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Rapid access with diversity to enantiopure flexible PNA monomers following asymmetric orthogonal strategies

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ABSTRACT

Different synthetic procedures are described in the rapid elaboration of flexible PNA monomers based on the 6-amino-8-base-octanoate and 5-amino-7-base-heptanoate scaffolds. Asymmetric Aza-Michael monoaddition is successfully applied to starting materials derived from sebacic/azelaic long-chain diacids and 6-membered oxacyclohexane commercial derivatives. Chain length, orthogonality of the ester functionalities, and *Z*/*E* isomerism of these prime substrates yielded high-valuable multifunctional intermediates through this asymmetric conjugate addition. Key features are the diversity toward PNA monomer synthesis, orthogonal chemoselective transformations, and Mitsunobu nucleobase substitution as an exceptional approach to introduce nucleobases in the final step.

1. Introduction

Peptide nucleic acids PNA are a class of *xeno*-nucleic acids (non-natural nucleic acid homologues)[1] with potential applications in gene-targeted therapeutics,[2] biosensing,[3] biomaterials,[4] and supramolecular constructs.[5] Ribose-phosphate backbone replacement by a poly-amide chain increases the binding affinity of natural DNA to PNA, as has been extensively tested experimentally and theoretically. The enzymatic resistance to endogenous nucleases is also improved, allowing a larger residence time and activity. Additionally, the peptide nature is easily exploited through solid-phase protocols in oligomer elaborations.[6] These high-valuable properties have been extensively studied since the pioneering work of Nielsen.[7] The original 2-aminoethyl-glycine nucleic acid[8] has been the starting model for the design and synthesis of new PNA-monomers with improved or tuned properties in the search of antigene and antisense molecules.[9] In this sense, backbone modifications allow the preorganization profile of the final peptide-nucleotides to be controlled.[10] Flexible peptide nucleic acids are a subdivision of *xeno*-nucleic acids with a low conformational restriction, with attractive profiles in preorganization management, through homopolymers or PNA-composite elaboration. Relevant examples of flexible derivatives are Leumann's[11] 5-amino-7-thymine-heptanoate monomer and Ku-wahara's[12] 5-amino-7-thymine-3-oxaheptanoate unit, both synthetized using chiral pool approaches.

Herein we report the synthesis of orthogonally protected 5/6-amino-7/8-base-hepta/octanoate PNA monomers through different short asymmetric approaches, starting from different long-chain Michael acceptors. As has been demonstrated,[13] chirality of the monomeric units imposes a defined complementary hybridization scheme toward DNA/RNA: parallel or antiparallel. The methodologies applied allow flexible chiral PNA units with attractive potentiality in biomedicine,[14] food analysis, and authentication[15] or bioimaging to be obtained.[16]

2. Results and discussion

Scheme 1 shows a general vision of the synthetic plan. Fully protected PNA monomers are elaborated using δ-valerolactone, 3,4-dihydro-2*H*-pyran, and sebacic/azelaic acids as prime materials. From sebacic and azelaic acids we obtained the derivatives (*E*,*E*)-**1a**, (*E*,*Z*)-**1c**, and (*E*,*E*)-**1d**,[17] scalable to gram quantities, following the methodology described by Scheffer.[18] The straightforward protocol afforded the (*E*,*E*) Michael double acceptors in excellent yields as major products, while the (*E*,*Z*) acceptors were obtained in minor amounts. Chromatography of the reaction crudes allows the isolation of the single olefin isomers. Separately, one-pot transformation of δ-valerolactone[19] and 3,4-dihydro-2*H*-pyran[20] to the Michael acceptor (*E*)-**1b** was also accomplished through Horner–Wadsworth–Emmons homologation. These affordable materials are high-valuable building blocks due to the

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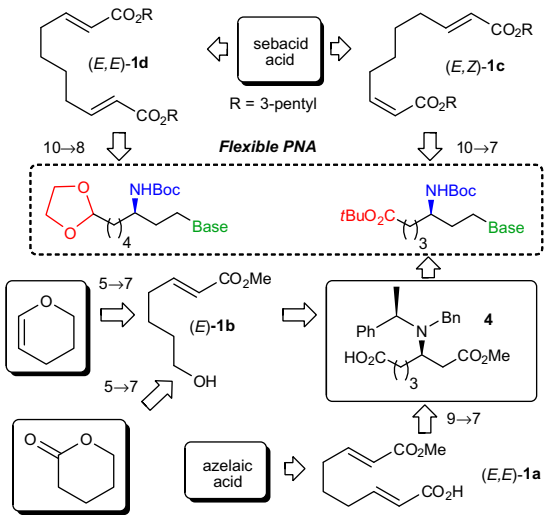


Scheme 1. General synthetic plan.

