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Diastereoselective Additions to (3*S*)-3-Aminodehydrocaprolactams: Development of a Versatile Synthesis of New Substituted Cyclic L-Lysines

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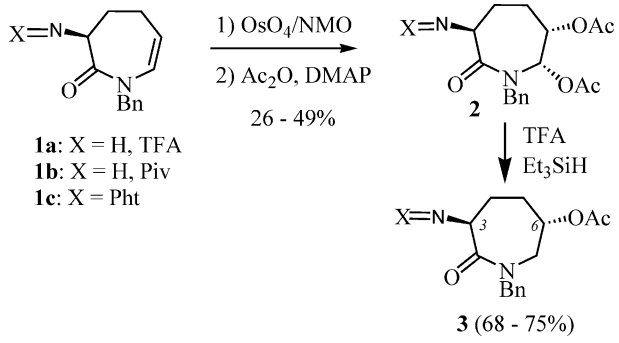
Easily obtained cyclic 6,7-dehydro-L-lysine was employed as starting template to generate variously substituted enantiopure 3-aminocaprolactams. *syn*-Dihydroxylation, hydroxymethoxylation, halomethoxylation and subsequent eliminations were performed with this starting enelactam, thus leading, in regio- and stereoselective manners, to new mono-, di- and trisubstituted 3-aminocaprolactams. Structural and mechanistic aspects of these reactions, as well as the origin of the high diastereoselectivities observed in this study are discussed.

Introduction

3-Aminocaprolactam, also called cyclic lysine, is a structural feature of some naturally occurring compounds.[1] It is also frequently involved in the structure of drug candidates[2] and used as scaffold for peptidomimetic-based inhibitors.[3] The utility of substituted ε-caprolactams has entailed the development of a variety of methodologies aiming at the synthesis of new analogues. Ring expansion by Beckmann rearrangement is a powerful method for the industrial production of ε-caprolactam (monomer of nylon-6 and plastics)[4] as well as for the synthesis of more sophisticated caprolactams.[5] Lactamization was the method of choice for a long time. Recently, Lindström and Somfai[6] developed a new stereoselective access to polysubstituted ε-caprolactams via an aza-Ireland–Claisen rearrangement starting from *N*-acyl-2-vinylaziridines. Ring-closing olefin metathesis (RCM), which provides practical access to various substituted monounsaturated caprolactams, is now the most popular method for the construction of highly functionalized caprolactams.[7] In most of these methods, the caprolactam substituents are introduced prior to the ring-forming key step. We recently reported on a new synthesis of enantiopure protected 3-amino-6-hydroxycaprolactams **3** which relies on a highly diastereoselective *syn*-dihydroxylation of (3*S*)-3-amino-6,7-dehydrocaprolactams **1** (Scheme 1).[8]



1a: X = H, TFA
1b: X = H, Piv
1c: X = Pht

Scheme 1. *syn*-Dihydroxylation of enelactams **1**.

This unexpected high diastereoselectivity prompted us to examine the reactivity of enelactams **1** towards various electrophilic reagents, aiming at the synthesis of useful new 3-aminocaprolactam-based scaffolds bearing substituents at positions C-6, C-7 and/or C-5.

Results and Discussion

We started by re-examining the oxidative addition to enelactam **1a**. Indeed, diacetates **2** obtained through a *syn*-dihydroxylation/diacetylation sequence were isolated in moderate to low yields, mainly because of the laborious workup of the corresponding diols. The best results were obtained with 3-phthalimido-dehydrocaprolactam **1c**, which was derived from **1a** through a two-step *trans*-protection. The latter led to the corresponding diacetate **2a** with a yield of only 26%. In order to improve the oxidation yield of the easily available substrate **1a**, we investigated oxidations in non-aqueous media. We first examined a two-step electrophilic addition by using a methanolic solution of *m*-CPBA

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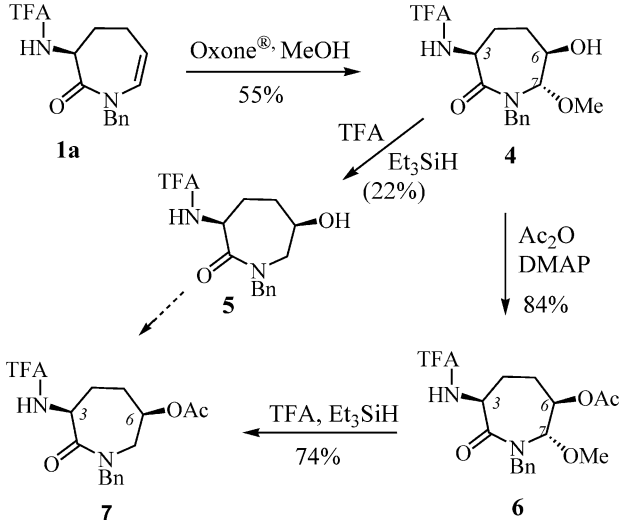
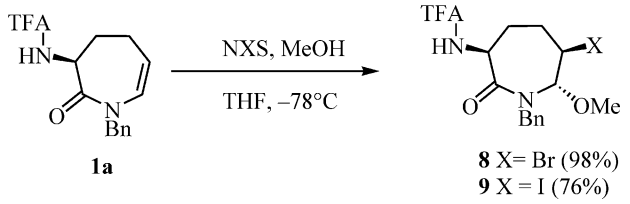
and sodium hydrogen carbonate as described in the literature with some enecarbamates and enamides.[9] Under these conditions, our enelactam **1a** was unreactive. Next, we employed Oxone® (potassium monopersulfate) in methanol,[10] and obtained the desired 6-hydroxy-7-methoxycaprolactam **4** in 55% isolated yield as a single diastereomer (Scheme 2). Careful examination of the NMR spectroscopic data of **4** (vide infra) suggested an *anti* addition with the 6-hydroxy substituent being *syn* to the 3-trifluoroacetamido group. A chemical correlation was required to secure this unexpected facial selectivity. To this end, adduct **4** was submitted to N,O-acetal reduction, leading to alcohol **5** in poor yield. Acetate **7** was finally obtained in higher overall yield when the acetylation step was performed before N,O-acetal reduction (Scheme 2). The resulting monoacetate caprolactam **7** exhibited a different specific rotation value and different sets of signals, both in ^{1}H and ^{13}C-NMR in comparison with those of compound **3a**. Thus, unlike osmium tetraoxide, monopersulfate oxidant seems to approach the enelactam moiety selectively *syn* to the pre-existent C-3 substituent, leading to a transient epoxide (or *N*-acyliminium) which undergoes an *anti* addition of methanol.



Scheme 2. Hydroxymethoxylation of enelactam **1a**.

Despite the different mechanistic aspects of these two oxidation modes (one step for OsO_4 and two steps for Oxone®/MeOH), we expected the same relative configuration, at least at the C-6 position. To further explore the stereochemical outcome of stepwise electrophilic additions with enelactam **1a**, we examined its reaction with NBS/MeOH and NIS/MeOH combinations[11] in THF at –78 °C. Both combinations afforded the corresponding 6-halo-7-methoxy lactams **8** and **9** in good yields as single diastereomers (Scheme 3).

