70. (b) Marchand-Brynaert, J.; Ghosez, L. In *Recent Progress in Chemical Synthesis of Antibiotics*; Ohno, M., Lukacs, G., Eds.; Springer Verlag Inc: Berlin, Heidelberg, 1990.
4. (a) Marchand-Brynaert, J.; Bounkhala-Krouz, Z.; Van Keulen, B. J.; Vanlierde, H.; Ghosez, L. *Isr. J. Chem.* **1989**, *29*, 247. (b) Carretero, J. C.; Davies, J.; Marchand-Brynaert, J.; Ghosez, L. *Bull. Soc. Chim. Fr.* **1990**, *127*, 835. (c) Dive, G.; Dumas, S.; Génicot, Ch.; Kumli, F.; Love, Ch.; Marchand-Brynaert, J.; Ghosez, L. *Antibiotics and Antiviral Compounds*; VCH: Weinheim, 1993; pp 177–186. (d) Durand, T.; Marchand-Brynaert, J.; Ghosez, L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2309. (e) Marchand-Brynaert, J.; Mougenot, P.; Combret, Y.; Belotti, D.; Guillot, N.; Ghosez, L. *Il Farmaco* **1995**, *50*, 455. (f) Mougenot, P.; Marchand-Brynaert, J.; Ghosez, L. *J. Pharmacie Belg.* **1995**, *L2-3*, 237. (g) Marchand-Brynaert, J.; Durand, T.; Ghosez, L. *J. Pharmacie Belg.* **1995**, *L2-3*, 249. (h) Payne, D. J.; Bateson, J. H.; Gasson, B. C.; Proctor, D.; Khushi, T.; Farmer, T. H.; Tolson, D. A.; Bell, D.; Skett, P. W.; Marshall, A. C.; Reid, R.; Ghosez, L.; Combret, Y.; Marchand-Brynaert, J. *Antimicrobial Agents and Chemotherapy* **1997**, *41*, 135.
5. See also (a) Lowe, G.; Swain, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1279. (b) Lowe, G.; Swain, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 391. (c) Cocuzza, A. J.; Boswell, G. A. *Tetrahedron Lett.* **1985**, *26*, 1631. (d) Agathocleous, D.; Cox, G.; Page, M. I. *Tetrahedron Lett.* **1986**, *27*, 1631. (e) Martyres, D. C.; Baldwin, J. E. *Tetrahedron* **2001**, *57*, 4999.
6. (a) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843. (b) Seebach, D.; Stucky, G. *Angew.Chem., Int. Ed. Engl.* **1988**, *27*, 1351. (c) Seebach, D.; Stucky, G.; Renaud, P. *Chimia* **1988**, 176. (d) Stucky, G.; Seebach, D. *Chem. Ber.* **1989**, *122*, 2365. (e) Seebach, D.; Srucky, G.; Pfammater, E. *Chem. Ber.* **1989**, *122*, 2377. (f) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B.; Stucky, G.; Petter, W.; Escalante, J.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913. (g) Lamatsch, B.; Seebach, D.; Ha, T. K. *Helv. Chim. Acta* **1992**, *75*, 1095.
7. See for example: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
8. Cagnon, J. R.; Le Bideau, F.; Marchand-Brynaert, J.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 2291.
9. (a) Harpp, D. N.; Bao, L. Q. *J. Org. Chem.* **1975**, *40*, 3420. (b) Fritzlanghals, E. *Tetrahedron: Asymmetry* **1994**, *5*, 981. (c) Dolbier, W. R.; Lee, S. K.; Phanstiel, O. *Tetrahedron* **1991**, *47*, 2065. (d) Fritzlanghals, E.; Schutz, G. *Tetrahedron Lett.* **1993**, *34*, 293.
10. Tinant, B.; Declercq, J.P.; Gaoqiang, Y.; Ghosez, L. Unpublished results.
11. (a) DoMinh, T.; Strausz, O. *J. Am Chem. Soc.* **1970**, *92*, 1766. (b) Bellus, D. *J. Org. Chem.* **1979**, *44*, 1208. (c) Matsui, S.; Cinnabar, K.; Saigo, K. *Tetrahedron Lett.* **1999**, *40*, 899. (d) See also Kumli, F. *Dissertation*, University of Louvain, 1996.
12. (a) Ghosez, L.; Cossement, E.; Binamé, R. *Tetrahedron Lett.* **1974**, *15*, 997. (b) Ghosez, L. In *Stereoselective Synthesis of Natural Products*; Bartmann, W., Winterfeldt, E., Eds.; Excerpta Medica: Amsterdam-Oxford, 1978; p 73.
13. (a) Brook, P. R.; Harrison, J. M.; Duke, A. J. *J. Chem. Soc., Chem. Commun.* **1970**, 589. (b) Brady, W. T.; Hieble, J. P. *J. Org. Chem.* **1971**, *36*, 2033. (c) Brook, P. R.; Harrison, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 997.
14. Tammura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.