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Synthesis of Enantiopure α-Chlorocyclobutanones and Cyclobutanols as Scaffolds for the Diverted Synthesis of Serine Protease Inhibitors

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Dedicated to Professor Alain Krief

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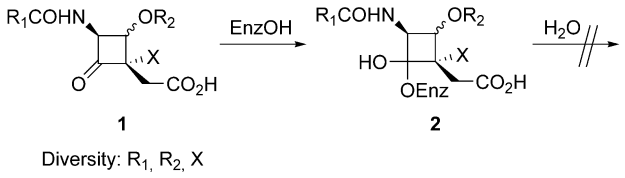
Synthetic paths towards highly functionalized α-chlorocyclobutanone scaffolds susceptible to lead to serine proteases inhibitors were explored. The syntheses started from bicyclic α-chlorocyclobutanones **3**, which are readily available from Seebach's oxazolines. It was found that the carbonyl group of the bicyclic α-chlorocyclobutanones was highly electrophilic and readily reacted with a hydroxy group to give, for example, cyclized compound **4**. Also, the presence of this reactive carbonyl group did not allow the regeneration of the protected amine and hydroxy groups. Thus, the functional manipulation of these bicyclic α-chlorocyclobutanones required prior reduction of the carbonyl group to the corresponding cyclobutanol. Accordingly, enantiopure cyclobutanone **3d** was stereoselectively reduced to *exo*-cyclobutanol **15**. Allylation of the alcohol followed by TEMPO-catalyzed oxidation of the primary alcohol of the side chain and benzylation of the resulting carboxylic acid yielded compound **19**. Cleavage of the oxazolidine ring occurred smoothly to yield densely functionalized cyclobutanol scaffold **20**. A similar route allowed the efficient preparation of cyclobutanol scaffolds **14** and **25a–d** in 25–27 % yields. TEMPO-catalyzed oxidation of the cyclobutanol gave an excellent yield of corresponding cyclobutanones **26a**,**b**

Introduction

β-Lactams have been the subject of extensive synthetic, theoretical and pharmacological studies owing to their ability to act as inhibitors of important classes of serine proteases.[1] They act as acylating agents of a serine residue of the protease leading to an acyl enzyme intermediate that cannot further react or leads to an inactive form of the enzyme. The emergence of resistance to β-lactam antibiotics has become a major threat to public health.

A major, though not unique, form of resistance results from the bacterial expression of β-lactamases.[2] These enzymes react with the β-lactam to form an acyl enzyme that undergoes fast hydrolysis to regenerate the enzyme and a derivative of the antibiotic. In principle, this type of resistance could be overcome by replacing the acylating lactam group by an alkylating or hydroxy-alkylating group.[3] In this context, we became interested in the synthesis of cyclobutanone scaffolds **1** (Scheme 1), which could be used for the diverted total synthesis of serine protease inhibitors.[4] The cyclobutanone is structurally similar to the β-lactam: both carbonyl groups are part of a strained ring, which should favour nucleophilic addition of a serine residue. Also, the additional presence of an electronegative substituent X (F, Cl, Br···) would further increase the electrophilic character of the carbonyl group. The scaffolds should carry functional groups that could be readily modified by click chemistry to generate diversity. We selected an amine group at C-2, which could be readily converted into a variety of amides (analogy with penicillins and cephalosporins), and a *cis*-hydroxy group at C-3, which could be easily acylated or alkylated. An acetic acid side chain at C-4 should allow hydrogen bonding of the carboxylate group with an OH group of the protein, as in the case of β-lactam antibiotics.



Scheme 1. Possible interaction of an α-halocyclobutanone with a serine protease.

In principle, these scaffolds should be readily accessible in enantiopure form by following the retrosynthetic pathway outlined in Scheme 2. We have already reported on the remarkable [2+2] cycloadditions of Seebach's oxazolines[5] to in situ generated chloroketenes.[6] The reaction unexpec-

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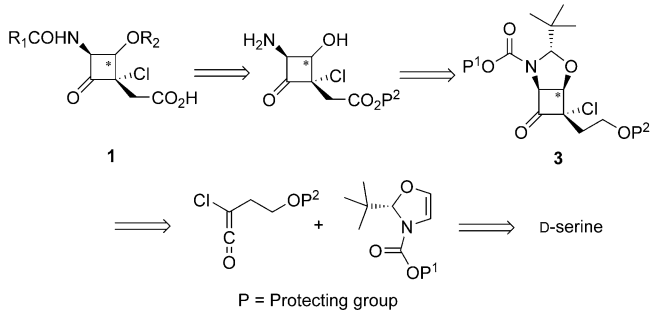
tedly yielded adduct **3** as the major regioisomer. This paper reports studies of the transformations of compounds **3** in targeted scaffolds **1**. These model studies were performed on the enantiomers of **3**, which are readily available in large amounts from cheap L-serine. Eventually it will be shown that the final synthetic route will allow the targeted configurations to be obtained..



Scheme 2. Retrosynthetic analysis for α-chlorocyclobutanone scaffold **1**.

Results and Discussion

Required bicyclic cyclobutanones **3a**–**d** were prepared following the procedure described in our previous publication (Scheme 3).[6b] All attempts to cleave the protecting group P^2 (e.g., by catalytic hydrogenolysis of **3a**) led to hemiketal **4** resulting from intramolecular attack of the free hydroxy group on the highly reactive carbonyl group.[7] This was a dead end as far as the synthesis of scaffolds **1** was concerned. We were thus forced to reduce the ketone group before cleaving the protecting group P^2. The reduction of **3a** was performed with $NaBH_4$ to give *exo*-cyclobutanol **5** in 50% yield. The reaction was rather slow (15 h). This probably resulted from the steric crowding on each face of the carbonyl group. The use of $Zn(BH_4)_2$ in ether did not significantly improve the yields (55%). The selective formation of the *exo*-alcohol was not unexpected: this configuration would result from attack of the hydride reagent to the face opposite to the bulky *tert*-butyl group. Also, Brook et al. already reported that hydride transfer from $NaBH_4$ on haloketones took place on the face opposite to the halogen substituent.[8] The alcohol was protected as TBDMS ether **6**. Cleavage of the benzyl group by catalytic hydrogenolysis quantitatively yielded alcohol **7**, which was oxidized with pyridinium dichromate (PDC) in DMF, a reagent which is rather tolerant to acid- and base-sensitive functional groups. Here again the reaction was very slow and gave a moderate yield of carboxylic acid **8** after approximately 24 h. The structure and configuration of **8** were confirmed by X-ray diffraction analysis (Figure 1).[9] The carboxylic acid was esterified with benzyl bromide in the presence of sodium hydrogen carbonate. Cleavage of the TBDMS ether in methanol containing *p*TsOH (1.2 equiv.) gave the corresponding cyclobutanol. Notably, PDC did not oxidize the secondary hydroxy group at room temperature: after 12 h starting material was recovered unchanged. However, Swern oxidation exclusively gave cyclobutanone **12** in the presence of triethylamine (3 equiv.). Compound **12** obviously resulted from easy dehydrochlorination of the β-chloroester in the presence of the base. Reducing the amount of base to 2 equivalents led to a mixture of **11** and **12**, which were separated by flash chromatography (Scheme 4).

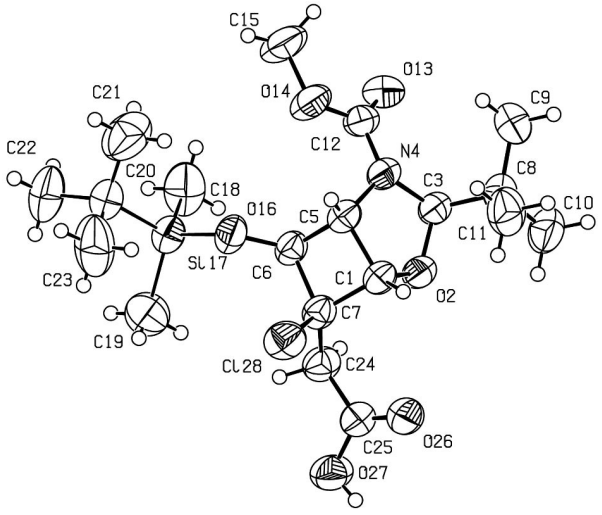
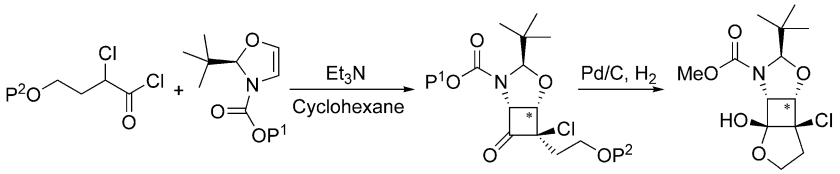


Figure 1. ORTEP drawing of the X-ray crystal structure of **8**.

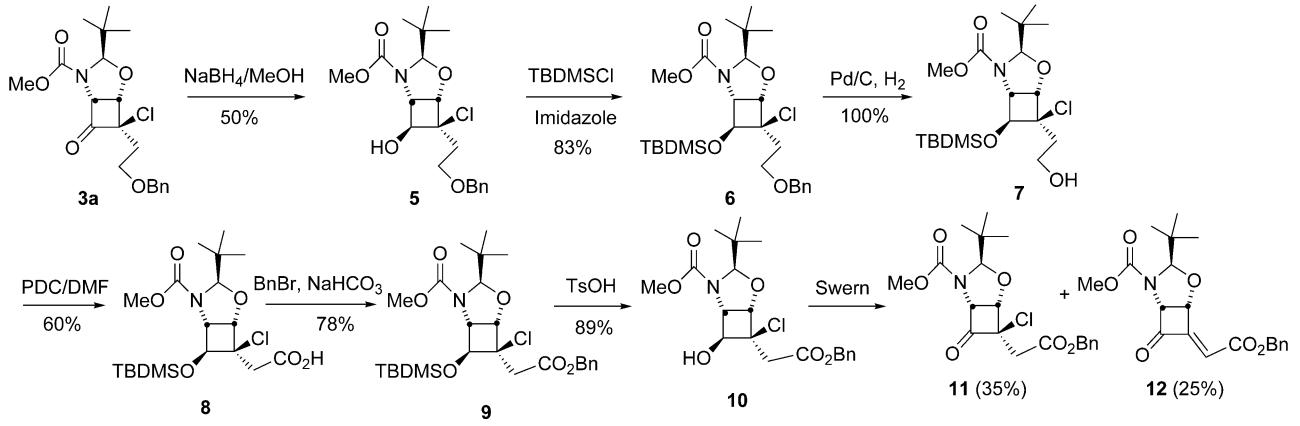
The cleavage of the oxazolidine ring was studied on model compounds **3e**,**f**, which were prepared according to a literature procedure. Unfortunately, all attempts (4 N HCl, TFA, BF_3 in AcOH, etc.) to cleave the oxazolidine ring of **3e** and **3f** led to unchanged starting materials or complex



3a: P^1 = Me, P^2 = Bn, 72%,
6 : 1 mixture of regioisomers
3b: P^1 = Me, P^2 = *t*BuPh$_2$Si, 80%
3c: P^1 = *t*Bu, P^2 = Bn, 56%
3d: P^1 = *t*Bu, P^2 = *t*BuPh$_2$Si, 75%

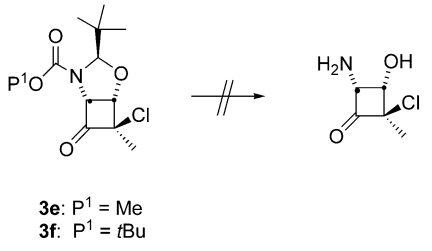
4: 80% from **3a**

Scheme 3. Synthesis of enantiopure N- and O-protected α-chlorocyclobutanones **3** followed by hydrogenolysis of the benzyl group.