The relative stereochemistry assignment of these adducts is mainly based on NMR spectroscopic data. Considering the partial double bond character of the amide C–N bond, and according to literature,[12] we assumed, for all these saturated caprolactams **2**–**9**, a chair-like conformation having the lactam C–N bond at the "flat" end. Both 3-H couplings



Scheme 3. Halomethoxylation of enelactam **1a**.

and the significant NOESY correlation with a C-5 proton observed in lactams **2**–**9** indicate that these compounds preferably adopt a chair-like conformation as drawn in Figure 1. Based on this conclusion, assignment of the relative configurations of 3,6,7-trisubstituted caprolactams **4**, **6**, **8** and **9** was possible by careful inspection of the relevant proton couplings (3-H, 5-Hax, 6-H and 7-H). Protons at the C-6 and C-7 positions exhibited small coupling constants, in agreement with their equatorial orientations. An additional argument in favour of an axial position for the C-7 methoxy group was a significant deshielding of C-5 after reduction of the N,O-acetal moiety, i.e. in compounds **5**, **7** and **14** (vide infra); the C-5 shielding observed in the corresponding methoxylated compounds **4**, **6**, **8**, and **9** was consistent with a γ-*gauche* effect of the C-7 methoxy substituent, thus proving its axial orientation (see Newman projection in Figure 1). Further inspection of ^{13}C-NMR spectra of diacetates **2** and their corresponding monoacetates **3** revealed the same γ-*gauche* effect.[8]

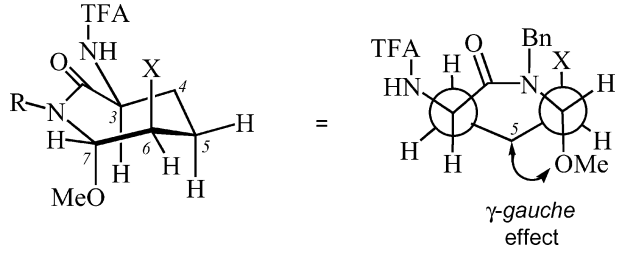
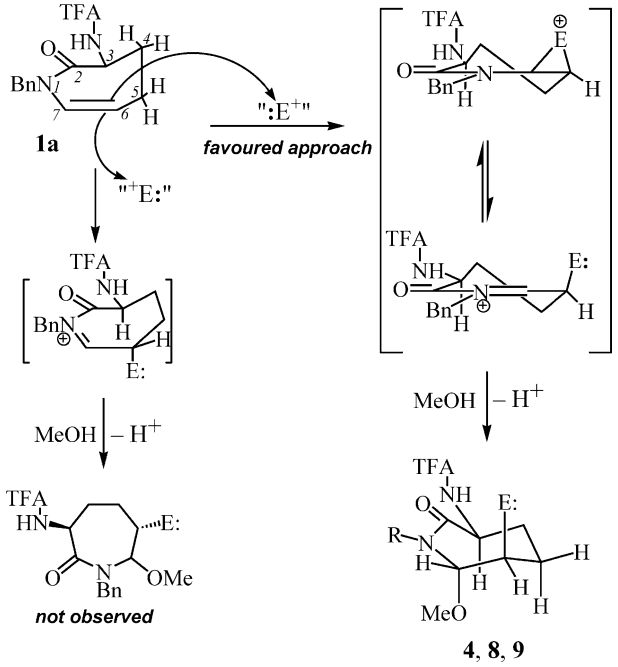


Figure 1. Conformation of lactams **4**, **6**, **8** and **9**.

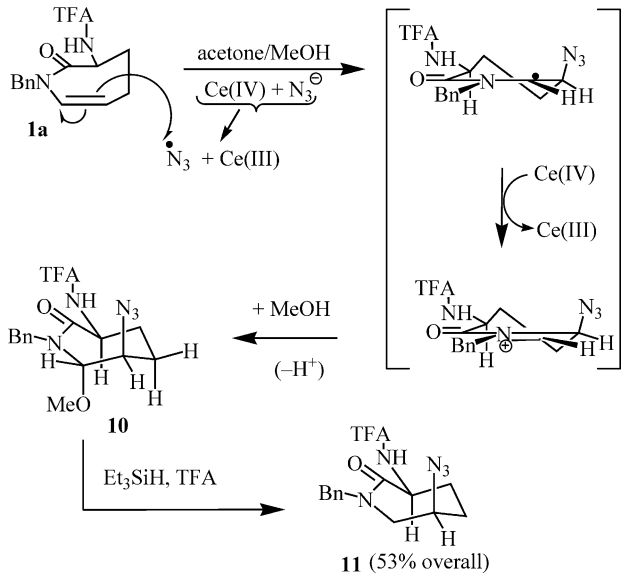
The high diastereselectivities observed in electrophilic addition sequences described above may be explained by the proposed mechanism shown in Scheme 4. We consider a two-step mechanism, where the electrophilic species adds to the enelactam carbon–carbon double bond leading to an iminium via (or to) a three-membered ring intermediate (an epoxide with persulfate or a halonium ring in the case of NXS), followed by addition of (or nucleophilic substitution by) methanol. Thus, the facial selectivity of the first step is critical for the configuration of C-6 and that of the second step for the C-7 configuration. We consider that, depending on the conjugation level in enelactam **1a**, atoms C-3, C-2, N-1, C-7, C-6 and C-5 are more or less coplanar, and one may therefore assume an envelope-like (or twisted boat-like) conformation for the enelactam ring, where the 3-trifluoroacetamido (NHTFA) substituent would act as a conformational lock. Examination of such a conformation shows that the β face (*syn* to NHTFA group) is slightly hindered by the C-4 pseudoaxial proton. As a consequence, we pre-

viously proposed that the favoured approach of OsO_4 would take place at the less hindered face, i.e. the α face.[8] Here we consider that, despite this facial difference, the electrophilic species approach on the β-face is probably favoured since it proceeds via a half chair-like transition state, while on the α face it would proceed via a boat-like transition state (Scheme 4). Then, for both steric and stereoelectronic effects, methanol adds exclusively *anti* to the C-6 substituent.[13]



Scheme 4. Rationale for the observed diastereoselectivities.

Our next goal was to introduce an aza-substituent at the C-6 position, which we first intended to obtain by hydroboration-amination of enelactam **1a**, following a procedure reported by Brown.[14] Unfortunately, treatment of substrates **1** with various hydroboranes, either failed or gave the amide reduction when excess hydroborane was used.[8] We next, examined a two-step methodology which relied on a β-azido-α-methoxylation and subsequent N,O-acetal reduction. This azidomethoxylation was originally described by Chavan et al.[15] in the case of enol ethers, moreover, we and others have already successfully extended this addition to endocyclic enecarbamates.[16] Thus, the slow addition of a solution of cerium ammonium nitrate (CAN) to a mixture of sodium azide and substrate **1a** in a mixture of methanol and acetone maintained at –90 °C, allows the regioselective obtention of the desired 6-azido-7-methoxy derivative **10** (Scheme 5), which undergoes substantial decomposition during purification by column chromatography. Similar decomposition was observed when the reaction temperature was raised during the dropwise addition of CAN solution. We therefore decided to submit the crude adduct to a chemoselective reduction of the N,O-acetal moiety by treating the crude 6-azido-7-methoxy derivative **10** with triethylsilane in trifluoroacetic acid (TFA), thus producing compound **11**, which was easily purified by silica gel column chromatography, in 53% overall yield. According to its NMR spectroscopic data, compound **11** was found to have a *cis* relative stereochemistry as shown in Scheme 5. We believe that the unstable azidomethoxy derivative **10** also resulted from an *anti*-addition, as explained in Scheme 5, according to a general mechanism proposed by Fujimoto et al.[17] Despite some mechanistic differences, we assume that the stereochemical outcome of this azidomethoxylation follows the same rules as suggested above for hydroxy- and halo-methoxylation reactions (Scheme 4).