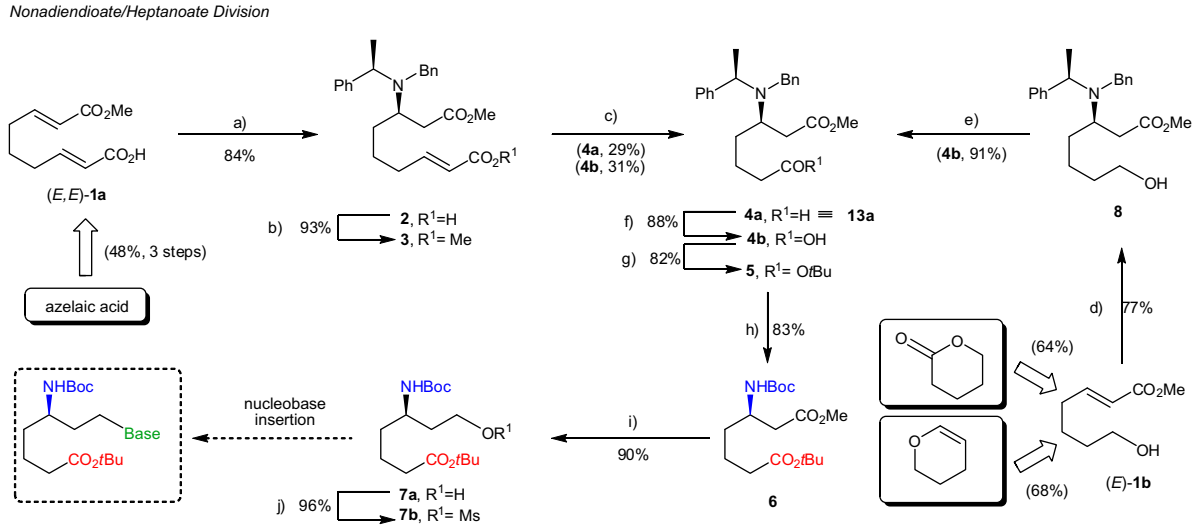
multiple synthetic transformations that may undergo[17,21] and have been successfully used in our group in the elaboration of other homochiral PNA monomers,[22] morphan-like β-amino acids,[23] and homopipecolic acid.[22b]

Stereoselective C–N bond generation, chain contraction, and orthogonal functional group interconversions complete the path to the schematized PNA monomers. The synthetic routes are organized into two divisions: the mixed nonadiendioate/heptanoate group and the decadiendioate group. These major divisions differ in the synthetic methodologies applied as well as the chain length of the substrate, which were adjusted from 10→8/7 in the first one and from 9/5→7 in the latter.

Nonadiendioate route starting point is the Michael orthogonal acceptor **1a** (Scheme 2). Aza-Michael asymmetric addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide afforded monoadduct **2** in good yields, with total control of the new stereocenter generated.[24] This polyfunctional compound has been investigated in the elaboration of 2-amino-9-thymine-nonanoate monomer and (*R*)-homopipecolic acid.[22b] This acid was later transformed to the dimethyl ester **3** with $TMSCH_2N_2$, as has been demonstrated in the literature as requisite to overcome ozonolysis problems.[25] Ozonolytic cleavage was carried out after prior hydrogen chloride gas, in order to avoid *N*-oxide formation.[26] Hydrogen peroxide oxidative conditions lead to a 1:1 mixture of **4a**–**b** in moderate yields. Aldehyde **4a** is essentially the same intermediate as **13a**, which may be protected as dioxolane in the following decandiendioate route. Mild oxidation of aldehyde **4a** to acid **4b** was achieved with $NaClO_2$ in a phosphate buffered solution, improving the productivity of the route to this acid.