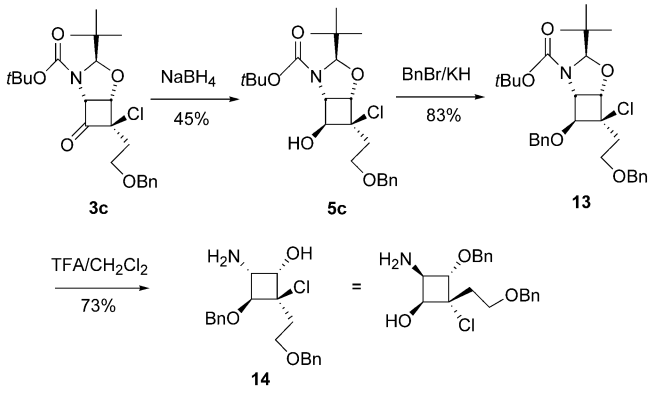


Scheme 4. Synthesis of enantiopure fully protected α-chlorocyclobutanone **11** carrying an acetic side chain.

mixtures of unidentified products (Scheme 5). The problems associated with the cleavage of the oxazolidine ring probably resulted from the high functional density of these bicyclic molecules and, in particular, from the presence of a highly electrophilic carbonyl group. We thus prepared benzyl ether **13** (Scheme 6), its methyl carbamate analogue was submitted to various acidic exposure to refluxing 4 N HCl in ethyl ether or BF_3·2AcOH at room temperature, no reaction occurred. It was completely degraded in a mixture of BF_3/TFA at room temperature after 1 d.

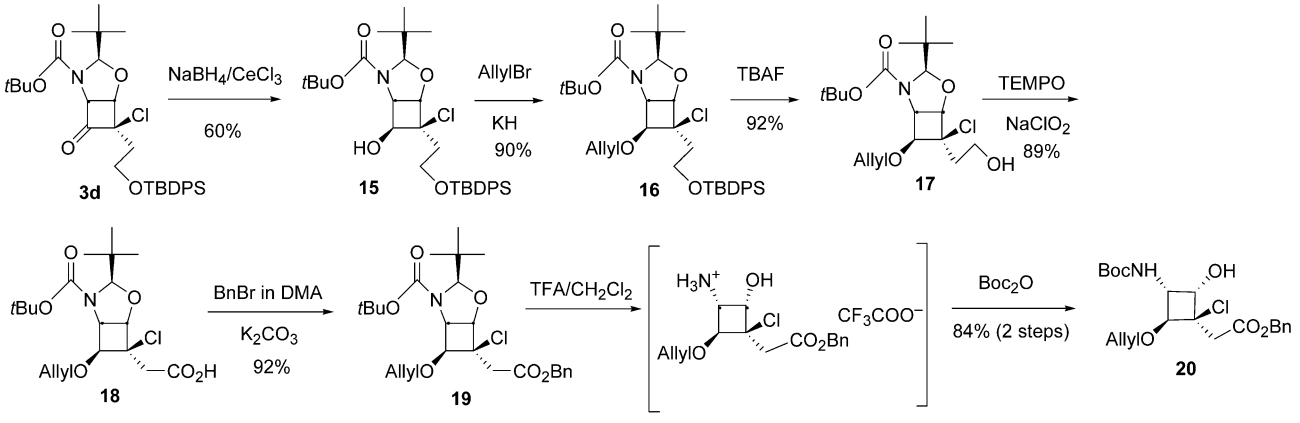


Scheme 5. Attempted cleavage of the oxazoline ring of α-chlorocyclobutanones **3**.

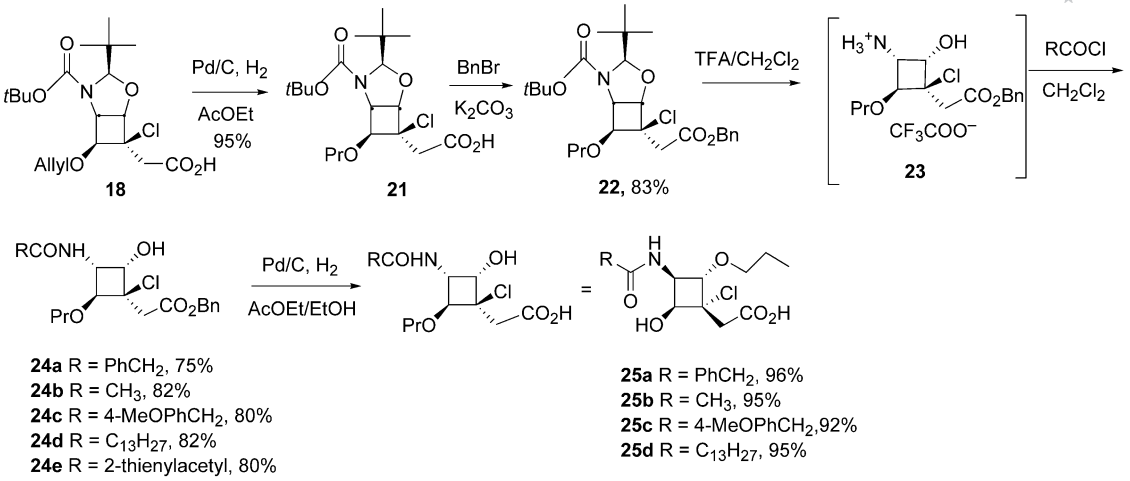


Scheme 6. Cleavage of the oxazolidine ring of α-chlorocyclobutanol benzyl ethers **13**.

Densely functionalized and enantiopure cyclobutane scaffold **14** offers plentiful opportunities for diverted synthesis of serine protease inhibitors. It contains two differentiated hydroxy groups that could be selectively oxidized to a cyclobutanone formally derived from L-serine (oxidation of the protected hydroxy group) or a cyclobutanone formally derived from D-serine (oxidation of the free OH group). This latter opportunity is illustrated in the sequence of reactions described in Schemes 7 and 8.



Scheme 7. Synthesis of an orthogonally protected highly functionalized cyclobutanol **20**.



Scheme 8. Synthesis of cyclobutanol scaffolds.

The synthesis started from **3d**. The reduction of the ketone group with $NaBH_4$ was faster in the presence of 10% $CeCl_3$[10] to give 60% of cyclobutanol **15**, which was converted into corresponding allyl ether **16** in 90% yield. After removal of the *tert*-butyldiphenylsilyl protecting group, resulting primary alcohol **17** was efficiently oxidized to corresponding carboxylic acid **18** by sodium chlorite in the presence of a catalytic amount of TEMPO.[11] These oxidative conditions gave much better yields (89%) than PDC in DMF (slow reaction, 50%) or IBX (55%). The cleavage of the oxazolidine ring took place smoothly and quantitatively to give an ammonium salt, which was directly converted into cyclobutanol **20** by treatment with di-*tert*-butyl dicarbonate in an ultrasonic bath. This two-step sequence gave 84% of α-chlorocyclobutanol **20**.

The presence of an allyl substituent in compound **18** offered possibilities for diversification of this ether substituent, for example, after oxidative cleavage. In this model synthesis of a representative α-amino cyclobutanone scaffold, we simply chose to hydrogenate the allyl group (Scheme 8). Resulting propyl ether **21** was formed quantitatively. Its structure and configuration were confirmed by X-ray diffraction analysis (Figure 2).[9] The carboxylic acid was readily converted into corresponding benzyl ester **22**. Cleavage of the oxazolidine ring with trifluoroacetic acid followed by acylation of the amine group of **23** yielded **24a**–**e**. Hydrogenolysis of the benzyl group yielded four enantiopure cyclobutanol scaffolds **25a**–**d**.

We have thus developed efficient routes towards highly functionalized and enantiopure cyclobutanols that should be useful for the diverted synthesis of analogues of β-lactam antibiotics. In contrast with the corresponding cyclobutanones that are highly electrophilic, these cyclobutanols are rather stable and susceptible to further diversification by functional group manipulations. *The ketone group should be introduced at the end of the syntheses.* We found that sodium hypochlorite and a catalytic amount of TEMPO smoothly converted cyclobutanols **24a**,**b** into cyclobutanones **26a** and **26b** (Scheme 9).

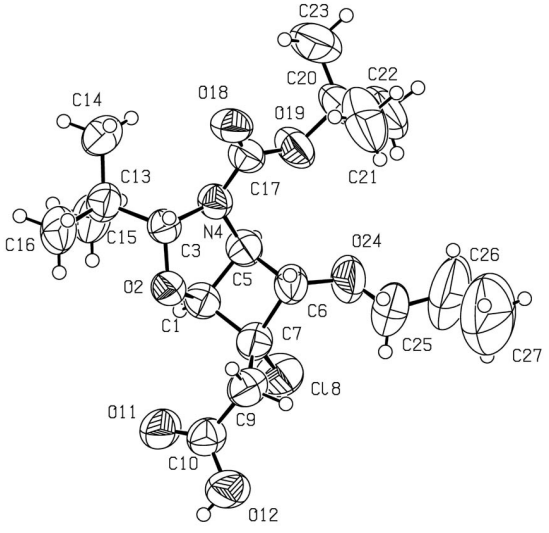
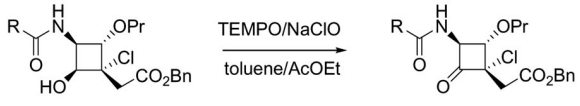


Figure 2. ORTEP drawing of the X-ray crystal structure of **21**.

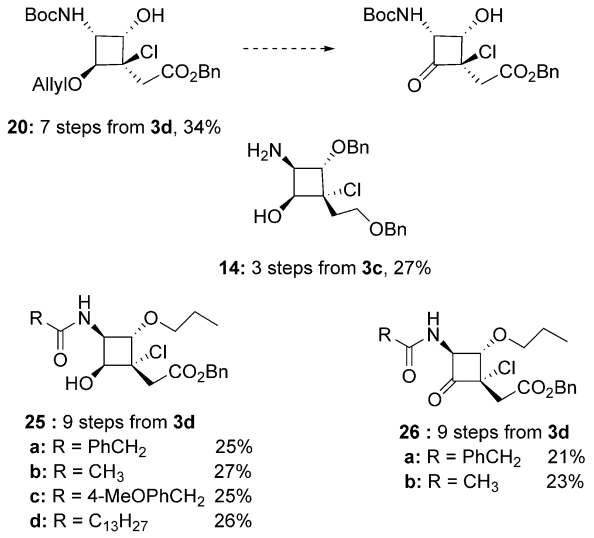


Scheme 9. Conversion of cyclobutanols **24** into two models of the targeted α-chlorocyclobutanones.