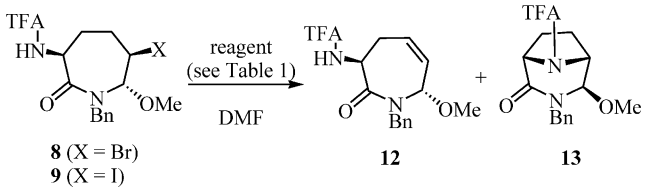
Scheme 5. Azidomethoxylation of enelactam **1a**.

Next, in order to vary the C-6 substituent nature, 6-halo-7-methoxylactams **8** and **9** were allowed to react with various acetate and cyanide salts as nucleophiles. Despite the favourable axial orientation of their halide substituent, these substrates never led to the desired substitution compounds. At room temperature **8** and **9** were unreactive in presence of acetate salts (Table 1, entry 1). However, at 60 °C both substrates led to the competitive elimination compound **12**, along with variable amounts of the bridged bicyclic compound **13** (Scheme 6, Table 1, entries 2–5). The latter was found to be a mixture of rotamers [70:30 based on ^{1}H NMR]. On the other hand, when reacted with nBu$_4$NCN at 60 °C in DMF, 6-bromolactam **8** led to a 1:1 mixture of **12** and **13**, with no traces of the desired 6-cyanolactam (entry 6). Substrate **9** was found to react smoothly at room temperature with nBu$_4$NCN, leading to **12** and **13** in 35% and 60% yields respectively (entry 7). Use of DBU instead of acetate or cyanide salts resulted in the same mixture, with the elimination compound **12** predominating (entries 8, 9).[18]

These results clearly indicate that in the case of substrates **8** and **9**, acetate and cyanide salts act only as bases by abstracting selectively the axial C-5 proton, as expected from the relative stereochemistry of these substrates (Figure 1). We initially believed that the axially oriented C-7 methoxy group may impede the nucleophile's approach along the C(6)–O bond axis, and hence inhibit the desired intermo-

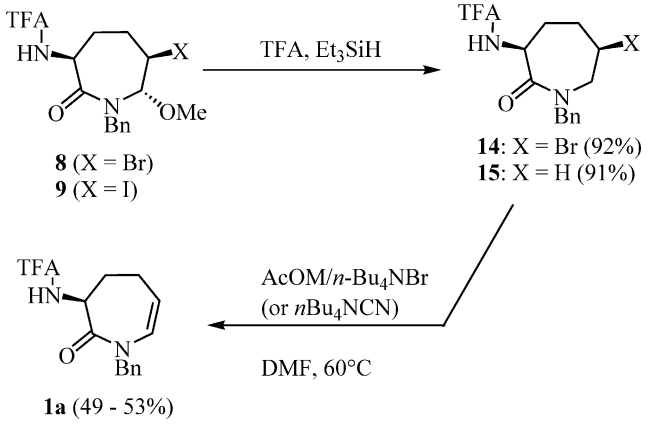
Table 1. Reactivity of **8** and **9** with acetate, cyanide salts and DBU.

Entry	Substrate	Reagents	*T* [°C]	Results
1	**8** or **9**	AcOK/*n*Bu$_4$NBr	room temp.	no conversion
2	**8**	AcOK/*n*Bu$_4$NBr	60	**12** (17%) + **13** (trace)
3	**8**	AcOCs	60	**12** (50%) + **13** (trace)
4	**9**	AcOK/*n*Bu$_4$NBr	60	**12** (52%) + **13** (30%)
5	**9**	AcOCs	60	**12** (53%) + **13** (22%)
6	**8**	*n*Bu$_4$NCN	60	**12** (37%) + **13** (37%)
7	**9**	*n*Bu$_4$NCN	room temp.	**12** (35%) + **13** (60%)
8	**8**	DBU	80	**12** (59%) + **13** (9%)
9	**9**	DBU	80	**12** (51%) + **13** (20%)



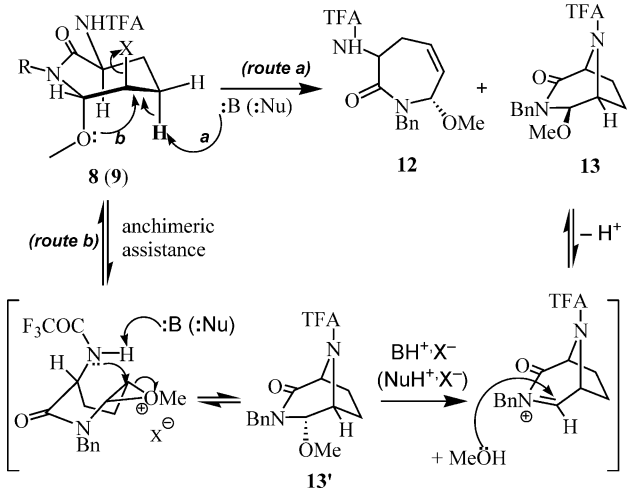
Scheme 6. Reactivity of **8** and **9** with acetate, cyanide salts and DBU.

lecular nucleophilic displacement. We therefore decided to react the same acetate and cyanide salts with halogenated substrates where the methoxy group was substituted by a hydrogen atom. Only the 6-bromo derivative **14** could be obtained by regioselective reduction of the N,O-acetal motif with trimethylsilane in TFA. Under similar conditions, the 6-iodo-7-methoxy analogue **9** underwent reduction at both carbons C-6 and C-7, leading to the unsubstituted 3-amino-1-benzylcaprolactam **15** (Scheme 7). Demethoxylated compound **14** was allowed to react with acetate or cyanide salts. No conversion of **14** was observed at room temperature; however, heating at 60 °C in DMF exclusively afforded enelactam **1a**, whatever the nucleophile (base) employed (Scheme 7). This elimination proceeded by abstraction of the most acidic proton among the two axially oriented at C-5 and C-7 positions, thus leading to the thermodynamic product **1a**.



Scheme 7. Reactivity of **14** with acetate and cyanide salts.