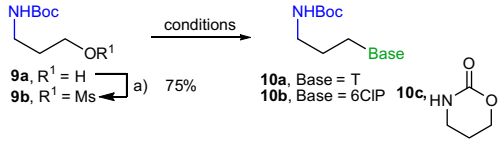
Parallel to this sequence, heptanoate route was developed (Scheme 2), starting with the Aza-Michael diastereoselective addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to adduct **8**, in a 77% yield. Jones oxidation allowed the satisfactory preparation of intermediate **4b**, converging both routes. These last two steps demonstrate an alternative synthetic procedure to intermediate **4b**, in higher yield and productivity. From **4b**, the amino and carboxylic functionalities were protected through *tert*-butyl protecting groups in two steps. *tert*-Butyl esterification of acid **4b** with Boc_2O and DMAP catalyst afforded diester **5** in a 82% yield, while the amine group was released and reprotected under hydrogen in the presence of Boc_2O, to give the protected carbamate **6** in a 83% yield. Although both functionalities are *tert*-butyl like, nowadays there are several reported procedures which justify the orthogonality of both functional groups.[27] Finally, the methyl ester was transformed into a more suitable functional group for nucleobase insertion such as alcohol **7a** and mesylate **7b**. Chemoselective reduction of ester **6** to alcohol **7a** was carried out with lithium borohydride in excellent yields, without degradation of the *tert*-butyl ester moiety. Activation of the hydroxyl group was achieved through mesylation to **7b** in 96% yield.

As nucleobases are poor nucleophiles in general, certain special-conditions are required to increase nucleobase coupling. Additionally, the 1-mesylate-3-Boc-amine propanoate fragment is known to overcome cyclization to cyclic carbamate in basic conditions.[28] Hence, a detailed reaction study was undertaken using protected substrates **9a–b**; which keeps the problematic region of the original system. Table 1 summarizes the different reaction assays.



Scheme 2. Reagents and conditions: (a) (*R*)-*N*-benzyl-*N*-α-methylbenzylamine, *n*-BuLi, THF, −78 °C; (b) $TMSCH_2N_2$, toluene/MeOH 1:1, rt; (c) HCl (g), O_3 (g), −78 °C, then H_2O_2, rt; (d) (*R*)-*N*-benzyl-*N*-α-methylbenzylamine, *n*-BuLi, THF, −78 °C; (e) CrO_3, H_2SO_4, acetone, rt; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, rt; (g) Boc_2O, DMAP, *t*BuOH, 30 °C; (h) H_2-$Pd(OH)_2$/C, Boc_2O, AcOEt, 50 psi; (i) $LiBH_4$, THF, rt; (j) MsCl, Py, DMAP, DCM, rt.

Table 1
Screening of different nucleobase coupling conditions to model system **9a–b**



Entry	9	Conditions	Temp[a]	Base[b]	10[c]	Yield[d]
1	**9b**	TBAI, K_2CO_3, DMF	70	—	**10c**	29
2	**9b**	TBAI, K_2CO_3, DMF	70	T	**10a**	27
3	**9b**	TBAI, K_2CO_3, DMF	150	T	**10a**	12
4	**9b**	TBAI, DBU, DMF	70	T	**10a**	33
5	**9b**	TBAI, DBU, DMF	150	T	**10a**	6
6	**9b**	TBAI, K_2CO_3, DMF	rt	6ClP	**10a**	25
7	**9b**	TBAI, K_2CO_3, DMF	70	6ClP	**10a**	20
8	**9a**	PBu_3, DIAD, THF	rt	6ClP	**10b**	68

Reagents and conditions: (a) MsCl, Py, DMAP, DCM, rt.
[a] Celsius.
[b] T = Thymine; 6ClP = 6-Chloropurine.
[c] Main product (except entry 8).
[d] Yield of **10a–b**.

Entries 1–7 describe basic media reaction conditions in DMF, first used by Taddei.[29]

In general, the reaction affords low yields of the substitution product at 70/150 °C, mixed with cyclic carbamate **10c** (1,3-oxazinan-2-one). This secondary compound is suspected to be generated either by base (DBU or K_2CO_3) or nucleobase mediation.

Repeating the reaction under the same conditions but in absence of nucleobase afforded a 1:1 mixture of substrate and cyclic carbamate, demonstrating that the cyclization process does not require the presence of a nucleobase. In order to maximize the conversion, Mitsunobu methodology was also applied due to the successful results in other nucleobase chemistry.[30] Employing PBu_3 combined with DIAD and the nucleobase in THF allowed the substitution compound to be obtained as the single product in a 68% yield. No cyclic carbamate **10c** was detected this time.