Conclusions

In summary, we presented a synthetic strategy that provides easy access to highly functionalized enantiopure cyclobutanols and cyclobutanones as scaffolds for the synthesis of serine protease inhibitor analogues to β-lactams. Scheme 10 displays the various compounds that were prepared in enantiopure form from readily available starting materials **3**. The functional density of these scaffolds should

allow high levels of diversity to be efficiently achieved, which would allow biologically relevant regions of the chemical space to be explored.



Scheme 10. Cyclobutanol and cyclobutanone scaffolds accessible from **3c**,**d**.

The present series originates from L-serine, which by virtue of the synthetic strategy, generates acylamino and acetic acid side chain absolute configurations identical to those observed in β-lactam antibiotics. The synthetic strategy presents the additional advantage of being potentially stereodivergent: an appropriate selection of the alcohol function to be oxidized should provide access to diastereomeric cyclobutanones. If the allyl group could not be cleaved in a satisfactory manner, the method should readily allow the use of alternative protecting groups.

Experimental Section

General Remarks: NMR spectra were recorded with a Varian Gemini 300BB (300 MHz for ^{1}H and 75 MHz for ^{13}C). High-resolution spectra were recorded with a Bruker 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 spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). The MS spectra were recorded with a Varian MAT-44 or Finnigan MAT-TSQ 70 apparatus. Infrared spectra were recorded with a Biorad FTS-135. The optical rotation values were measured with 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 by using Merck 60 40–63 μm silica and predistilled technical grade solvents. Triethylamine and CH_2Cl_2 were distilled from CaH_2. Et_2O, THF, cyclohexane and toluene were distilled over Na with benzophenone as indicator. DMF and DMA were dried with 3 Å MS.

Methyl (2*R*,3a*R*,3b*R*,6a*R*,6b*S*)-2-*tert*-Butyl-6a-chloro-3b-hydroxyhexahydrofuro[3′.2′:3.4]cyclobuta[1.2-*d*][1.3]oxazole-3(2*H*)-carboxylate (4): Carboxylate **3a** (100 mg, 0.25 mmol), palladium on activated carbon (10% Pd, 1.4 mg, 12.6 μmol) and ethyl acetate (5 mL) were added to a 25-mL flask at room temperature. Then, hydrogen was flushed into the flask. After 12 h, the mixture was filtered through Celite, washed with diethyl ether, dried with $MgSO_4$ and the solvents evaporated. Flash chromatography of the residue gave **4** (0.06 g, 80%). R_f = 0.33 [petroleum ether (PE)/AcOEt, 2:1]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.32 (s, 1 H, NCHO), 4.69 (d, J = 6.7 Hz, 1 H, CHN), 4.38 (d, J = 6.7 Hz, 1 H, CHO), 4.12 (m, 2 H, CH_2O), 3.72 (s, 3 H, OMe), 2.75 (m, 2 H, CH_2), 0.87 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1 (C=O), 102.8 (COH), 101.8 (NCHO), 81.4 (CHO), 71.0 (CCl), 68.0 (CH_2O), 63.1 (CHN), 52.6 (OMe), 38.7 (*t*Bu), 34.6 (CH_2), 24.8 (*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 3456, 2972, 1718 ($C{=}O_{carbamate}$), 1363, 1201 cm^{-1}. MS (FAB Q1MS): *m*/*z* (%) = 306 (100) [M + 1], 288 (28) [M – OH], 248 (17) [M – *t*Bu], 217 (59), 91 (69). $C_{13}H_{20}ClNO_5$ (305.75): calcd. C 51.06, H 6.59, N 4.58; found C 51.05, H 6.47, N 4.42.

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-hydroxy-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (5): Sodium borohydride (20.9 mg, 0.55 mmol) was added at room temperature to a solution of **3a** (146 mg, 0.37 mmol) in methanol (4 mL). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After 15 h the reaction mixture was diluted with diethyl ether (10 mL) and washed with 0.1 N HCl and then with brine. The organic layer was dried and concentrated. Flash chromatography (PE/AcOEt/*i*PrOH, 100:5:5; R_f = 0.25) gave alcohol **5** (73 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.34 (m, 5 H, Ph), 5.28 (s, 1 H, NCHO), 4.76 (dd, J = 6.4, 0.9 Hz, 1 H, CHO), 4.50 (s, 2 H, CH_2Ph), 4.19 (dd, J = 6.4, 4.6 Hz, 1 H, CHN), 3.95 (dd, J = 4.6, 0.9 Hz, 1 H, CHOH), 3.73 (s, 3 H, OMe), 3.71 (m, 2 H, CH_2O), 2.69 (br., 1 H, OH), 2.27 (ddd, J = 14.6, 6.1, 6.1 Hz, 1 H, CH_2), 2.15 (ddd, J = 14.6, 6.7, 6.7 Hz, 1 H, CH_2), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4 (C=O), 138.1 (C_{arom}), 128.3, 127.7, 127.5 (CH_{arom}), 101.5 (NCHO), 83.1 (CHO), 78.8 (CHOH), 73.2 (CH_2Ph), 72.0 (CCl), 65.9 (CH_2O), 63.1 (CHN), 52.7 (OMe), 38.7 (*t*Bu), 34.9 (CH_2), 25.2 (*t*Bu) ppm. IR (film): $\tilde{\nu}$ = 3438, 2958, 1712 ($C{=}O_{carbamate}$), 1367, 1128 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 398 (29) [M + 1], 340 (9) [M – *t*Bu], 307 (15), 154 (100), 136 (77).

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-(*tert*-butyldimethylsilyl)oxy-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (6): To a solution of **5** (2.15 g, 5.40 mmol) in DMF (23 mL) was successively added imidazole (1.1 g, 16.21 mmol) and a solution of *tert*-butyldimethylsilyl chloride (1.22 g, 8.11 mmol) in DMF (5 mL) at 0 °C. The resulting mixture was stirred for 40 h at room temperature and then cooled to 0 °C. H_2O (3 mL) was added, and the mixture was stirred for 10 min. The resulting solution was poured into water (70 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried and the solvents evaporated. Flash chromatography (PE/ether, 6:1; R_f = 0.27) gave pure **6** (2.3 g, 83%). M.p 87–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.35 (m, 5 H, Ph), 5.31 (s, 1 H, NCHO), 4.78 (dd, J = 6.6, 0.9 Hz, 1 H, CHO), 4.50 (s, 2 H, CH_2Ph), 4.1 (dd, J = 6.6, 3.1 Hz, 1 H, CHN), 3.95 (dd, J = 3.1, 0.9 Hz, 1 H, CHOSi), 3.70 (s, 3 H, OMe), 3.69 (m, 2 H, CH_2O), 1.95–2.33 (m, 2 H, CH_2), 0.93 (s, 9 H, *t*Bu), 0.86 (s, 9 H, Si*t*Bu), 0.05 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3 (C=O), 138.3 (C_{arom}), 128.3, 127.7, 127.5 (CH_{arom}), 101.2 (NCHO), 84.3 (CHO), 74.6 (CHOSi), 72.9 (CH_2Ph), 71.2 (CCl), 66.8 (CH_2O), 62.9 (CHN), 52.7 (OMe), 38.9 (*t*Bu), 36.1 (CH_2), 25.8 (*t*Bu), 25.2 (Si*t*Bu), 18.1 (Si*t*Bu), –5.0 ($SiMe_2$) ppm. IR (film): $\tilde{\nu}$ = 2958, 1731 ($C{=}O_{carbamate}$), 1448, 1364, 1098 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 512 (4) [M + 1], 454 (17) [M – *t*Bu], 307 (15),

154 (100), 136 (64). $[\alpha]_D^{20}$ = +0.51 (*c* = 0.95, $CHCl_3$). $C_{26}H_{42}ClNO_5Si$ (512.15): calcd. C 60.97, H 8.26, Cl 6.82, N 2.73; found C 61.01, H 8.11, Cl 6.54, N 2.63.

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-(*tert*-butyldimethylsilyl)oxy-7-(2-hydroxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (7): Hydrogen was flushed through a suspension of palladium on activated carbon (10% Pd, 530 mg, 498 μmol) in a solution of **6** (2.55 g, 4.98 mmol) in ethyl acetate (40 mL) at room temperature. The reaction was complete after 8 h (TLC monitoring, PE/*i*PrOH/AcOEt, 100:5:5; R_f = 0.37). The mixture was passed through a Celite pad and then evaporated to give pure **7** (2.1 g, 100%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.31 (s, 1 H, NCHO), 4.86 (dd, *J* = 6.8, 0.7 Hz, 1 H, CHO), 4.15 (dd, *J* = 6.8, 3.2 Hz, 1 H, CHN), 3.90 (dd, *J* = 3.2, 0.7 Hz, 1 H, CHOSi), 3.83 (m, 2 H, CH_2O), 3.73 (s, 3 H, OMe), 1.81–2.28 (m, 2 H, CH_2), 0.94 (s, 9 H, *t*Bu), 0.88 (s, 9 H, Si*t*Bu), 0.08 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.3 (C=O), 101.2 (NCHO), 84.2 (CHO), 71.2 (CH_2O), 67.4 (CCl), 62.8 (CHN), 59.4 (CHOSi), 52.8 (OMe), 38.9 (*t*Bu), 37.7 (CH_2), 25.8 (*t*Bu), 25.2 (Si*t*Bu), 18.3 (Si*t*Bu), –5.0 ($SiMe_2$) ppm. IR (film): $\tilde{\nu}$ = 3454, 2958, 1724 ($C{=}O_{carbamate}$), 1361, 1101 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 422 (9) [M + 1], 364 (19) [M – *t*Bu], 307 (17), 154 (100), 136 (64).

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-(*tert*-butyldimethylsilyl)oxy-7-hydroxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (8): A solution of **7** (1.6 g, 3.79 mmol) and pyridinium dichromate (5 g, 13.26 mmol) in DMF (15 mL) was stirred at 0 °C then room temperature till disappearance of the starting material (TLC monitoring; 2 d). The reaction was quenched by the addition of water (40 mL), and the mixture was extracted with diethyl ether (4 × 60 mL). The organic layers were washed with brine, dried with $MgSO_4$ and concentrated to give a colourless oil. Purification by flash chromatography (PE/AcOEt/*i*PrOH, 100:5:5; R_f = 0.27) gave **8** (colourless crystals 1.0 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 5.30 (s, 1 H, NCHO), 4.9 (d, *J* = 6.1 Hz, 1 H, CHO), 4.14 (dd, *J* = 6.1, 3.1 Hz, 2 H, CHN, CHOSi), 3.73 (s, 3 H, OMe), 2.98 (AB, *J* = 16.5 Hz, 2 H, CH_2), 0.95 (s, 9 H, *t*Bu), 0.89 (s, 9 H, Si*t*Bu), 0.13 (s, 6 H, $SiMe_2$) ppm. ^{1}H NMR (500 MHz, C_6D_6, 47 °C): δ = 5.32 (s, 1 H, NCHO), 4.86 (d, *J* = 6.3 Hz, 1 H, CHO), 4.26 (d, *J* = 3.1 Hz, 1 H, CHOSi), 4.12 (dd, *J* = 6.3, 3.1 Hz, 1 H, CHN), 3.46 (s, 3 H, OMe), 2.71–2.85 (AB, *J* = 16.6 Hz, 2 H, CH_2), 1.1 (s, 9 H, Si*t*Bu), 0.80 (s, 9 H, *t*Bu), 0.19 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 173.6 (C=O), 154.3 (C=O), 101.1 (NCHO), 84.0 (CHO), 76.0 (CHN), 68.1 (CCl), 63.2 (CHOSi), 52.7 (OMe), 41 (CH_2), 38.9 (*t*Bu), 25.6 (*t*Bu), 25.2 (Si*t*Bu), 18.1 (Si*t*Bu), –5.1 ($SiMe_2$) ppm. IR (film): $\tilde{\nu}$ = 3434, 1736 (C=O), 1724 ($C{=}O_{carbamate}$), 1361, 1101 cm^{-1}. $[\alpha]_D^{20}$ = +0.92 (*c* = 0.92, $CHCl_3$). MS (FAB + Q1MS): *m*/*z* (%) = 436 (45) [M + 1], 378 (49) [M – *t*Bu], 300 (24), 185 (33), 128 (60), 73 (100). X-ray diffraction analysis: wavelength: 0.71069 Å; crystal system: orthorhombic; unit cell dimensions: *a* = 10.275 (3) Å, α = 90°; *b* = 11.353 (4) Å, β = 90°; *c* = 20.779 (7) Å, γ = 90°.