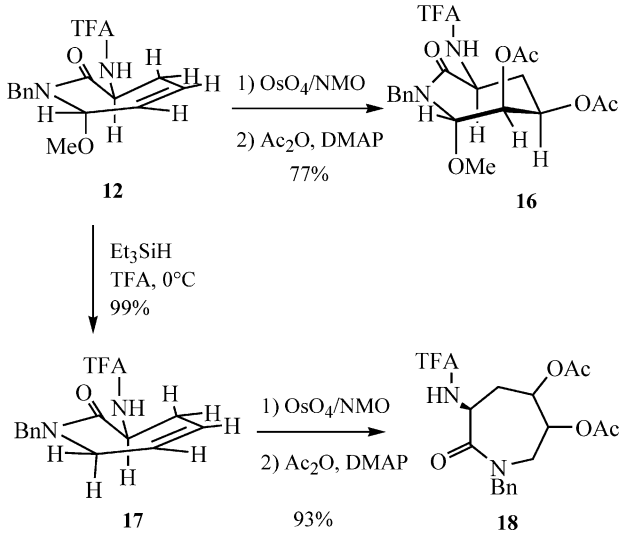
Unfortunately, despite this decreasing strain at C-7 position, the bimolecular β-elimination remains highly favoured over the desired intermolecular nucleophilic displacement. On the other hand, the absence of a bridged bicyclic compound in the case of substrate **14** may help to explain the unexpected formation of the bridged bicyclic lactam **13**, which takes place with retention of the relative configuration at C-6 and epimerization at C-7 positions (Scheme 6). Along with the stereoelectronically favoured β-elimination leading to compound **12** (Scheme 8, route a), we invoke an anchimeric participation of the methoxy group[19] of substrates **8** and **9** (Scheme 8, route b). Indeed, we first assume an intramolecular nucleophilic displacement of the halide by the methoxy group leading to a transient bicyclic epoxonium ion, which would then react with the appended nucleophile to generate compound **13′** through two successive inversions of the relative configuration at the C-6 position. In compound **13′** the C(7)–O bond eclipses the C(5)–H bond, therefore an acid-catalyzed epimerization of the N,O-acetal carbon (C-7) takes place via the corresponding iminium, thus leading to **13** (Scheme 8, route b).[20,21]



Scheme 8. Plausible mechanism for the formation of **13**.

To introduce another oxy substituent at the C-5 position, we took advantage of the new carbon–carbon double bond of compound **12**. The latter was submitted to a *syn*-dihydroxylation/diacetylation sequence to afford the desired *syn* vicinal diacetate **16** as a single diastereomer, in 77% overall yield (Scheme 9). The relative configuration of **16** was assigned as shown in Scheme 9, based on NMR spectroscopic data. COSY as well as HMBC correlations allowed unambiguous assignment of the 6-H and 5-H protons. The latter gives significant NOESY correlation to 3-H, suggesting that the C-3 and C-5 substituents are both on the same side of the ring. As expected for a *syn*-dihydroxylation, and as supported by the small $^3J_{6H–7H}$ and $^3J_{6H–5H}$ values, the C-6 acetate is also *syn* to the C-3 and C-5 substituents. This facial selectivity may be explained by assuming a boat-like reactive conformation for substrate **12**, to which OsO_4 would preferably add on the concave β-face, while the allylic pseudoaxial methoxy group would prevent OsO_4 approach on the convex α-face. In order to check the effect of this

methoxy substituent, we examined such a dihydroxylation/acetylation sequence with a substrate lacking the C-7 substituent. The desired substrate **17** was obtained in quantitative yield by reacting **12** with triethylsilane in TFA as catalyst and solvent at 0 °C. When performed at room temperature, this reduction yielded a ca. 8:2 mixture of regioisomers **17** and **1a**.[22] As anticipated, *syn*-dihydroxylation of **17** and subsequent diacetylation of the resulting vicinal diol afforded **18** as a 7:3 mixture of inseparable diastereomers (Scheme 9).



Scheme 9. *syn*-Dihydroxylation/acetylation of **12** and **17**.

Conclusions

In conclusion, a variety of mono-, di- and trisubstituted enantiopure 3-aminocaprolactams **4**–**18** were conveniently obtained in generally good to excellent yields and diastereoselectivities. For further developments, we intend to harness these versatile 3-aminocaprolactams as templates in the field of peptidomimetics, as well as for building up small-molecule libraries in connection with structural features of some biologically relevant natural products.

Experimental Section

General Procedures: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone ketyl radical immediately prior to use. CH_2Cl_2 and DMF were distilled from calcium hydride. All reactions were carried out under argon, and were monitored by thin-layer chromatography with Merck 60 F_{254} precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (0.2 –0.5 mm); the solvent systems are given as v/v. Our analytical data were obtained by using chromatographically homogeneous samples (TLC and gas chromatography). Most of our new compounds were submitted to elemental analysis after being maintained several hours under vacuum; unfortunately no one of them gave fitting data for all three elements (C, N and H). We believe that this polar and somewhat hydrophilic compounds form solvates, either with water or column chromatography solvents. Therefore; we opted for high-resolution mass spectrometry (HRMS), although this is an additional proof of structure but not of purity. Melting points are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were measured with a Perkin–Elmer 341 polarimeter equipped with a sodium (589 nm) lamp at 20 °C. Electrospray ionisation (ESI), and high-resolution mass spectra (HRMS), were recorded by the "Service de Spectrométrie de Masse" at ICSN, Gif-sur-Yvette. Nuclear magnetic spectra were recorded with either a Bruker ARX 250 (250 MHz for ^1H and 62.5 for ^{13}C) or a Bruker Avance 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. Spectra were recorded in $CDCl_3$ at 300 K (unless indicated otherwise). Chemical shifts δ were expressed in ppm relative to TMS at $\delta = 0$ ppm for ^1H and to $CDCl_3$ at $\delta = 77.16$ ppm for ^{13}C, and coupling constants J in Hertz (Hz).

(3*S*,6*S*,7*S*)-1-Benzyl-6,7-diacetoxy-3-(trifluoroacetamido)azepane-2-one (2a): To a stirred solution of enamine **1a** (312 mg, 1 mmol) in CH_3CN/H_2O/acetone (1:1:1, 6 mL) were added *N*-methylmorpholine *N*-oxide monohydrate (NMO·H_2O) (270 mg, 2 mmol) and a solution of osmium tetroxide (1 wt.-% in H_2O, 1.3 mL), dropwise. After 16 h at room temperature, the reaction mixture was diluted with EtOAc (30 mL), and $Na_2S_2O_3$ (2 g) was added. After 30 min of stirring, the suspension was filtered, the solid residue was thoroughly washed with EtOAc, and the organic layer was concentrated in vacuo to give the corresponding crude diol as a colorless oil (380 mg). The crude mixture was then dissolved in CH_2Cl_2 (10 mL), and DMAP (733 mg, 6 mmol) was added. Acetic anhydride (564 μL, 6 mmol) was added dropwise, and the mixture was stirred overnight at room temperature. The reaction mixture was washed with an aqueous saturated solution of NH_4Cl (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel (EtOAc/cyclohexane, 2:8) gave pure compound **2a** (110 mg, 26% over 2 steps) as a pale yellow oil. R_f(EtOAc/cyclohexane, 2:8) = 0.3. $[a]_D^{20} = -38$ (c = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2925, 1752, 1726, 1662, 1210, 1163, 734 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.95 (d, J = 5.0 Hz, 1 H), 7.34–7.24 (m, 5 H), 6.05 (d, J = 2.0 Hz, 1 H, H_7), 5.02 and 4.48 (q_{AB}, J_{AB} = 14.6 Hz, 2 H, PhCH_2), 4.78 (dd, J = 5.0, 10.6 Hz, 1 H), 4.57 (ddd, J = 11.6, 4.5, 2.0 Hz, 1 H), 1.66–2.35 (m, 4 H), 2.13 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.5, 169.6, 169.0, 156.3 (q, J = 37 Hz), 135.9, 128.9 (2 C), 128.5 (2 C), 128.2, 115.7 (q, J = 286 Hz), 80.9, 72.1, 53.3, 53.0, 27.8, 26.4, 20.6 (2 C) ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{21}F_3N_2NaO_6$ [M + Na]$^+$ 453.1249, found 453.1230.