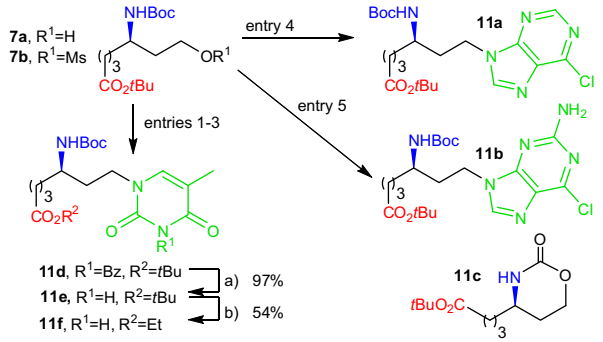
These analyses' results were translated to the original system (Table 2). When Taddei conditions are applied to mesylate **7b**, a 1:1 regioisomeric mixture of substitution products is obtained, with traces of cyclic carbamate **11c**. When N^3-Bz-thymine is used, the single regioisomer **11d** was obtained also accompanied with a small amount of carbamate **11c**. This protected form of thymine[31] has been extensively used in PNA chemistry, as a consequence of a better solubility, as well as avoiding the nucleophilic competition between N^1/N^3.

Finally, Mitsunobu conditions were separately applied to alcohol **7a** with N^3-Bz-thymine, 6-chloropurine, and 2-amino-6-chloropurine, successfully giving the PNA fully-protected monomers **11a**, **11b**, and **11d** in good yields. These purine monomers **11a**, **11b** are not only immediate predecessors of adenine and guanine, but also of modified purine analogs such as hypoxanthine, 2-aminopurine, 2,6-diaminopurine, or thioguanine, which are readily accessible. Thereby, Mitsunobu coupling conditions are superior to Taddei basic media ones. Additionally, **11d** was transformed into Leumann's enantiomer **11f** in two steps: chemoselective cleavage of the benzoyl group of the pyrimidine ring followed by one-pot transesterification from **11e.** Comparison of the specific rotation value of **11f**, $[\alpha]_D^{20} = -11.2$ (*c* 0.24, MeOH), with Leumann's enantiomer,[11] $[\alpha]_D^{20} = +12.1$ (*c* 0.01, MeOH), shows good agreement. The stereochemical integrity achieved in the first Michael stereoselective addition (>95% d.e.) is maintained.

Scheme 3 shows the complete reaction paths of the decadiendioate division. Initial diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **1c–d** afforded adducts **12a–b** in moderate to good yields, but with a clear difference: the *Z*-olefin in **1c** is isomerized from (*Z*)-α/β to (*E*)-β/γ, while the *E*-olefin remains unaltered. This reaction behavior is common when using lithium amides with (*Z*)-α/β unsaturated esters, which undergoes deconjugation instead of Michael addition, as it has been previously reported by our group.[21] This attractive strategy is readily exploited in the next stage: ozonolytic cleavage afforded aldehydes **13a–b** in good yields, which are one methylene homologues, affording a simple procedure to obtain two sets of compounds differing in the chain length. After that, aldehydes **13a–b** were protected through dioxolane formation with ethyleneglycol in acid media, with 76% and 82% yields, respectively. One-pot protecting group interconversion was carried out for compounds **14a–b** through palladium-catalyzed benzylic removal under a hydrogen atmosphere, in the presence of Boc_2O, affording carbamates **15a–b** in excellent yields.