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-(*tert*-butyldimethylsilyl)oxy-7-hydroxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (9): To a solution of **8** (1 g, 2.29 mmol) in DMA (20 mL) was added benzyl bromide (785 mg, 4.59 mmol) and sodium hydrogen carbonate (580 mg, 6.88 mmol). The mixture was stirred at room temperature for 24 h. Then, water (50 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried and concentrated. Flash chromatography (PE/ether, 6:1; R_f = 0.3) of the residue gave **9** (0.91 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.38 (m, 5 H, Ph), 5.26 (s, 1 H, NCHO), 5.15 (s, 2 H, CH_2Ph), 4.88 (d, *J* = 6.3 Hz, 1 H, CHO), 4.15 (dd, *J* = 6.3, 3.4 Hz, 1 H, CHN), 4.10 (d, *J* = 3.4 Hz, 1 H, CHOSi), 3.73 (s, 3 H, OMe), 3.0 (AB, *J* = 16.0 Hz, 2 H, CH_2), 0.94 (s, 9 H, *t*Bu), 0.85 (s, 9 H, Si*t*Bu), 0.08 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (C=O), 154.3 (C=O), 135.6 (C_{arom}), 129.0, 128.5, 128.1 (CH_{arom}), 101.1 (NCHO), 83.8 (CHO), 68.3 (CH_2Ph), 66.5 (CCl), 63.1 (CHN), 63.0 (CHOSi), 52.7 (OMe), 41.2 (CH_2), 38.9 (*t*Bu), 25.6 (*t*Bu), 25.2 (Si*t*Bu), 18.1 (Si*t*Bu), 5.1 ($SiMe_2$) ppm. IR (film): $\tilde{\nu}$ = 2963, 1732 (C=O), 1726 ($C{=}O_{carbamate}$), 1361, 1107 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 526 (20) [M + 1], 468 (25) [M – *t*Bu], 418 (11), 300 (15), 185 (26), 128 (38), 91 (100).

Methyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-hydroxy-7-benzyloxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (10): A mixture of **9** (1.15 g, 2.19 mmol) and *para*-toluenesulfonic acid monohydrate (0.71 g, 2.62 mmol) in methanol (100 mL) was stirred at room temperature for 2 d. The mixture was neutralized with saturated aqueous sodium hydrogen carbonate, and the methanol was removed under reduced pressure. The residue was treated with water (10 mL), and the resulting mixture was extracted with AcOEt (3 × 20 mL). The organic layers were dried and concentrated. The residue was purified by flash chromatography (PE/AcOEt/*i*PrOH, 100:5:5; R_f = 0.27) to give **10** (0.8 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.38 (m, 5 H, Ph), 5.26 (s, 1 H, NCHO), 5.16 (s, 2 H, CH_2Ph), 4.80 (dd, *J* = 6.3, 0.8 Hz, 1 H, CHO), 4.23 (dd, *J* = 6.0, 4.8 Hz, 1 H, CHN), 4.07 (m, 1 H, CHOH), 3.73 (s, 3 H, OMe), 3.1 (br., 1 H OH), 3.05 (AB, *J* = 17.0 Hz, 2 H, CH_2), 0.88 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7 (C=O), 155.3 (C=O), 135.2 (C_{arom}), 128.6, 128.3, 128.1 (CH_{arom}), 101.6 (NCHO), 82.4 (CHO), 78.1 (CHOH), 67.8 (CCl), 66.8 (CH_2Ph), 64.3 (CHN), 52.9 (OMe), 40.5 (CH_2), 38.9 (*t*Bu), 25.2 (*t*Bu) ppm. IR (film): $\tilde{\nu}$ = 346, 1738 (C=O), 1726 ($C{=}O_{carbamate}$), 1361, 1120 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 412 (48) [M + 1], 354 (17) [M – *t*Bu], 290 (11), 185 (10), 154 (45), 136 (33), 91 (100). $C_{20}H_{26}ClNO_6$ (411.88): calcd. C 58.32, H 6.36, N 3.40; found C 57.75, H 6.08, N 3.43.

Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-Butyl)-7-chloro-6-oxo-7-(benzyloxycarbonylmethyl)-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (11) and Elimination Product (12): A solution of **10** (70 mg, 170 μmol) in dichloromethane (0.5 mL) was added dropwise to a solution of oxalyl chloride (45 μL, 510 μmol) and methyl sulfoxide (62 μL, 850 μmol) in dichloromethane (0.7 mL) at –60 °C. The mixture was stirred for 30 min. Triethylamine (71 μL, 510 μmol) was added, and the reaction mixture was stirred for 5 min and then warmed up to room temperature. Water (1 mL) was added, and the aqueous layer was further extracted with dichloromethane (5 mL). The organic layers were washed with brine, dried and concentrated. Flash chromatography (PE/AcOEt/*i*PrOH, 100:5:5) gave **11** (24 mg, 35%), R_f = 0.28 and **12** (16 mg, 25%), R_f = 0.33. Data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 5 H, Ph), 5.35 (d, *J* = 5.5 Hz, 1 H, CHO), 5.20 (s, 1 H, NCHO), 5.08–5.26 (AB, *J* = 12.3 Hz, 2 H, CH_2Ph), 5.0 (d, *J* = 5.5 Hz, 1 H, CHN), 3.75 (s, 3 H, OMe), 2.94–3.25 (AB, *J* = 17.0 Hz, 2 H, CH_2), 0.88 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.2 (C=O), 167.8 (C=O), 155.4 (C=O), 135.4 (C_{arom}), 128.7, 128.5, 128.2 (CH_{arom}), 102.3 (NCHO), 81.2 (CHO), 74.5 (CHN), 73.8 (CCl), 67.1 (CH_2Ph), 52.8 (OMe), 38.9 (*t*Bu), 36.2 (CH_2), 25.2 (*t*Bu) ppm. Data for **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.42 (m, 5 H, Ph), 6.45 (d, *J* = 1.5 Hz, 1 H, =CH), 5.65 (dd, *J* = 5.7, 1.5 Hz, 1 H, CHO), 5.45 (s, 1 H, NCHO), 5.27 (AB, *J* = 13.1 Hz, 2 H, CH_2Ph), 4.93 (d, *J* = 5.7 Hz, 1 H, CHN), 3.73 (s, 3 H, OMe), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.2 (C=O), 163.6 (C=O), 156.9 (C=O), 154.0 (=C=), 135.0 (C_{arom}), 128.7, 128.5, 128.1 (CH_{arom}), 120.5 (=CH), 101.8 (NCHO), 76.5 (CHO), 74.4

(CHN), 67.6 (CH_2Ph), 52.7 (OMe), 39.2 (*t*Bu), 25.2 (*t*Bu) ppm. MS(FAB + Q1MS): *m*/*z* (%) = 374 (5) [M + 1], 281 (11), 207 (13), 154 (23), 128 (30), 91 (100).

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-hydroxy-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (5c):** Reduction of **3c** (4 mmol) by $NaBH_4$ following the procedure used for the reduction of **3a**. Purification by flash chromatography (PE/AcOEt/PrOH, 100:5:4; R_f = 0.27). Yield 45%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.38 (m, 5 H, Ph), 5.25 (s, 1 H, NCHO), 4.76 (dd, *J* = 6.2, 0.8 Hz, 1 H, CHO), 4.51 (s, 2 H, CH_2Ph), 4.12 (dd, *J* = 6.2, 4.4 Hz, 1 H, CHN), 3.90 (dd, *J* = 4.4, 0.8 Hz, 1 H, CHOH), 3.71 (m, 2 H, CH_2O) 2.69 (br., 1 H, OH), 2.10–2.31 (m, 2 H, CH_2), 1.47 (s, 9 H, O*t*Bu), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5 (C=O), 138.0 (C_{arom}), 128.5, 127.9, 127.5 (CH_{arom}), 101.1 (NCHO), 82.4 (CHO), 81.4 (O*t*Bu), 78.2 (CHOH), 73.4 (CH_2Ph), 67.1 (CCl), 66.3 (CH_2O), 63.2 (CHN), 38.8 (*t*Bu), 34.2 (CH_2), 28.2 (O*t*Bu), 25.5 (*t*Bu) ppm. IR (film): $\tilde{\nu}$ = 3447, 2958, 1721 ($C{=}O_{carbamate}$), 1364, 1121 cm^{-1}. MS (FAB + Q1MS): *m*/*z* (%) = 440 (5) [M + 1], 382 [M – *t*Bu], 340 (100), 292 (15), 91 (14).

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-benzyloxy-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (13):** A solution of **5c** (600 mg, 1.36 mmol) in THF (9 mL) was added dropwise to a suspension of potassium hydride (30% dispersion in mineral oil, 260 mg, 1.91 mmol) in THF (9 mL). After 10 min, benzyl bromide (350 mg, 2.05 mmol) was added slowly at 0 °C. The mixture was stirred at room temperature for 2 h and then poured into a solution of saturated aqueous solution of NH_4Cl, extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried and the solvents evaporated. Flash chromatography (PE/ether, 5:1; R_f = 0.33) gave pure **13** (0.6 g, 83%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.43 (m, 5 H, Ph), 5.25 (s, 1 H, NCHO), 4.77 (dd, *J* = 6.8, 0.8 Hz, 1 H, CHO), 4.65 (s, 2 H, CH_2Ph), 4.50 (s, 2 H, CH_2Ph), 4.24 (dd, *J* = 6.8, 3.6 Hz, 1 H, CHN), 3.82 (dd, *J* = 3.6, 0.8 Hz, 1 H, CHOBn), 3.71 (m, 2 H, CH_2O), 2.01–2.31 (m, 2 H, CH_2), 1.47 (s, 9 H, O*t*Bu), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.2 (C=O), 138.3 (C_{arom}), 128.5, 127.9, 127.5 (CH_{arom}), 100.7 (NCHO), 83.8 (O*t*Bu), 83.4 (CHO), 80.7 (CHOBn), 73.0 (CH_2Ph), 72.0 (CH_2Ph), 70.4 (CH_2O), 66.3 (CCl), 61.2 (CHN), 38.8 (*t*Bu), 36.2 (CH_2), 28.3 (O*t*Bu), 25.3 (*t*Bu) ppm. IR (film): $\tilde{\nu}$ = 2958, 1725 ($C{=}O_{carbamate}$), 1356, 1116, 760 cm^{-1}. MS (CI + Q1MS LMR): *m*/*z* (%) = 530 (8) [M + 1], 472 (6) [M – *t*Bu], 430 (100), 334 (15), 107 (28), 91 (24). HRMS (CI) calcd. for $C_{30}H_{40}ClNO_5$ 532.2644, found 532.2644.