(3*S*,6*S*)-6-Acetoxy-1-benzyl-3-(trifluoroacetamido)azepan-2-one (3a): Triethylsilane (0.26 mL, 1.61 mmol) was added to a solution of compound **2a** (100 mg, 0.23 mmol) in trifluoroacetic acid (2 mL), and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 2:8) to afford pure compound **3a** (62 mg, 72%) as a pale yellow solid. R_f(EtOAc/cyclohexane, 7:3) = 0.25. $[a]_D^{20}$ = +9 (c = 1.0, CH_2Cl_2); m.p. 121–123 °C. IR (neat): $\tilde{\nu}$ = 3256, 2925, 1724, 1638, 1228, 1176, 1160, 1037, 727, 703 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.98 (d, J = 4.5 Hz, 1 H), 7.36–7.22 (m, 5 H), 5.05 and 4.27 (q_{AB}, J_{AB} = 14.5 Hz, 2 H, PhCH_2), 4.66 (dd, J = 10.5, 5.7 Hz, 1 H), 4.52–4.42 (m, 1 H), 3.43 (dd, J = 15.0, 9.8 Hz, 1 H), 3.28 (d, J = 10.5 Hz, 1 H), 1.73–2.23 (m, 4 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.2, 170.2, 156.5 (q, J = 37 Hz), 136.2, 129.1 (2 C), 128.5 (2 C), 128.3, 115.9 (q, J = 286 Hz),

69.7, 52.4, 52.0, 51.0, 32.7, 28.7, 21.2 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{19}F_3N_2NaO_4$ [M + Na]$^+$ 395.1190, found 395.1195.

(3*S*,6*R*,7*S*)-1-Benzyl-6-hydroxy-7-methoxy-3-(trifluoroacetamido)-azepan-2-one (4): At room temperature, compound **1a** (500 mg, 1.6 mmol) dissolved in MeOH (5 mL) was added dropwise to a suspension of $NaHCO_3$ (3.37 g, 40.08 mmol) and Oxone® (12.32 g, theoretically 40.12 mmol of potassium peroxymonosulfate) in methanol (35 mL). The reaction mixture was stirred for 36 h at room temperature. The suspension was filtered, the solid residue was thoroughly washed with CH_2Cl_2 and the organic layer was washed successively with an aqueous saturated solution of $NaHCO_3$ (70 mL) and brine (70 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give, after column chromatography (EtOAc/cyclohexane, 1:1), pure compound **4** (317 mg, 55%) as a colourless oil. R_f(EtOAc/cyclohexane, 1:1) = 0.3. $[\alpha]_D^{20}$ = +21 (*c* = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3344, 2925, 1713, 1644, 1210, 1161, 700 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 3.6 Hz, 1 H), 7.55–7.44 (m, 5 H), 5.40 and 4.35 (q_{AB}, J_{AB} = 14.5 Hz, 2 H, PhC*H*$_2$), 4.79 (dd, *J* = 12.4, 6.15 Hz, 1 H), 4.72 (d, *J* = 4.6 Hz, 1 H), 4.32–4.28 (m, 1 H), 3.06 (s, 3 H), 2.59–2.41 (m, 1 H), 2.07–1.96 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.6, 156.5 (q, *J* = 38 Hz), 137.4, 129.7 (2 C), 129.2 (2 C), 128.6, 116.2 (q, *J* = 286 Hz), 92.2, 67.6, 56.9, 53.8, 53.2, 29.2, 24.6 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{19}F_3N_2NaO_4$ [M + Na]$^+$ 383.1195, found 383.1199.

(3*S*,6*R*)-1-Benzyl-6-hydroxy-3-(trifluoroacetamido)azepan-2-one (5): Triethylsilane (309 μL, 1.95 mmol) was added to a solution of compound **4** (100 mg, 0.28 mmol) in trifluoroacetic acid (5 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 1:1) to afford pure compound **5** (20 mg, 22%) as a colourless oil. R_f(EtOAc/cyclohexane, 1:1) = 0.2. IR (neat): $\tilde{\nu}$ = 2920, 2853, 1737, 1713, 1204, 1184, 1099 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.01 (br. s, 1 H), 7.33–7.24 (m, 5 H), 5.18 and 4.23 (q_{AB}, J_{AB} = 14.6 Hz, 2 H), 4.71–4.54 (m, 1 H), 3.98–4.08 (m, 1 H), 3.57–3.24 (m, 2 H), 2.05–1.51 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.3, 156.4 (q, *J* = 36 Hz), 136.3, 129.1 (2 C), 128.5 (2 C), 128.2, 116.0 (q, *J* = 284 Hz), 68.4, 54.2, 52.6, 52.4, 36.7, 28.8 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{17}F_3N_2NaO_3$ [M + Na]$^+$ 353.1089, found 353.1093.

(3*S*,6*R*,7*S*)-6-Acetoxy-1-benzyl-7-methoxy-3-(trifluoroacetamido)-azepan-2-one (6): To a solution of compound **4** (85 mg, 0.236 mmol) in CH_2Cl_2 (3 mL) was added successively DMAP (87 mg, 0.708 mmol) and acetic anhydride (66 μL, 0.708 mmol). After 16 h of stirring at room temperature, the reaction mixture was washed with an aqueous saturated solution of NH_4Cl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel (EtOAc/cyclohexane, 3:7) gave pure compound **6** (81 mg, 85%) as a white solid. R_f(EtOAc/cyclohexane, 3:7) = 0.4. $[\alpha]_D^{20}$ = +8 (*c* = 0.485, CH_2Cl_2); m.p. 108–110 °C. IR (neat): $\tilde{\nu}$ = 3276, 2925, 1724, 1644, 1207, 1181, 1153, 1091 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 4.5 Hz, 1 H), 7.37–7.22 (m, 5 H), 5.09–5.02 (m, 1 H), 4.93 and 4.20 (q_{AB}, J_{AB} = 14.5 Hz, 2 H, PhC*H*$_2$), 4.82 (dd, *J* = 10.6, 4.8 Hz, 1 H), 4.66 (d, *J* = 4.9 Hz, 1 H), 2.97 (s, 3 H), 2.40 (m, 1 H), 2.05–1.75 (m, 3 H), 1.79 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.3, 170.3, 156.1 (q, *J* = 37 Hz), 136.8, 129.4 (2 C), 129.0 (2 C), 128.3, 115.9 (q, *J* = 286 Hz), 89.2, 69.0, 56.7, 53.7, 53.0, 26.2, 25.0, 20.7 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{21}F_3N_2NaO_5$ [M + Na]$^+$ 425.1300, found 425.1318.