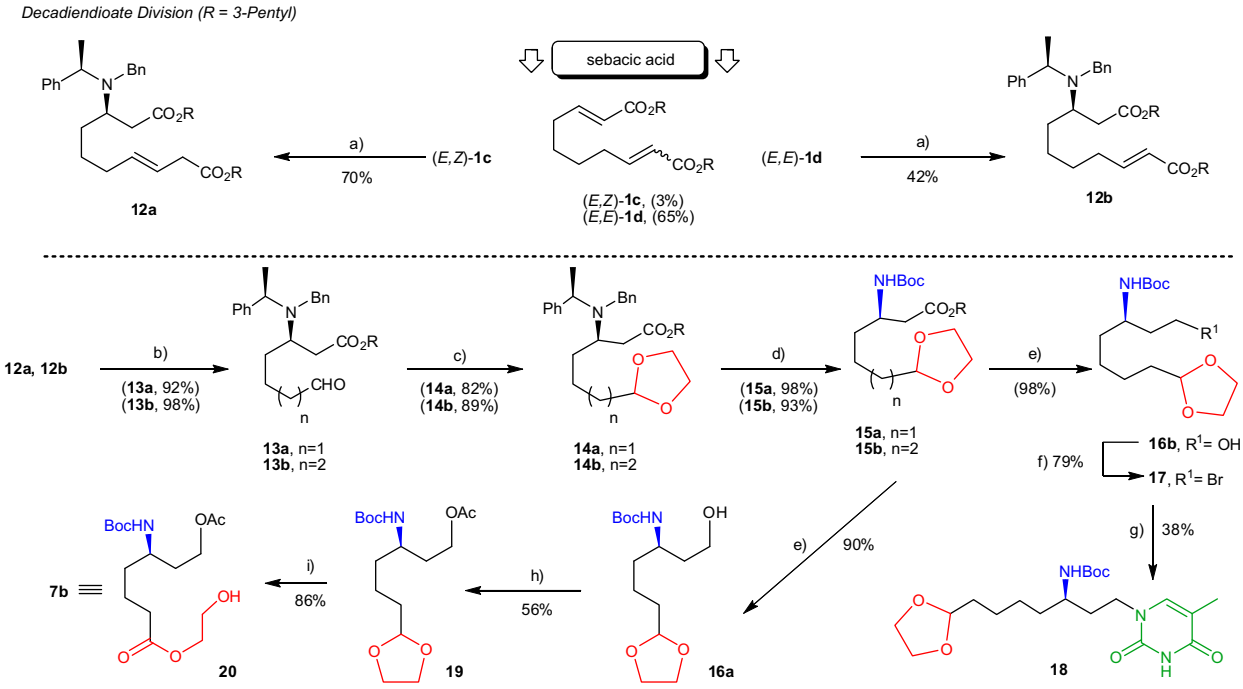
Finally, chemoselective reduction of the ester to alcohol was achieved with DIBAL-H, obtaining hydroxyl compounds **16a–b** in excellent yields. At this point of the route, each homologue is subjected to divergent transformations. Functional group interconversion over **16b** through Appel procedure afforded bromide **17** in a 79% yield. Final thymine substitution following Taddei's protocol allowed the double protected thymine PNA monomer **18** to be obtained in moderate yields. Despite its non-acidic character, this protected monomer is an interesting prototype to imine-derived nucleic derivatives, where the imine functionality not only serves as monomer linker, but may be broadly modified. Separately, acetylation of alcohol **16a** to acetate **19** was carried out, followed by ozonolytic cleavage. After the oxidative transformation, 2-hydroxy ethyl ester **20** was obtained in a 86% yield. Substitution of the acetate functionality by nucleobases will afford a PNA monomer in a similar way to compound **7b**.

Table 2
Screening of nucleobase insertion conditions to system **7a–b**



Entry	7	Conditions	Temp[a]	Base[b]	11	Yield
1	**7b**	TBAI, K_2CO_3, DMF	70	T	**11e**[c]	35[c]
2	**7b**	TBAI, DBU, DMF	70	TBz	**11c**	23
3	**7a**	PBu_3, DIAD, THF	rt	TBz	**11c**	75
4	**7a**	PBu_3, DIAD, THF	rt	6-ClP	**11a**	61
5	**7a**	PBu_3, DIAD, THF	rt	2A6ClP	**11b**	53

Reagents and conditions: (a) LiOH·H_2O, MeOH/THF/H_2O 3:1:1, rt; (b) HCl (g), EtOH, then Boc_2O, rt.
[a] Celsius.
[b] T = thymine; TBz = N^3-Bz-thymine; 6ClP = 6-Chloropurine; 2A6ClP = 2-Amino-6-chloropurine.
[c] 1:1 mixture of thymine regioisomers with traces of cyclic carbamate **11c**.



Scheme 3. Reagents and conditions: (a) *N*-benzyl-*N*-α-methylbenzylamine, *n*BuLi, THF, −78 °C; (b) HCl (g), O_3 (g), −78 °C, then Me_2S, rt; (c) ethylene glycol, *p*TsOH, benzene, 80 °C; (d) H_2-Pd(OH)$_2$/C, Boc_2O, AcOEt, 50 psi; (e) DIBAL-H, THF, −78 °C; (f) CBr_4, PPh_3, DCM, rt; (g) thymine, TBAI, K_2CO_3, DMF, 70 °C; (h) Ac_2O, Py, rt; (i) O_3 (g), DCM, −78 °C.