(1*R*,2*S*,3*R*,4*S*)-4-Amino-3-(benzyloxy)-2-[2-(benzyloxy)ethyl]-2-chlorocyclobutanol (14): Trifluoroacetic acid (320 μL) was added dropwise at room temperature to a mixture of **13** (100 mg, 188.6 μmol) in dichloromethane (630 μL) and water (100 μL). The mixture was stirred for 5 h. Then, $NaHCO_3$ was added to reach pH 8, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 100:5; R_f = 0.32) gave pure **14** (0.05 g, 73%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.2 (br., 3 H, NH_2, OH), 7.28–7.34 (m, 10 H, Ph), 5.25 (s, 1 H, NCHO), 4.52 (s, 2 H, CH_2Ph), 4.46 (s, 2 H, CH_2Ph), 4.11 (m, 1 H, CHO), 3.82 (m, 1 H, CHN), 3.67 (m, 2 H, CH_2O), 3.40 (m, 1 H, CHOBn), 2.21 (m, 1 H, CH_2), 1.61 (m, 1 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.9 (C_{arom}), 128.5, 127.9, 127.5 (CH_{arom}), 81.0 (CHOH), 73.7 (CH_2Ph), 72.5 (CH_2Ph), 71.5 (CCl), 70.1 (CHOBn), 65.3 (CH_2O), 51.3 (CHN), 35.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3426, 2958, 1728 (C=O), 1121, 760 cm^{-1}. MS (CI + Q1MS): *m*/*z* (%) = 362 (20) [M + 1], 282 (23),256 (12), 163 (13), 129 (65), 89 (100).

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-hydroxy-7-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (15):** Sodium borohydride (1.6 g, 42.64 mmol) was added portionwise, at –30 °C to –10 °C, to a solution of **3d** (5 g, 8.53 mmol) and cerium chloride heptahydrate (1.6 g, 4.26 mmol) in THF (70 mL), The mixture was stirred for 1.5 h, treated with a saturated aqueous solution of NH_4Cl (40 mL) and then extracted with AcOEt. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (PE/ether, 6:1; R_f = 0.17) to give **15** (3.0 g, 60%). M.p 74–76 °C. ^1H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 7.38–7.71 (m, 10 H, 2Ph), 5.26 (s, 1 H, NCHO), 4.72 (dd, *J* = 6.1, 0.9 Hz, 1 H, CHO), 4.14 (dd, *J* = 6.1, 4.6 Hz, 1 H, CHN), 3.94 (ddd, *J* = 7.3, 4.6, 0.9 Hz, 1 H, CHOH), 3.89 (m, 2 H, CH_2O), 2.57 (d, *J* = 7.3 Hz, 1 H, OH), 2.19 (m, 2 H, CH_2), 1.50 (s, 9 H, O*t*Bu), 1.07 (s, 9 H, Si*t*Bu), 0.88 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 154.1 (C=O), 133.5 (C_{arom}), 135.5, 129.6, 127.6 (CH_{arom}), 101.2 (NCHO), 83.1 (CHO), 80.9 (O*t*Bu), 78.9 (CHOH), 72.5 (CCl), 63.8 (CHN), 59.9 (CH_2O), 38.7 (*t*Bu), 37.4 (CH_2), 28.2 (O*t*Bu), 26.9 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 3460 (OH), 2961, 1712 (C=O), 1368 (OH), 1111 cm^{-1}. MS (CI + Q1MS): *m*/*z* (%) = 589 (2) [M + 1], 488 (100) [M + 1 – Boc], 454 (20), 410 (18). MS (CI/Q1MS): *m*/*z* (%) = 587 (64) [M – 1], 501 (50), 465 (100),255 (28). $[\alpha]_D^{20}$ = +0.45 (*c* = 0.52, $CHCl_3$). $C_{32}H_{46}ClNO_5Si$ (588.25): calcd. C 65.34, H 7.88, Cl 6.02, N 2.38; found C 65.86, H 7.98, Cl 5.59, N 2.24.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-allyloxy-7-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (16):** A solution of **15** (2.9 g, 4.93 mmol) in THF (32 mL) was added dropwise to a suspension of potassium hydride (30% dispersion in mineral oil, 1.32 g, 9.86 mmol) in THF (16 mL) under an atmosphere of argon at 0 °C. After 20 min at 0 °C, allyl bromide (1.19 g, 9.86 mmol) was added slowly, and the suspension was stirred at room temperature for 3 h and then poured into a mixture of ice and saturated NH_4Cl. After extraction with diethyl ether (3 × 20 mL), the combined organic layers were washed with brine, dried and the solvents evaporated. The residue was chromatographed (PE/ether, 10:1; R_f = 0.45) to give **16** (2.8 g, 90%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.71 (m, 10 H, 2Ph), 5.9 (m, 1 H, CH=), 5.27 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1 H, CH_2=), 5.25 (s, 1 H, NCHO), 5.18 (ddd, *J* = 10.3, 1.5, 1.5 Hz, 1 H, CH_2=), 4.69 (dd, *J* = 6.6, 0.7 Hz, 1 H, CHO), 4.18 (dd, *J* = 6.6, 3.9 Hz, 1 H, CHN), 4.1 (m, 2 H, CH_2O_{allyl}), 3.85 (m, 2 H, CH_2OSi), 3.64 (dd, *J* = 3.9, 0.7 Hz, 1 H, $CHOCH_2$), 2.01–2.36 (m, 2 H, CH_2), 1.49 (s, 9 H, O*t*Bu), 1.05 (s, 9 H, Si*t*Bu), 0.85 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1 (C=O), 144.4 (CH=), 133.8 (C_{arom}), 135.6, 129.7, 127.7 (C_{arom}), 112.3 (CH_2=), 100.1 (NCHO), 96.2 (CHO), 91.6 ($CHOCH_2$), 86.2 (CHN), 80.1 (O*t*Bu), 74.2 (CH_2O_{allyl}), 71.1 (CCl), 62.9 (CH_2O), 40.9 (CH_2), 39.4 (*t*Bu), 28.3 (*Ot*Bu), 26.8 (Si*t*Bu), 25.6 (*t*Bu), 19.1 (*Sit*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 3080, 2958, 1716 (C=O), 1364, 781 cm^{-1}. MS (EI + Q1MS LMR): *m*/*z* (%) = 570 (5) [M – *t*Bu], 470 (33), 351 (32), 281 (100), 227 (32), 126 (47), 97 (42). $[\alpha]_D^{20}$ = +0.52 (*c* = 0.62, $CHCl_3$). $C_{35}H_{50}ClNO_5Si$ (628.31): calcd. C 66.90, H 8.02, Cl 5.64, N 2.22; found C 66.89, H 8.20, Cl 6.06, N 2.18.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-allyloxy-7-(2-hydroxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (17):** Tetrabutylammonium fluoride trihydrate (844 mg, 2.67 mmol) in THF (6 mL) was added at 0 °C to a solution of **16** (1.4 g, 2.23 mmol) in THF (22 mL). The mixture was stirred for 3 h at

room temperature, treated with brine (20 mL) and extracted with diethyl ether (3 × 30 mL). The extraction residue was purified by flash chromatography (PE/*i*PrOH, 100:4; R_f = 0.22) to give pure **17** (0.8 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 5.94 (m, 1 H, CH=), 5.32 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1 H, CH_2=), 5.29 (s, 1 H, NCHO), 5.21 (ddd, *J* = 10.3, 1.5, 1.5 Hz, 1 H, CH_2=), 4.79 (dd, *J* = 6.4, 0.8 Hz, 1 H, CHO), 4.23 (dd, *J* = 6.4, 3.9 Hz, 1 H, CHN), 4.16 (ddd, *J* = 12.2, 5.5, 1.5 Hz, 1 H, CH_2O_{allyl}), 4.10 (ddd, *J* = 12.2, 5.5, 1.5 Hz, 1 H, CH_2O_{allyl}), 3.87 (m, 2 H, CH_2OH), 3.70 (dd, *J* = 3.9, 0.8 Hz, 1 H, $CHOCH_2$), 2.07–2.26 (m, 2 H, CH_2), 1.49 (s, 9 H, O*t*Bu), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 153.1 (C=O), 133.9 (CH=), 117.6 (CH_2=), 100.8 (NCHO), 83.7 (CHO), 83.2 ($CHOCH_2$), 80.9 (O*t*Bu), 71.2 (CH_2O_{allyl}), 70.1 (CCl), 61.1 (CHN), 58.6 (CH_2O), 39.5 (CH_2), 38.8 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 2974, 1710 (C=O), 1368, 1171 cm^{-1}. MS (EI + Q1MS LMR): *m*/*z* (%) = 332 (21) [M – *t*Bu], 276 (61), 232 (58), 227 (82), 171 (100), 127 (20). $[\alpha]_D^{23}$ = +0.57 (*c* = 0.6, $CHCl_3$). $C_{19}H_{32}ClNO_5$ (389.91): calcd. C 58.52, H 8.27, Cl 9.09, N 3.59; found C 58.69, H 8.11, Cl 8.88, N 3.47.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-allyloxy-7-hydroxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (18):** A solution of **17** (530 mg, 1.36 mmol) and TEMPO (14.9 mg, 95.14 μmol) in acetonitrile (6.8 mL) and sodium phosphate buffer (0.67 M, pH 6.7, 4 mL/mmol) was stirred at 35 °C. Then, aqueous solutions of sodium chlorite (2 M in water, 307 mg, 2.72 mmol) and sodium hypochlorite (410 μL, 27.18 μmol) were added simultaneously over a period of 2 h (*caution: do not mix them before addition*). The mixture was stirred at 35 °C until the reaction was complete (5 h). Water (8 mL) was added, and the pH was adjusted to 8.0 with 2 N NaOH. The reaction was quenched by pouring into cold (0 °C) Na_2SO_3 (0.35 g in 5 mL of water) then stirred for 30 min at room temperature. Then, methyl *tert*-butyl ether (MTBE, 5 mL) was added, and the organic layer was separated and discarded. More MTBE (8 mL) was added, and the mixture was brought up to pH 3–4 with 2 N HCl. The combined organic layers were washed with water and brine and concentrated to give the crude acid. Flash chromatography (PE/*i*PrOH, 100:6; R_f = 0, 2) gave **18** (0.49 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94 (m, 1 H, CH=), 5.32 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1 H, CH_2=), 5.26 (s, 1 H, NCHO), 5.21 (ddd, *J* = 10.3, 1.5, 1.5 Hz, 1 H, CH_2=), 4.86 (dd, *J* = 6.6, 0.8 Hz, 1 H, CHO), 4.23 (dd, *J* = 6.6, 3.9 Hz, 1 H, CHN), 4.01–4.19 (m, 2 H, CH_2O_{allyl}), 3.86 (dd, *J* = 3.9, 0.8 Hz, 1 H, $CHOCH_2$), 2.98 (AB, *J* = 16.5 Hz, 2 H, CH_2), 1.49 (s, 9 H, O*t*Bu), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C=O), 152.8 (C=O), 133.8 (CH=), 118.2 (CH_2=), 100.7 (NCHO), 83.3 (CHO), 83.0 ($CHOCH_2$), 81.1 (O*t*Bu), 71.4 (CH_2O_{allyl}), 66.7 (CCl), 61.1 (CHN),41.2 (CH_2), 38.9 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 3567, 2964, 1728 (C=O), 1710 (C=O), 1367, 1121 cm^{-1}. MS (CI + Q1MS): *m*/*z* (%) = 404 (8) [M + 1], 346 (8) [M – *t*Bu], 304 (100), 268 (12), 227 (6), 88 (20). MS (CI/Q1MS): *m*/*z* = 402 [M – 1]. $[\alpha]_D^{23}$ = +0.70 (*c* = 0.89, $CHCl_3$). $C_{19}H_{30}ClNO_6$ (403.90): calcd. C 56.50, H 7.49, N 3.47; found C 56.32, H 7.60, N 3.80.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-allyloxy-7-benzyloxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0.]heptane-4-carboxylate (19):** Benzyl bromide (480 mg, 2.72 mmol, 2 equiv.), potassium carbonate (190 mg, 1.36 mmol, 1 equiv.) and sodium hydrogen carbonate (230 mg, 2.72 mmol, 2 equiv.) were added to a solution of carboxylic acid **18** in *N*,*N*-dimethylacetamide (DMA, 12 mL). The mixture was stirred for 5 h at room temperature and then quenched with water (1 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic phase were dried and concentrated. Flash chromatography (PE/ether, 5:1; R_f = 0.27) of the residue gave pure **19** (0.62 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.47 (m, 5 H, Ph), 5.99 (m, 1 H, CH=), 5.34 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1 H, CH_2=), 5.28 (s, 1 H, NCHO), 5.22 (ddd, *J* = 10.3, 1.5, 1.5 Hz, 1 H, CH_2=), 5.19 (s, 2 H, CH_2Ph), 4.82 (dd, *J* = 6.6, 0.8 Hz, 1 H, CHO), 4.24, (dd, *J* = 6.6, 3.9 Hz, 1 H, CHN), 4.21–4.02 (m, 2 H, CH_2O_{allyl}), 3.87 (dd, *J* = 3.9, 0.8 Hz, 1 H, $CHOCH_2$), 3.0 (AB, *J* = 15.7 Hz, 2 H, CH_2), 1.49 (s, 9 H, *t*BuO), O.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, APT): δ = 168.9 (C=O), 153.0 (C=O), 133.8 (CH=), 135.6 (C_{arom}), 128.6, 128.2, 128.0 (C_{arom}), 118.2 (H_2C=), 100.7 (NCHO), 83.6 (CHO), 83.2 ($CHOCH_2$), 80.9 (O*t*Bu), 71.3, (CH_{2allyl}), 67.2 (CH_2Ph), 66.7, (C-Cl), 61.1 (CHN), 41.7 (CH_2), 38.9, 28.3, 25.2 (*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 2967, 1741 (C=O), 1714 (C=O), 1361, 1117, 760 cm^{-1}. MS (EI + Q1MS LMR): *m*/*z* (%) = 436 (45) [M – *t*Bu], 380 (52), 358 (61), 336 (100), 127 (17). $C_{26}H_{36}ClNO_6$ (494.02): calcd. C 63.21, H 7.34, N 2.83; found C 63.40, H 7.32, N 2.78.