(3*S*,6*R*)-6-Acetoxy-1-benzyl-3-(trifluoroacetamido)azepan-2-one (7): Triethylsilane (166 μL, 1.043 mmol) was added to a solution of compound **6** (60 mg, 0.149 mmol) in trifluoroacetic acid (2 mL), and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 3:7) to afford pure compound **7** (41 mg, 74%) as a colourless oil. R_f(EtOAc/cyclohexane, 3:7) = 0.3. $[\alpha]_D^{20}$ = +65 (*c* = 0.885, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2920, 2853, 1721, 1651, 1494, 1241, 1207, 1158, 729, 698 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 4.7 Hz, 1 H), 7.35–7.18 (m, 5 H), 5.20 and 3.95 (q_{AB}, J_{AB} = 14.7 Hz, 2 H, PhC*H*$_2$), 4.98 (m, 1 H), 4.57 (dd, *J* = 9.0, 4.0 Hz, 1 H), 3.80 (dd, *J* = 16.0, 4.6 Hz, 1 H), 3.55 (d, *J* = 16.0 Hz, 1 H), 2.08–1.86 (m, 4 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.4, 170.6, 156.6 (q, *J* = 37 Hz), 136.5, 129.2 (2 C), 128.6 (2 C), 128.4, 116.0 (q, *J* = 286 Hz), 67.7, 53.5, 52.9, 49.4, 32.2, 26.0, 21.3 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{19}F_3N_2NaO_4$ [M + Na]$^+$ 395.1195, found 395.1190.

(3*S*,6*R*,7*S*)-1-Benzyl-6-bromo-7-methoxy-3-(trifluoroacetamido)-azepan-2-one (8): At –90 °C, a solution of *N*-bromosuccinimide (198 mg, 1.11 mmol) in THF (5 mL) was added dropwise to a solution of compound **1a** (312 mg, 1 mmol) in methanol (15 mL). The reaction mixture was allowed to warm to room temperature over 2.5 h and then concentrated in vacuo. Column chromatography of the crude mixture on silica gel (EtOAc/cyclohexane, 1:9) gave pure compound **8** (347 mg, 98%) as a white solid. R_f(EtOAc/cyclohexane, 1:9) = 0.25. $[\alpha]_D^{20}$ = +5 (*c* = 1.0, CH_2Cl_2); m.p. 158–160 °C. IR (neat): $\tilde{\nu}$ = 3339, 2946, 1716, 1644, 1483, 1266, 1207, 1150, 1078, 745, 701 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 5.8 Hz, 1 H), 7.35–7.24 (m, 5 H), 5.62 and 3.85 (q_{AB}, J_{AB} = 14.7 Hz, 2 H, PhC*H*$_2$), 4.66 (ddd, *J* = 8.7, 5.8, 4.4 Hz, 1 H), 4.61 (d, *J* = 4.4 Hz, 1 H), 4.44 (ddd, *J* = 4.5, 3.3, 3.3 Hz, 1 H), 2.79–2.71 (m, 1 H), 2.72 (s, 3 H), 2.10–1.93 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.7, 155.0 (q, *J* = 38 Hz), 136.7, 129.7 (2 C), 128.9 (2 C), 128.2, 115.9 (q, *J* = 288 Hz), 91.1, 56.9, 54.3, 52.4, 50.5, 30.1, 25.3 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{18}BrF_3N_2NaO_3$ [M + Na]$^+$ 445.0351 (^{79}Br) and 447.0330 (^{81}Br), found 445.0352 (^{79}Br) and 447.0333 (^{81}Br).

(3*S*,6*R*,7*S*)-1-Benzyl-6-iodo-7-methoxy-3-(trifluoroacetamido)-azepan-2-one (9): At –90 °C, a solution of *N*-iodosuccinimide (360 mg, 1.6 mmol) in THF (8 mL) was added dropwise to a solution of compound **1a** (500 mg, 1.6 mmol) in methanol (24 mL). The reaction mixture was allowed to warm to room temperature overnight and then concentrated in vacuo. Column chromatography of the crude mixture on silica gel (EtOAc/cyclohexane, 2:8) gave pure compound **9** (573 mg, 76%) as a pale yellow solid. R_f(EtOAc/cyclohexane, 2:8) = 0.25; m.p. decomposition. IR (neat): $\tilde{\nu}$ = 3328, 2930, 1721, 1646, 1207, 1150, 745, 701 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.02 (br. s, 1 H), 7.36–7.24 (m, 5 H), 5.63 and 3.86 (q_{AB}, J_{AB} = 14.7 Hz, 2 H), 4.85–4.74 (m, 1 H), 4.65–4.58 (m, 2 H), 2.72 (s, 3 H), 2.69–2.63 (m, 1 H), 2.06–1.82 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.8, 156.5 (q, *J* = 38 Hz), 137.0, 129.6 (2 C), 129.1 (2 C), 128.7, 116.2 (q, *J* = 286 Hz), 92.3, 57.2, 55.3, 53.2, 31.8, 30.4, 27.3 ppm. MS (ESI): *m*/*z* (%) = 493.1 (100) [M + Na]$^+$.

(3*S*,6*R*)-6-Azido-1-benzyl-3-(trifluoroacetamido)azepan-2-one (11): Sodium azide (306 mg, 4.64 mmol) was added to a solution of compound **1a** (1 g, 3.2 mmol) in acetone/MeOH (4:1, 50 mL). At –90 °C, a solution of cerium ammonium nitrate (CAN) (5.26 g, 9.6 mmol) in acetone (130 mL) was added dropwise over 1.5 h. The reaction mixture was allowed to warm to room temperature overnight and then diluted with H_2O (100 mL). The aqueous layer was

extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 40 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude compound **10** (1.25 g) was dissolved in trifluoroacetic acid (8 mL), triethylsilane (3.56 mL, 22.4 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 8:2) to afford pure compound **11** (605 mg, 53% over 2 steps) as a white solid. R_f(EtOAc/cyclohexane, 8:2) = 0.3. $[\alpha]_D^{20}$ = +8 (c = 1.00, CH_2Cl_2); m.p. 115–117 °C. IR (neat): $\tilde{\nu}$ = 3271, 2925, 2098, 1716, 1638, 1184, 727 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.04 (br. s, 1 H), 7.33–7.19 (m, 5 H), 5.50 and 3.96 (q_{AB}, J_{AB} = 14.9 Hz, 2 H, PhCH_2), 4.56 (dd, J = 8.5, 5.6 Hz, 1 H), 3.96–3.90 (m, 1 H), 3.49 (d, J = 15.7 Hz, 1 H), 3.33 (dd, J = 15.7, 4.7 Hz, 1 H), 1.69–2.29 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.9, 156.4 (q, J = 38 Hz), 136.3, 129.0 (2 C), 128.6 (2 C), 128.0, 115.9 (q, J = 286 Hz), 56.9, 53.2, 52.5, 49.1, 31.4, 25.8 ppm. HRMS (ESI): m/z calcd. for $C_{15}H_{16}F_3N_5NaO_2$ $[M + Na]^+$ 378.1154, found 378.1163.