3. Conclusion

This article demonstrates the utility of the described starting materials in applied synthesis. Aza-Michael asymmetric monoaddition to orthogonally functionalized α,β-unsaturated esters led to attractive polyfunctional intermediates with broad synthetic applications. Long chain diesters (decadiendioate) or orthogonally protected medium-size esters (nonadiendioate) undergo exclusively mono-addition of lithium amides. *Z*/*E* isomerism of olefin conjugated esters plays a relevant role: after lithium amide monoaddition, *Z* olefins are rearranged to *E*-nonconjugated esters, while the *E* homologues were found unaltered. Following the combination of this asymmetric induction with orthogonal transformations allows the development of high-value synthetic methodologies in the preparation of flexible enantiopure peptide nucleic acids. Imine-based protected nucleic acid **18** was obtained in a 7% of overall yield, while its homologue **20** yielded 22%, both following similar transformations. Leumann's fully protected thymine-enantiomer **11d** has been obtained in an overall 31% and 24 yield from **1b** and **1a**, respectively, while it was obtained in a 4% by Leumann. Purine based monomers **11a**–**b** were also obtained in a 25% and 22% yield, respectively, giving immediate predecessors of adenine, guanine, modified, hypoxanthine, 2-aminopurine, 2,6-diaminopurine or thioguanine analogs. These purine PNAs are fully protected monomers (carboxylic acid, amine and nucleobase). Mitsunobu-type nucleobase substitution procedures allow a significant increase in conversion yields compared to original Taddei's technique.

4. Experimental

4.1. General

All chemical reagents were purchased from Sigma-Aldrich or Acros. High-purity reaction solvents were purified accordingly to literature procedures. All reactions were carried out in borosilicate Pyrex® type glassware and under inert conditions, using Ar as inert gas. Reaction monitoring was followed by TLC, type Merck 60 F254, which visualization was achieved with UV light and ninhydrin as appropriate stain. Flash chromatography was carried out on Kieselgel 40 (Merck, 0.040–0.063) silica. Yields and characterization data belong to chromatography purified compounds. Retention factor was measured from the purified compounds (R_f). Deuterated solvents were purchased from Carlo Erba. Optical rotations were measured on a Perkin Elmer 241 polarimeter in 1 dm cells ($[\alpha]_D^{20}$). Infrared spectra were recorded on a Shimadzu IRAffinity-1 (IR). NMR experiments were recorded on a Varian 200 VX (^{1}H NMR/200 MHz, ^{13}C NMR/50 MHz) and on a Bruker DRX 400 (^{1}H NMR/400 MHz). 2D HMBC and HMQC or representative compounds were also recorded to assign protons and carbons on new structures. Chemical shifts are reported in ppm (parts per million) relative to referenced values. High-resolution mass spectrometry (HRMS) analyses were performed on an Applied Biosystems QSTAR XL (ESI, electrospray ionization) and in a VG-TS 250 (EI, electronic impact), at 70 eV (*m*/*z*).

4.2. (2*E*,7*E*)-9-Methoxy-9-oxonona-2,7-dienoic acid (*E*,*E*)-1a[22b]

In a two-necked round bottom flask provided with a condenser, 20 g of azelaic acid (CAS: 123-99-9, 188.2 g/mol, 106 mmol) was placed together with 27 mL of $SOCl_2$ (thionyl chloride, CAS: 7719-09-7, 118.9 g/mol, 372 mmol). The second neck was sealed and the suspension was magnetically stirred and heated at reflux (75 °C) for 90 min. The solids were gradually dissolved. After 90 min, the reaction was cooled to room temperature and a dropping funnel filled with Br_2 (bromine, CAS: 7726-95-6, 159.8 g/mol) was place in the second neck. Next, 19 mL of Br_2 (372 mmol) was added dropwise. The dark red mixture was irradiated with two 200 W incandescent light bulbs and stirring was continued for 12 h. The lamps were switched off and the mixture was cooled in an ice bath. Next, 86 ml of MeOH was carefully added dropwise, which generated vapors. The orange mixture was allowed to stir for an additional 90 min. Finally, an excess of satd $NaHCO_3$ was added and stirred for 30 min. The reaction mixture was extracted