Benzyl 2-[(1*R*,2*S*,3*R*,4*S*)-3-(*tert*-Butyloxycarbonyl)amino-1-chloro-2-hydroxy-4-allyloxycyclobutyl]acetate (20): Trifluoroacetic acid (2.4 mL) was added dropwise at room temperature to a solution of **19** (620 mg, 1.25 mmol, 1 equiv.) in dichloromethane (3.2 mL). The mixture was stirred for 2 h. Evaporation of the solvent gave a crude residue that was used without further purification. It was treated with sodium hydrogen carbonate (412 mg, 4.91 mmol, 4 equiv.), di-*tert*-butyl dicarbonate (304 mg, 1.35 mmol, 1.1 equiv.) and methanol (3.5 mL) The mixture was heated at 40 °C for 4 h in an ultrasonic bath. The reaction mixture was filtered off, and the filtrate was concentrated. Flash chromatography (PE/*i*PrOH, 100:5; R_f = 0.33) yielded pure **20** (0.44 g, 84%). M.p. 96–98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.28 (m, 5 H, Ph), 5.86 (m, 1 H, HC=), 5.29 (ddd, *J* = 17.4, 1.5, 1.5 Hz, 1 H, H_2C=), 5.05 (d, *J* = 12.5 Hz, 2 H, CH_2Ph), 4.49 (ddd, *J* = 8.0, 7.3, 7.3 Hz, 1 H CHN), 4.43 (dd, *J* = 7.3, 2.4 Hz, 1 H, CHOH), 4.02 (m, 2 H, CH_2O_{allyl}), 3.82 (d, *J* = 7.3 Hz, 1 H, $CHOCH_2$), 3.61 (d, *J* = 2.4 Hz, 1 H, OH), 2.86 (AB, *J* = 15.3 Hz, 2 H, CH_2), 1.50 (s, 9 H, O*t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C=O), 155.9 (C=O), 136.6 (C_{arom}), 135.5 (CH=), 128.6, 128.2, 128.0 (CH_{arom}), 117.5 (CH_2=), 85.2 ($CHOCH_2$), 80.2 (O*t*Bu), 74.9 (CHOH), 71.3 (CH_2O_{allyl}), 69.7 (CH_2Ph), 53.7 (CHN), 42.9 (CH_2), 29.1 (O*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 3360, 2343, 1716 ($C{=}O_{ester}$), 1701 (C=O), 1165 cm^{-1}. MS (Cl + Q1MS LMR): *m*/*z* (%) = 426 (12) [M + 1], 370 (100), 326 (41), 262 (24), 91 (37). MS (ClQ1MS LMR): *m*/*z* = 424 (100) [M – 1]. $C_{21}H_{28}ClNO_6$ (425.90): calcd. C 59.50, H 6.18, Cl 8.36, N 3.30; found C 59.36, H 6.27, Cl 8.16, N 3.23.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-propyloxy-7-hydroxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (21):** Hydrogen was flushed at room temperature through a suspension of palladium on activated carbon (10%, 420 mg, 396 μmol) in a solution of **18** (1.6 g, 3.96 mmol) in ethyl acetate (32 mL). After 8 h, the hydrogenation was complete. The mixture was filtered through Celite, and the filtrate was evaporated to yield pure **21** (1.54 g, 95%). R_f = 0.37 (PE/*i*PrOH/AcOEt, 100:5:5). M.p 100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.6 (s, 1 H, OH), 5.26 (s, 1 H, NCHO), 4.86 (dd, *J* = 6.6, 0.8 Hz, 1 H, CHO), 4.20 (dd, *J* = 6.6, 3.8 Hz, 1 H, CHN), 3.80 (dd, *J* = 3.8, 0.8 Hz, 1 H, $CHOCH_2$), 3.54 (m, 2 H, CH_2O), 2.95 (AB, *J* = 16.3 Hz, 2 H, CH_2), 1.64 (m, 2 H, CH_2), 1.46 (s, 9 H, O*t*Bu), 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.89 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5 (C=O), 154.6 (C=O), 100.6 (NCHO), 83.5 (CHO), 80.9 (O*t*Bu), 77.4 ($CHOCH_2$), 72.3 (CH_2O), 67.0 (CCl), 60.9 (CHN), 41.6 (CH_2COOH), 38.9 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu), 22.9 (CH_2), 10.5 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3587, 2964, 1727 (C=O), 1711 (C=O), 1364, 1121 cm^{-1}. MS (CI CH_4/N_2O + Q1MS): *m*/*z* (%) =

406 (4) [M + 1], 306 (30), 288 (6), 154 (10), 89 (17), 59 (100). $[\alpha]_D^{23}$ = +0.67 (*c* = 0.55, $CHCl_3$). $C_{19}H_{32}ClNO_6$ (495.91): calcd. C 56.22, H 7.95, Cl 8.73, N 3.45; found C 55.98, H 8.08, Cl 8.24, N 3.39. X-ray diffraction analysis: Wavelength: 0.71069 Å; crystal system: orthorhombic; unit cell dimensions: *a* = 10.722 (2) Å; *α* = 90°; *b* = 10.088 (5) Å; *β* = 110°; *c* = 11.531 (3) Å; *γ* = 90°.

***tert*-Butyl (1*S*,3*R*,5*S*,6*S*,7*S*)-3-(*tert*-Butyl)-7-chloro-6-propyloxy-7-benzyloxycarbonylmethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate (22):** A mixture of benzyl bromide (1.07 g, 6.16 mmol, 2 equiv.), sodium hydrogen carbonate (520 mg, 6.16 mmol), potassium carbonate (430 mg, 3.08 mmol) and **21** (1.25 g, 3.08 mmol) in DMA (27 mL) was stirred at room temperature for 5 h. Water (15 mL) was then added, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried and concentrated. Flash chromatography (PE/ether, 6:1; R_f = 0.22) gave **22** (1.26 g, 83%). M.p 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.30–7.37 (m, 5 H, Ph), 5.22 (s, 1 H, NCHO), 5.16 (s, 2 H, CH_2Ph), 4.81 (dd, *J* = 6.6, 0.6 Hz, 1 H, CHO), 4.18 (dd, *J* = 6.6, 3.8 Hz, 1 H, CHN), 3.78 (dd, *J* = 3.8, 0.6 Hz, 1 H, $CHOCH_2$), 3.48 (m, 2 H, CH_2O), 2.96 (AB, *J* = 15.8 Hz, 2 H, CH_2COOBn), 1.64 (m, 2 H, CH_2), 1.46 (s, 9 H, O*t*Bu), 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.86 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 168.9 (C=O), 154.2 (C=O), 135.6 (C_{arom}), 128.6, 128.2, 128.0 (CH_{arom}), 100.6 (NCHO), 83.5 (CHO), 80.7 (O*t*Bu), 77.4 ($CHOCH_2$), 72.2 (CH_2Ph), 67.4 (CH_2O), 66.6 (CCl), 60.9 (CHN), 41.9 (CH_2COOH), 38.9 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu), 22.6 (CH_2), 10.5 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2960, 1721 (C=O), 1711 (C=O), 1364, 1121, 760 cm^{-1}. MS (CI CH_4/N_2O + Q1MS): *m*/*z* (%) = 496 (3) [M + 1], 396 (100). $[\alpha]_D^{23}$ = +0.57 (*c* = 0.32, $CHCl_3$). $C_{26}H_{38}ClNO_6$ (496.04): calcd. C 62.96, H 7.72, Cl 7.15, N 2.82; found C 63.13, H 7.30, Cl 6.68, N 2.73.