(3*S*,7*S*)-1-Benzyl-7-methoxy-3-(trifluoroacetamido)-2,3,4,7-tetrahydro-1*H*-azepin-2-one (12): DBU (300 μL, 2 mmol) was added to a solution of compound **8** (84.6 mg, 0.2 mmol) in DMF (2 mL), and the mixture was stirred for 3 h at 80 °C. The reaction mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 7:3) to afford pure compound **12** (40 mg, 59%) as a pale yellow solid and compound **13** (6 mg, 9%) as pale yellow oil. For **12**: R_f(EtOAc/cyclohexane, 7:3) = 0.25. $[\alpha]_D^{20}$ = –8 (c = 1.00, CH_2Cl_2); m.p. 91–93 °C. IR (neat): $\tilde{\nu}$ = 3276, 1718, 1649, 1210, 1184, 1145, 1070, 729, 696 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.09 (d, J = 4.0 Hz, 1 H), 7.74–7.37 (m, 5 H), 6.07–5.94 (m, 2 H), 5.67 (ddd, J = 12.1, 6.2, 4.0 Hz, 1 H), 5.26 and 4.57 (q_{AB}, J_{AB} = 15.0 Hz, 2 H, PhCH_2), 4.90–4.83 (m, 1 H), 3.41 (s, 3 H), 2.97 (ddd, J = 18.3, 4.2, 4.2 Hz, 1 H), 2.45–2.19 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.3, 156.5 (q, J = 37 Hz), 137.0, 131.3, 129.2 (2 C), 128.5 (2 C), 128.3, 126.0, 116.2 (q, J = 286 Hz), 87.8, 56.9, 53.3, 50.7, 31.3 ppm. HRMS (ESI): m/z calcd. for $C_{16}H_{17}F_3N_2NaO_3$ $[M + Na]^+$ 365.1089, found 365.1097.

(1*S*,4*R*,5*R*)-3-Benzyl-4-methoxy-8-(trifluoroacetyl)-3,8-diazabicyclo[3.2.1]octan-2-one (13): R_f(EtOAc/cyclohexane, 7:3) = 0.2. ^1H NMR (500 MHz, $CDCl_3$) (major/minor rotamers ratio 7:3, H numbers are those of the corresponding position according to IUPAC nomenclature): δ = 7.34–7.27 (m, 3 H), 7.19–7.17 (m, 2 H), 5.33 and 3.80 (q_{AB}, J_{AB} = 15 Hz, 0.6 H, PhCH_2, minor rotamer), 5.29 and 3.87 (q_{AB}, J_{AB} = 15.0 Hz, 1.4 H, PhCH_2, major rotamer), 4.95–5.15 (br. d, J = 3.5 Hz, 0.3 H^1 and 0.7 H^5), 4.76 (br. s, 0.7 H^1), 4.63 (br. d, J = 7.5 Hz, 0.3 H^5), 3.96 (br. d, J = 1.5 Hz, 0.7 H^4), 3.86 (br. d, J = 1.5 Hz, 0.3 H^4), 3.36 (s, 2.1 H, OMe, major rotamer), 3.33 (s, 0.9 H, OMe, minor rotamer), 2.20–2.14 (m, 1.4 $H^{7,7'}$, major rotamer and 0.3 H^6, minor rotamer), 2.11–2.02 (m, 0.7 H^6, major rotamer and 0.6 $H^{7,7'}$, minor rotamer), 1.55–1.49 (m, 0.3 $H^{6'}$), 1.44–1.40 (m, 0.7 $H^{6'}$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) for major conformer: δ = 166.8, 153.5 (q, J = 19 Hz), 136.0, 129.0 (2 C), 128.2 (2 C), 128.0, 115.9 (q, J = 284 Hz), 88.1, 59.9, 55.2, 51.4, 45.2, 30.4, 22.0 ppm; for minor conformer: δ = 167.5, 154.8 (q, J = 17 Hz), 136.0, 129.0 (2 C), 128.2 (2 C), 128.0, 116.1 (q, J = 287 Hz), 88.1, 58.0, 56.1, 54.8, 44.9, 28.1, 24.4 ppm. HRMS (ESI): m/z calcd. for $C_{16}H_{17}F_3N_2NaO_3$ $[M + Na]^+$ 365.1089, found 365.1075.

(3*S*,6*R*)-1-Benzyl-6-bromo-3-(trifluoroacetamido)azepan-2-one (14): Triethylsilane (526 μL, 3.31 mmol) was added to a solution of compound **8** (200 mg, 0.472 mmol) in trifluoroacetic acid (5 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 15:85) to afford the pure compound **14** (170 mg, 92%) as a white solid. R_f(EtOAc/cyclohexane, 15:85) = 0.3. $[\alpha]_D^{20}$ = +15 (c = 0.785, CH_2Cl_2); m.p. 125–127 °C. IR (neat): $\tilde{\nu}$ = 3349, 2920, 2853, 1718, 1649, 1483, 1437, 1204, 1161, 902, 729, 696 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H), 7.36–7.18 (m, 5 H), 5.62 and 3.97 (q_{AB}, J_{AB} = 15.0 Hz, 2 H, PhCH_2), 4.53–4.45 (m, 2 H), 3.73 (d, J = 16.0 Hz, 1 H), 3.51 (dd, J = 16.0, 5.1 Hz, 1 H), 2.35–2.33 (m, 2 H), 2.07–2.02 (m, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.1, 155.5 (q, J = 38 Hz), 136.3, 129.1 (2 C), 128.4 (2 C), 128.2, 115.9 (q, J = 287 Hz), 53.9, 52.8, 52.1, 49.4, 37.2, 26.0 ppm. MS (ESI): m/z (%) = 415.0 (50), 417.0 (50) $[M + Na]^+$.

(*S*)-1-Benzyl-3-(trifluoroacetamido)azepan-2one (15): Triethylsilane (356 μL, 2.24 mmol) was added to a solution of compound **9** (150 mg, 0.32 mmol) in trifluoroacetic acid (3 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 2:8) to afford pure compound **15** (91 mg, 91%) as a colourless oil. R_f(EtOAc/cyclohexane, 2:8) = 0.35. $[\alpha]_D^{20}$ = +1 (c = 1.00, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3245, 2925, 1711, 1636, 1181, 1153, 716 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.95 (br. s, 1 H), 7.25–7.11 (m, 5 H), 4.64, 4.39 (q_{AB}, J_{AB} = 14.7 Hz, 2 H, PhCH_2), 4.51 (dd, J = 10.6, 5.8 Hz, 1 H), 3.37–3.12 (m, 2 H), 2.03–1.98 (m, 1 H), 1.87–1.60 (m, 3 H), 1.52–1.30 (m, 1 H), 1.14–1.07 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.9, 156.5 (q, J = 38 Hz), 136.9, 129.2 (2 C), 128.8 (2 C), 128.6, 116.2 (q, J = 286 Hz), 53.2, 52.2, 48.5, 31.3, 27.9, 27.3 ppm. MS (ESI): m/z (%) = 337.3 (100) $[M + Na]^+$.