with AcOEt 3 times. The organic extract was washed successively with water (3 times), a saturated solution of $NaHCO_3$ (3 times), a saturated solution of $Na_2S_2O_3$ (3 times), and brine (1 time). The resulting organic solution was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure, producing 38.77 g of dimethyl 2,8-dibromononanedioate (98%). 3 g of this compound (374.0 g/mol; 8.02 mmol) was dissolved in 60 mL of MeOH/THF/H_2O 3:3:1 in a round bottom flask. 420 mg of $LiOH{\cdot}H_2O$ (lithium hydroxide monohydrate, CAS: 1310-66-3, 41.9 g/mol, 10 mmol) was added and the resulting solution was stirred at room temperature for 5 h. The pH of the solution was checked (basic) and AcOEt was added. The mixture was partitioned between water and AcOEt and the aqueous solution was extracted again with AcOEt. The aqueous solution was acidified with HCl 1 M and extracted three times with DCM. This organic solution was washed with brine, dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated to dryness. Flash chromatography (Hexanes/AcOEt 8:2) afforded 1.7 g of 2,8-dibromo-9-methoxy-9-oxononanoic acid (59%). 1.7 g of this acid (360.0 g/mol; 4.72 mmol) was dissolved in 30 mL of DMF and the resulting solution was heated at reflux (150 °C) for 12 h. An excess of water was added and the reaction mixture was allowed to cool to room temperature. An excess of AcOEt was then added to the reaction mixture. The organic extract was washed successively with water (5 times), a satd solution of $Na_2S_2O_3$, (3 times) and brine (1 time). The dark organic solution was dried with anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography (Hexanes/AcOEt 85:15) afforded 785 mg of (2*E*,7*E*)-9-methoxy-9-oxonona-2,7-dienoic acid (*E*,*E*)-**1a** (84%). Overall yield 58%, 3 steps. R_f = 0.39 (Hexanes/AcOEt, 1:1) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.03 (dt, *J* = 15.6 6.9 Hz, 1H, H3), 6.93 (dt, *J* = 15.6 7.0 Hz, 1H, H-7), 5.83 (d, *J* = 15.7, 2H, H-2 and H-8), 3.72 (s, 3H, CO_2CH_3), 2.25 (4H, H-4 and H-6), 1.654 (quintet, *J* = 7.3 Hz, 2H, H-5) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3 (s, C-1), 167.2 (s, C-9), 150.9 (d, C-7), 148.7 (d, C-3), 121.6 (d, C-8), 121.4 (d, C-2), 51.6 (q, $COCH_3$), 31.5 (d, C-6), 31.5 (d, C-4), 26.2 (d, C-5) ppm; HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{10}H_{14}O_4Na$, 221.0784; found, 221.0786, Δ = 0.76 ppm.

4.3. Methyl (*E*)-7-hydroxyhept-2-enoate (*E*)-1b

In a round bottom flask, 3.0 g of δ-valerolactone (100.0 g/mol; 30 mmol) was dissolved in 10 mL of dry THF. The flask was sealed, purged with Ar, and cooled to −78 °C in a CO_2–acetone bath. Next 24 mL of DIBAL-H (diisobutylaluminum hydride, CAS: 1191-15-7, 142.2 g/mol, 36 mmol, 1.5 M toluene solution) were added and the reaction was magnetically stirred for 90 min. In a pear-shaped flask, 7.56 g of methyl diethylphosphonoacetate (CAS: 1067-74-9, 210.1 g/mol, 0.036 mmol) was dissolved in 24 mL of dry THF. This flask was sealed, purged with Ar and cooled at −78 °C. Next, 22.5 mL of *n*BuLi (*n*-butyllithium, CAS: 109-72-8, 64.1 g/mol, 45 mmol) was added, turning the solution yellowish. The solution was stirred 15 min at −78 °C, then warmed to 0 °C in an ice bath for 30 min and finally to −78 °C for 15 min. The yellowish solution was added dropwise over the reaction mixture. Once the addition was finished, the resulting mixture was magnetically stirred for 4 h at −78 °C. Then, the flask was allowed to warm to room temperature and stirred for 20 h more. Finally, the reaction was quenched with a saturated solution of sodium-potassium tartrate. 60 min later, the reaction mixture was extracted with AcOEt (3 times). The organic layers were combined and washed with satd $NaHCO_3$ (3 times) and brine (1 time). The AcOEt washed solution was dried with anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 1.509 g of ester **1b** (Hexanes/AcOEt 98:2, 64% yield). R_f = 0.46 (Hexanes/AcOEt, 1:1); IR (neat): ν_{max} = 3367 (O–H), 2937 (C–H), 1718 (C=O), 1436, 1201 (C–O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.95 (dt, *J* = 15.5 and 6.8 Hz, 1H, H-3), 5.81 (d, *J* = 15.7 Hz, 1H, H-2), 3.70 (s, 1H, CO_2CH_3), 3.63 (t, *J* = 5.7 Hz, 2H, H-7), 2.22 (q, *J* = 6.7 Hz, 2H, H-4), 1.87 (br s, 1H, OH), 1.60–1.52 (4H, H-5 and H-6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3 (s, C-1), 149.5 (d, C-3), 121.2 (d, C-2), 62.4 (t, C-7), 51.6 (s, CO_2CH_3), 32.2 (t, C-6), 32.0 (t, C-4), 24.4 (t, C-5) ppm; HRMS (ESI): *m*/*z* (M+Na) calcd for $C_8H_{14}O_3Na$, 181.0835; found, 181.0840, Δ = −2.76 ppm.