Benzyl [(1*R*,2*S*,3*R*,4*S*)-3-(Benzylcarbonyl)amino-1-chloro-2-hydroxy-4-propyloxycyclobutyl]acetate (24a): Trifluoroacetic acid (5.8 mL) was added dropwise at room temperature to a solution of **22** (1.25 g, 2.52 mmol) in dichloromethane (6 mL), The resulting solution was stirred for 70 min at room temperature and then water (9 μL) was added. After stirring for an additional 50 min, the solvent was removed under reduced pressure. Crude TFA salt **23** was used without further purification. A solution of **23** (300 mg, 679 μmol) in dichloromethane (2.6 mL) and a solution of sodium carbonate (110 mg, 1.02 mmol) in water (1.3 mL) were treated under vigorous stirring with phenylacetyl chloride (120 mg, 747 μmol). After 30 min at room temperature, the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$ and concentrated. Flash chromatography (PE/*i*PrOH, 100:5; R_f = 0.15) gave pure **24a** (0.23 g). Yield: 75% for two steps. ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C): *δ* = 7.26–7.40 (m, 10 H, 2Ph), 6.13 (d, *J* = 8.5 Hz, 1 H NH), 5.16 (s, 2 H, OCH_2Ph), 4.66 (ddd, *J* = 8.5, 7.7, 7.2 Hz, 1 H, CHN), 4.37 (ddd, *J* = 8.1, 7.2, 0.9 Hz, 1 H, CHOH), 3.75 (d, *J* = 8.1 Hz, 1 H, OH), 3.74 (dd, *J* = 7.7, 0.9 Hz, 1 H, $CHOCH_2$), 3.65 (s, 2 H, CH_2Ph), 3.36 (t, *J* = 6.7 Hz, 2 H, CH_2O), 2.98–3.06 (AB, *J* = 15 Hz, 2 H, CH_2CO_2Bn), 1.56 (m, 2 H, CH2), 0.89 (t, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): *δ* = 170.7 ($C{=}O_{amide}$), 170.6 (C=O), 134.9, 134.4 (C_{arom}), 129.3, 128.8, 128.4, 128.1, 127.2 (CH_{arom}), 84.0 ($CHOCH_2$), 73.3 (CHOH), 71.3 (CH_2O_{propyl}), 68.2 (CCl), 67.2 (OCH_2Ph), 50.5 (CHN), 43.6 (CH_2Ph), 42.0 (CH_2COOBn), 22.7 (CH_2), 10.3 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3380, 2927, 1718 (C=O), 1654 (C=O), 765 cm^{-1}. MS (D-APCI + C1MS): *m*/*z* (%) = 446 (100) [M + 1], 338 (28) [M – $PhCH_2CONH$], 282 (17). $[\alpha]_D^{23}$ = –0.33 (*c* = 0.45, $CHCl_3$). $C_{24}H_{28}ClNO_5$ (445.94): calcd. C 64.64, H 6.33, N 3.14; found C 64.67, H 6.40, N 3.08.

Benzyl [(1*R*,2*S*,3*R*,4*S*)-3-(Acetyl)amino-1-chloro-2-hydroxy-4-propyloxycyclobutyl]acetate (24b): Same procedure as for **24a**. Reaction performed on 0.5 mmol scale, 82% yield. R_f = 0.25 (PE/ether/*i*PrOH, 10:10:1). M.p 68–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.26–7.38 (m, 5 H, Ph), 6.47 (d, *J* = 8.5 Hz, 1 H NH), 5.48 (dd, *J* = 7.2, 1.0 Hz, 1 H, $CHOCH_2$), 5.14 (s, 2 H, OCH_2Ph), 4.81 (ddd, *J* = 8.5, 8.1, 7.2 Hz, 1 H, CHN), 4.21 (dd, *J* = 8.1, 1.0 Hz, 1 H, CHOH), 3.46 (m, 2 H, CH_2O), 2.95–3.07 (AB, *J* = 15.8 Hz, 2 H, CH_2CO_2Bn), 1.99 (s, 3 H CH_3CO), 1.46 (m, 2 H, CH_2), 0.90 (t, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 170.6 ($C{=}O_{amide}$), 168.1 (C=O), 134.4 (C_{arom}), 128.8, 128.4, 128.1 (CH_{arom}), 82.0 ($CHOCH_2$), 73.4 (CHOH), 72.3 (CH_2O_{propyl}), 68.0 (CCl), 67.2 (OCH_2Ph), 51.3 (CHN), 41.8 (CH_2COOBn), 22.7 (CH_2), 20.2 (CH_3CO), 10.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3434, 3299, 2954, 1733 (C=O), 1654 (C=O). MS (D-APCI + C1MS): *m*/*z* (%) = 370 (100) [M + 1]. $[\alpha]_D^{23}$ = –0.23 (*c* = 0.33, $CHCl_3$). $C_{18}H_{24}ClNO_5$ (369.84): calcd. C 58.46, H 6.54, N 3.78; found C 58.89, H 6.91, N 3.53.

Benzyl 1-[(1*R*,2*S*,3*R*,4*S*)-3-(*p*-Methoxybenzylcarbonyl)amino-1-chloro-2-hydroxy-4-propyloxycyclobutyl]acetate (24c): Same procedure as for **24a**. Yield: 80%. R_f = 0.15 (PE/*i*PrOH, 100:5), ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C): *δ* = 7.32–7.40 (m, 5 H, Ph), 7.17 (d, *J* = 8.6 Hz, 2 H, CH_{arom}), 6.88 (d, *J* = 8.6 Hz, 2 H, CH_{arom}), 6.13 (d, *J* = 8.5 Hz, 1 H NH), 5.15 (s, 2 H, CH_2Ph), 4.66 (ddd, *J* = 8.5, 7.7, 7.2 Hz, 1 H, CHN), 4.37 (dd, *J* = 7.2, 0.8 Hz, 1 H, CHOH), 3.80 (s 3 H, OMe), 3.75 (dd, *J* = 7.7, 0.8 Hz, 1 H, $CHOCH_2$), 3.53 (s, 2 H, CH_2PhOMe), 3.36 (t, *J* = 6.7 Hz, 2 H CH_2O), 2.98–3.06 (AB, *J* = 15 Hz, 2 H, CH_2CO_2Bn), 1.56 (m, 2 H, CH_2), 0.89 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): *δ* = 171.0 (C=O), 170.6 (C=O), 158.7, 134.9, 130.4 (C_{arom}), 128.5, 128.4, 128.1, 126.5, 114.3 (CH_{arom}), 84.0 ($CHOCH_2$), 73.3 (CHOH), 71.3 (CH_2O_{propyl}), 68.2 (CCl), 67.2 (CH_2Ph), 55.14 (OMe), 50.5 (CHN), 42.7 (CH_2PhOMe), 42.0 (CH_2COOBn), 22.7 (CH_2), 10.3 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3410, 2963, 1734 (C=O), 1653 (C=O), 1513 cm^{-1}. $[\alpha]_D^{23}$ = –0.23 (*c* = 0.38, $CHCl_3$). MS (FAB + Q1MS): *m*/*z* = 476 [M + 1]. MS (FAB/Q1MS): *m*/*z* = 474 [M – 1].

Benzyl 2-[(1*R*,2*S*,3*R*,4*S*)-1-Chloro-2-hydroxy-4-propoxy-3-(tetradecanoylamino)cyclobutyl]acetate (24d): Same procedure as for **24a**. Reaction performed on 0.5 mmol scale. Yield: 82%. M.p 57–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.26–7.38 (m, 5 H, Ph), 6.10 (d, *J* = 8.6 Hz, 1 H NH), 5.20 (s, 2 H, OCH_2Ph), 4.70 (ddd, *J* = 8.6, 8.14, 7.3 Hz, 1 H, CHN), 4.42 (dd, *J* = 8.1, 1.0 Hz, 1 H, $CHOCH_2$), 3.86 (m, 2 H, CHOH), 3.41 (t, *J* = 6.7 Hz, 2 H, CH_2O), 3.0–3.16 (AB, *J* = 15.0 Hz, 2 H, CH_2CO_2Bn), 2.2 (t, *J* = 7.66 Hz, 2 H, CH_2CON), 1.60 (m, 4 H, $2CH_2$), 1.25 (m, 20 H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 170.9 ($C{=}O_{amide}$), 168.3 (C=O), 134.2 (C_{arom}), 128.9, 128.4, 128.0 (CH_{arom}), 82.2 ($CHOCH_2$), 73.2 (CHOH), 72.1 (CH_2O_{propyl}), 68.1 (CCl), 67.2 (OCH_2Ph), 51.2 (CHN), 41.9 (CH_2COO), 36.5 (CH_2CON), 32.1, 29.8, 29.7, 29.6, 29.5, 25.8, 22.9, 22.8, 22.7 (CH_2), 14.3, 10.4, (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3368, 2918, 1731 (C=O), 1651 (C=O), 1541, 1189 cm^{-1}. MS (APCI + Cfull MS): *m*/*z* (%) = 538 (100) [M + 1], 430 (3). $[\alpha]_D^{23}$ = –0.27 (*c* = 0.24, $CHCl_3$). $C_{30}H_{48}ClO_5$ (524.15): calcd. C 66.95, H 8.99, N 2.60; found C 67.09, H 9.03, N 2.19. HRMS (ESI) calcd. for $C_{30}H_{48}ClNO_5$ 538.3299; found 538.3311.

Benzyl [(1*R*,2*S*,3*R*,4*S*)-1-Chloro-2-hydroxy-4-propoxy-3-{[2-(2-thienyl)acetyl]amino}cyclobutyl]acetate (24e): Same procedure as for **24a**. Reaction performed on 0.5 mmol scale. Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.29–7.38 (m, 5 H, Ph), 6.96–7.24 (m, 3 H, H_{pylan}), 6.31 (d, *J* = 9.1 Hz, 1 H, NH), 5.17 (s, 2 H, OCH_2Ph), 4.68

(m, 1 H, CHN), 4.39 (dd, J = 7.19, 0.9 Hz, 1 H, CHO), 3.81 (s, 2 H, CH_2CON), 3.76 (dd, J = 8.14, 0.9 Hz, 1 H, CHOH), 3.38 (t, J = 6.7 Hz, 2 H, CH_2O), 2.96–3.11 (AB, J = 15.3 Hz, 2 H, CH_2CO_2Bn), 1.58 (m, 2 H, CH_2), 0.90 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 ($C{=}O_{amide}$), 169.2 (C=O), 135.7, 134.4 (C_{arom}), 128.6, 128.2, 127.4, 126.8, 125.5 (CH_{arom}), 84.2 ($CHOCH_2$), 73.3 (CHOH), 71.4 (CH_2O_{propyl}), 68.2 (CCl), 67.4 (OCH_2Ph), 50.5 (CHN), 42.2 (CH_2COOBn), 37.6 (CH_2CON), 22.9 (CH_2), 10.5, (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3298, 2958, 1731 (C=O), 1654 (C=O). MS (D-APCI + C1MS): m/z (%) = 452 (60) [M + 1]. $C_{22}H_{26}ClNO_5S$ (451.96): calcd. C 58.46, H 5.79, N 3.09; found C 48.14, H 5.09, N 2.80.