(3*S*,5*R*,6*R*,7*S*)-1-Benzyl-5,6-diacetoxy-7-methoxy-3-(trifluoroacetamido)azepan-2-one (16): To a stirred solution of compound **12** (50 mg, 0.15 mmol) in CH_3CN/H_2O/acetone (1:1:1, 3 mL) were added NMO·H_2O (40 mg, 0.29 mmol) and a solution of osmium tetroxide (1 wt.-% in H_2O, 0.19 mL), dropwise. After 16 h at room temperature, the reaction mixture was diluted with EtOAc (5 mL), and $Na_2S_2O_3$ (300 mg) was added. After 30 min of stirring, the suspension was filtered through a Celite® pad, the solid residue was thoroughly washed with EtOAc, and the organic layer was concentrated in vacuo to give the corresponding crude diol as a colorless oil (44 mg). R_f(EtOAc/cyclohexane, 7:3) = 0.3. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.15 (d, J = 5.5 Hz, 1 H), 7.32–7.27 (m, 5 H), 5.40 and 3.93 (q_{AB}, J_{AB} = 14.6 Hz, 2 H, PhCH_2), 4.72–4.63 (m, 2 H), 4.29 (m, 1 H), 4.14 (br. s, 1 H), 3.02–3.34 (m, 2 H), 2.77 (s, 3 H), 2.15–1.85 (m, 2 H) ppm. The crude diol (44 mg, 0.12 mmol) was then dissolved in CH_2Cl_2 (2 mL), and DMAP (86 mg, 0.7 mmol) was added. Acetic anhydride (66 μL, 0.7 mmol) was added dropwise, and the mixture was stirred overnight at room temperature. The reaction mixture was washed with an aqueous saturated solution of NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel (EtOAc/cyclohexane, 4:6) gave pure compound **16** (52 mg, 78% over 2 steps) as a white solid. R_f(EtOAc/cyclohexane, 4:6) = 0.3. $[\alpha]_D^{20}$ = +25 (c = 1.00, CH_2Cl_2); m.p. 174–176 °C. IR (neat): $\tilde{\nu}$ = 2925, 1742, 1716, 1654, 1367, 1225 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.98 (d, J = 5.2 Hz, 1 H), 7.34–7.27 (m, 5 H), 5.55 (ddd, J = 11.9, 2.6, 2.6 Hz, 1 H), 5.44 (dd, J = 5.6, 2.6 Hz, 1 H), 4.98 and 4.19 (q_{AB}, J_{AB} = 14.5 Hz, 2 H, PhCH_2), 4.79 (ddd, J = 9.8, 5.7, 5.2 Hz, 1 H), 4.70 (d, J = 5.6 Hz, 1 H), 3.00 (s, 3 H), 2.25–2.03 (m, 2 H), 1.95 (s, 3 H), 1.84 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.1, 170.4,

169.8, 156.5 (q, J = 37 Hz), 136.7, 129.7 (2 C), 129.3 (2 C), 128.8, 116.1 (q, J = 286 Hz), 88.4, 68.9, 68.1, 57.3, 54.1, 49.8, 30.2, 21.1, 20.7 ppm. HRMS (ESI): m/z calcd. for $C_{20}H_{23}F_3N_2NaO_7$ $[M + Na]^+$ 483.1355, found 483.1343.

(*S*)-1-Benzyl-3-(trifluoroacetamido)-2,3,4,7-tetrahydro-1*H*-azepin-2-one (17): At 0 °C, triethylsilane (975 μL, 6.14 mmol) was added to a solution of compound **12** (300 mg, 0.88 mmol) in trifluoroacetic acid (15 mL), and the mixture was stirred for 5 h at 0 °C. The reaction mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography (EtOAc/cyclohexane, 2:8) to afford pure compound **17** (273 mg, 99%) as a white solid. R_f(EtOAc/cyclohexane, 2:8) = 0.25. $[\alpha]_D^{20}$ = –3 (c = 1.00, CH_2Cl_2); m.p. 80–82 °C. IR (neat): $\tilde{\nu}$ = 3220, 3070, 1721, 1636, 1192, 1145, 737, 698, 649 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.95 (d, J = 4.1 Hz, 1 H), 7.33–7.17 (m, 5 H), 5.83–5.63 (m, 2 H), 5.14 (ddd, J = 12.7, 4.1, 4.1 Hz, 1 H), 4.64 (app. t, $J_{app.}$ = 15.9 Hz, 2 H, PhCH_2), 4.26 (d, J = 17.9 Hz, 1 H), 3.38 (dd, J = 17.9, 7.2 Hz, 1 H), 2.75 (m, 1 H), 2.29 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.0, 156.6 (q, J = 37 Hz), 136.6, 129.6, 129.2 (2 C), 128.2 (2 C), 127.8, 124.8, 116.2 (q, J = 286 Hz), 52.3, 50.1, 45.5, 32.0 ppm. HRMS (ESI): m/z calcd. for $C_{15}H_{15}F_3N_2NaO_2$ $[M + Na]^+$ 335.0983, found 335.0974.

1-Benzyl-5,6-diacetoxy-3-(trifluoroacetamido)azepan-2-one (18): To a stirred solution of compound **17** (50 mg, 0.16 mmol) in CH_3CN/H_2O/acetone (1:1:1, 3 mL) were added NMO·H_2O (43 mg, 0.32 mmol) and a solution of osmium tetroxide (1 wt.-% in H_2O, 0.20 mL), dropwise. After 16 h at room temperature, the reaction mixture was diluted with EtOAc (5 mL), and $Na_2S_2O_3$ (300 mg) was added. After 30 min of stirring, the suspension was filtered through a Celite® pad, the solid residue was thoroughly washed with EtOAc, and the organic layer was concentrated in vacuo to give the corresponding crude diol as a colorless oil (52 mg). The crude diol was then disolved in CH_2Cl_2 (3 mL), and DMAP (106 mg, 0.87 mmol) was added. Acetic anhydride (82 μL, 0.87 mmol) was added dropwise and the mixture was stirred overnight at room temperature. The reaction mixture was washed with an aqueous saturated solution of NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel (EtOAc/cyclohexane, 2:8) afforded compound **18** (63 mg, 92% over 2 steps) as a colorless oil and as an inseparable 7:3 mixture of diastereomers. R_f(EtOAc/cyclohexane, 2:8) = 0.25. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.01 (br. s, 0.7 H), 7.85 (br. s, 0.3 H), 7.32–7.16 (m, 5 H), 5.29–5.08 (m, 3 H), 4.63–4.48 (m, 1 H) ppm. 3.93 (m, 1 H), 3.73–3.40 (m, 2 H), 2.40–1.82 (m, 2 H), 1.96–1.99 (m, 6 H) ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{21}F_3N_2NaO_6$ $[M + Na]^+$ 453.1249, found 453.1267.

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[21] See supplementary material for NMR spectroscopic data of compound **13**.
[22] Similar regioselectivity was observed when **12** was treated with TMSCN in the presence of $F_3B{\cdot}OEt_2$ at 0 °C in CH_2Cl_2. Indeed, substitution of the methoxy group by cyanide took place α to the nitrogen atom; moreover, as with triethylsilane, this nucleophilic displacement was followed by partial isomerization of the C=C double bond, leading to the corresponding conjugated α-cyanoenelactam.

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