[(1*R*,2*S*,3*R*,4*S*)-1-Chloro-2-hydroxy-4-propoxy-3-(benzylcarbonyl)-aminocyclobutyl]acetic Acid (25a): Hydrogen was flushed at room temperature through a suspension of palladium on activated carbon (10% Pd, 45.3 mg, 42.6 μmol) in a solution of **24a** (190 mg, 0.43 mmol) in ethyl acetate (2.5 mL). The reaction was complete after 8 h. Filtration through Celite followed by evaporation of the solvent gave **25a** (0.15 g, 96%). M.p 55–57 °C. ^1H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 7.25–7.35 (m, 5 H, Ph), 6.24 (d, J = 8.6 Hz, 1 H NH), 4.62 (ddd, J = 8.6, 8.2, 7.0 Hz, 1 H, CHN), 4.39 (dd, J = 7.0, 0.9 Hz, 1 H, CHOH), 3.80 (dd, J = 8.2, 0.9 Hz, 1 H, $CHOCH_2$), 3.61 (s, 2 H, CH_2Ph), 3.37 (m, 2 H, CH_2O), 2.99–3.07 (AB, J = 15 Hz, 2 H, CH_2CO_2H), 1.56 (m, 2 H, CH_2), 0.89 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 173.6 (C=O), 170.7 ($C{=}O_{amide}$), 134.4 (C_{arom}), 129.3, 128.8, 127.4 (CH_{arom}), 83.6 ($CHOCH_2$), 73.3 (CHOH), 71.4 (CH_2O_{propyl}), 67.9 (CCl), 51.0 (CHN), 43.5 (CH_2Ph), 41.6 (CH_2COOH), 22.7 (CH_2), 10.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3335, 2965, 1717 (C=O), 1653 (C=O). MS (D-APCI + C1MS): m/z (%) = 356 (100) [M + 1], 282 (51). MS (D-APCI/C1MS): m/z (%) = 354 (100) [M – 1]. $[\alpha]_D^{23}$ = –0.28 (c = 0.26, $CHCl_3$). $C_{17}H_{22}ClNO_5$ (355.81): calcd. C 57.39, H 6.23, N 3.94; found C 56.76, H 6.65, N 3.67.

[(1*R*,2*S*,3*R*,4*S*)-3-(Acetyl)amino-1-chloro-2-hydroxy-4-propyloxycyclobutyl]acetic Acid (25b): Same procedure as for **25a**. Reaction performed on 0.2 mmol scale. Yield: 95%. M.p 52–53 °C. ^1H NMR (300 MHz, CD_3OD): δ = 4.46 (dd, J = 8.6, 6.6 Hz, 1 H, CHN), 4.24 (dd, J = 6.6, 1.0 Hz, 1 H, CHOH), 3.91 (dd, J = 8.6, 1.0 Hz, 1 H, $CHOCH_2$), 3.45 (m, 2 H, CH_2O), 2.79–3.03 (AB, J = 15.8 Hz, 2 H, CH_2CO_2H), 1.96 (s, 3 H, CH_3CO), 1.54 (m, 2 H, CH_2), 0.89 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 173.2 (C=O), 172.6 ($C{=}O_{amide}$), 84.0 (CHO), 74.1 (CHOH), 72.9 (CH_2O_{propyl}), 70.7 (CCl), 53.2 (CHN), 42.2 (CH_2COOH), 24.1 (CH_2), 22.6 (CH_3CO), 11 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3420, 2967, 1721 (C=O), 1654 (C=O). MS (D-APCI + C1MS): m/z (%) = 280 (100) [M + 1], 262 (24). $[\alpha]_D^{23}$ = –0.20 (c = 0.42, $CHCl_3$). $C_{11}H_{18}ClNO_5$ (279.92): calcd. C 47.23, H 6.49, Cl 12.67, N 5.0; found C 47.56, H 6.91, Cl 10.93, N 4.46.

[(1*R*,2*S*,3*R*,4*S*)-1-Chloro-2-hydroxy-4-propoxy-3-(*p*-methoxybenzylcarbonyl)aminocyclobutyl]acetic Acid (25c): Same procedure as for **25a**. Reaction performed on 0.2 mmol scale. Yield: 92%. M.p 147–149 °C. ^1H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 7.25–7.35 (m, 5 H, Ph), 6.24 (d, J = 8.6 Hz, 1 H NH), 4.62 (ddd, J = 8.6, 8.2, 7.0 Hz, 1 H, CHN), 4.39 (dd, J = 7.0, 0.9 Hz, 1 H, CHOH), 3.80 (dd, J = 8.2, 0.9 Hz, 1 H, $CHOCH_2$), 3.61 (s, 2 H, CH_2Ph), 3.37 (m, 2 H, CH_2O), 2.99–3.07 (AB, J = 15 Hz, 2 H, CH_2CO_2H), 1.56 (m, 2 H, CH_2), 0.89 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 173.6 (C=O), 170.7 ($C{=}O_{amide}$), 134.4 (C_{arom}), 129.3, 128.8, 127.4 (CH_{arom}), 83.6 ($CHOCH_2$), 73.3 (CHOH), 71.4 (CH_2O_{propyl}), 67.9 (CCl), 51.0 (CHN), 43.5 (CH_2Ph), 41.6 (CH_2COOH), 22.7 (CH_2), 10.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3308, 2965, 1717 (C=O), 1653 (C=O), 860 cm^{-1}. MS (APCI + C1MS): m/z (%) = 386 (34) [M + 1], 368 (6) [M + 1 – H_2O]. $[\alpha]_D^{23}$ = –0.28 (c = 0.2, $CHCl_3$). $C_{18}H_{24}ClNO_6$ (385.84): calcd. C 56.03, H 6.27, N 3.63; found C 54.75, H 6.04, N 3.25.

[(1*R*,2*S*,3*R*,4*S*)-1-Chloro-2-hydroxy-4-propoxy-3-(tetradecanoylamino)cyclobutyl]acetic Acid (25d): Same procedure as for **25a**. Reaction performed on 0.2 mmol scale. Yield: 95%. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.34 (d, J = 8.6 Hz, 1 H, NH), 4.63 (ddd, J = 8.6, 8.14, 6.7 Hz, 1 H, CHN), 4.45 (dd, J = 6.7, 0.9 Hz, 1 H, $CHOCH_2$), 3.93 (d, J = 8.14 Hz, 1 H, CHOH), 3.43 (m, 2 H, CH_2O), 2.95–3.18 (AB, J = 15.3 Hz, 2 H, CH_2CO_2), 2.24 (t, J = 7.6 Hz, 2 H, CH_2CON), 1.61 (m, 4 H, $2CH_2$), 1.25 (m, 20 H, 10 CH_2), 0.92 (t, J = 7.2 Hz, 3 H, CH_3), 0.88 (t, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 ($C{=}O_{amide}$), 173.7 (C=O), 83.7 ($CHOCH_2$), 73.4 (CHOH), 71.6 (CH_2O_{propyl}), 68.2 (CCl), 51.0 (CHN), 42.1 (CH_2COO), 36.7 (CH_2CON), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 25.8, 22.9, 22.8, 22.7 (CH_2), 14.2, 10.5 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3364, 2924, 1718 (C=O), 1653 (C=O). MS (D-APCI + C1MS): m/z (%) = 448(100) [M + 1], 430 (26) [M + 1 – H_2O], 220 (4). $[\alpha]_D^{23}$ = +0.19 (c = 0.37, $CHCl_3$). HRMS (ESI) calcd. for $C_{23}H_{42}ClNO_5$ 448.2830; found 448.2818.

Benzyl [(1*S*,3*S*,4*S*)-3-(Benzylcarbonyl)amino-1-chloro-2-oxo-4-propyloxycyclobutyl]acetate (26a): A 0.5 M aqueous solution of sodium hypochlorite (130 μL, 64 μmol) and sodium hydrogen carbonate (15 mg; 175 μmol) was added dropwise at 0 °C with vigorous stirring to a solution of **24a** (26 mg, 58.3 μmol), TEMPO (0.5 mg, 2.9 μmol) and potassium bromide (7.6 mg, 64 μmol) in toluene/ethyl acetate (1:1, 500 μL) and water (42 μL). The reaction mixture was stirred for 15 min at 0 °C. The aqueous layer was separated and washed with toluene (10 mL). The combined organic layers were washed with a solution of KI (0.25 g) dissolved in 10% aqueous $KHSO_4$ (1 mL). The organic layer was washed successively with 10% aqueous sodium thiosulfate (1 mL, pH 7 phosphate buffer 0.2 M, 2 mL) and brine, dried with $MgSO_4$ and evaporated to give **26a** (22 mg, 85%). ^1H NMR (500 MHz, $CDCl_3$, 47 °C): δ = 7.22–7.44 (m, 10 H, 2Ph), 6.19 (br., 1 H NH), 5.09–5.14 (AB, J = 13 Hz, 2 H, OCH_2Ph), 4.88 (dd, J = 8.1, 6.4 Hz, 1 H, CHN), 4.54 (d, J = 6.4 Hz, 1 H, CHO), 3.61 (s, 2 H, CH_2Ph), 3.56 (ddd, J = 8.8, 7.1, 7.1 Hz, 1 H, CH_2O_{propyl}), 3.41 (ddd, J = 8.8, 6.4, 6.4 Hz, 1 H, CH_2O_{propyl}), 3.18–3.38 (AB, J = 15 Hz, 2 H, CH_2CO_2Bn), 1.56 (m, 2 H, CH_2), 0.89 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C): δ = 198.3 (C=O), 170.8 ($C{=}O_{amide}$), 168.9 (C=O), 135.0, 133.7 (C_{arom}), 129.3, 129.0, 128.8, 128.4, 128.1, 127.5 (CH_{arom}), 78.2 (CHO), 72.8 (CH_2O_{propyl}), 72.1 (CCl), 69.2 (CHN), 67.0 (OCH_2Ph), 42.7 (CH_2Ph), 41.8 (CH_2COOBn), 22.8 (CH_2), 10.4 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 2964, 1804 (C=O), 1734 (C=O), 1654 (C=O), 770 cm^{-1}. MS (APCI + C1MS): m/z (%) = 444 (58) [M + 1], 408 (100), 336 (12) [M – $PhCH_2CONH$], 290 (71).

Benzyl [(1*S*,3*S*,4*S*)-3-(Acetyl)amino-1-chloro-2-oxo-4-propyloxycyclobutyl]acetate (26b): Same procedure as for **26a**. Reaction performed on 0.12 mmol scale. Yield: 85%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.41 (m, 5 H, Ph), 6.3 (br., 1 H, NH), 5.10–5.19 (AB, J = 12.2 Hz, 2 H, OCH_2Ph), 4.95 (d, J = 5.7 Hz, 1 H, CHN), 4.56 (d, J = 5.7 Hz, 1 H, $CHOCH_2$), 3.48 (m, 2 H, CH_2O), 3.18–3.43 (AB, J = 16.7 Hz, 2 H, CH_2CO_2Bn), 2.03 (s, 3 H CH_3CO), 1.59 (m, 2 H, CH_2), 0.92 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8 (C=O), 170.0 ($C{=}O_{amide}$), 169.0 (C=O), 134.9 (C_{arom}), 128.6, 128.3, 128.0 (CH_{arom}), 78.3 (CHO), 72.8 (OCH_2Ph), 71.9 (CH_2O_{propyl}), 69.1 (CHN), 67.2 (CCl), 41.9 (CH_2COOBn), 22.9 (CH_2), 22.5 (CH_3CO), 10.6, (CH_3) ppm. IR (film): $\tilde{\nu}$ = 2967, 1802 (C=O), 1729 (C=O), 1657 (C=O). MS (APCI + C1MS): m/z (%) = 368 (7) [M + 1], 332 (50), 326 (100) [M – iPr], 308 (45), 290 (55), 260 (65), 234 (46).

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