4.4. Methyl (*E*)-7-hydroxyhept-2-enoate (*E*)-1b

In a round bottom flask, 3.84 g of 3,4-dihydro-2*H*-pyran was suspended in water. Next, 0.4 mL of HCl 1 M was added and the reaction was stirred at room temperature for 3 h, after which 7.62 g of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.055 mmol), 11.6 g of methyl diethylphosphonoacetate (CAS: 1067-74-9, 210.1 g/mol, 0.055 mmol) and 16 mL of DMSO were added. The reaction mixture was sealed, the inner atmosphere was replaced by inert gas and stirred at 50 °C overnight. The reaction mixture was extracted with AcOEt (3 times) and the organic solution was dried with anhydrous Na_2SO_4 and filtered through a paper filter. Solvent removal under reduced pressure and flash chromatography afforded 4.868 g of ester **1b** (Hexanes/AcOEt 98:2, 68% yield).

4.5. Di(pentan-3-yl) (2*E*,8*Z*)-deca-2,8-dienedioate (*E*,*Z*)-1c and di(pentan-3-yl) (2*E*,8*E*)-deca-2,8-dienedioate (*E*,*E*)-1d

In a two-necked round bottom flask provided with a condenser, 3 g of sebacic acid (CAS: 111-20-6, 202.2 g/mol, 14.8 mmol) was placed together with 4.7 mL of $SOCl_2$ (thionyl chloride, CAS: 7719-09-7, 118.9 g/mol, 61 mmol). The second neck was sealed and the suspension was magnetically stirred and heated at reflux (75 °C) for 90 min. The solids were gradually dissolved. After 90 min, the reaction was cooled to room temperature and a dropping funnel filled with Br_2 (bromine, CAS: 7726-95-6, 159.8 g/mol) was placed in the second neck. 2.4 mL of Br_2 (46.5 mmol) were added dropwise. The dark red mixture was irradiated with two 200 W incandescent light bulbs and stirring was continued for 12 h. The lamps were switched off and the mixture was cooled in an ice bath. Next, 19 ml of 3-pentanol was carefully added dropwise, generating vapors. The orange mixture was allowed to stir for an additional 90 min. Finally, an excess of satd $NaHCO_3$ was added and stirred for 30 min. The reaction mixture was extracted with AcOEt 3 times. The organic extract was washed successively with water (3 times), a saturated solution of $NaHCO_3$ (3 times), a saturated solution of $Na_2S_2O_3$ (3 times), and brine (1 time). The resulting organic solution was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure, producing 9.0 g of di-3-pentyl 2,9-dibromonodecadioate (99%). Next 5.02 g of this product (500.3 g/mol; 10.0 mmol) was dissolved in 20 mL of DMF and the resulting solution was heated under reflux (150 °C) for 12 h. An excess of water was added and the reaction mixture was allowed to cool to room temperature. An excess of AcOEt was then added to the reaction mixture. The organic extract was washed successively with water (5 times), a satd solution of $Na_2S_2O_3$ (3 times) and brine (1 time). The dark organic solution was dried with anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography (Hexanes/AcOEt 97:3) afforded 198.4 mg of di(pentan-3-yl) (2*E*,8*Z*)-deca-2,8-dienedioate (*E*,*Z*)-**1c** (3.2%) and 2.20 g of di(pentan-3-yl) (2*E*,8*E*)-deca-2,8-dienedioate (*E*,*E*)-**1d** (65%).

(*E*,*Z*)-**1c**: R_f = 0.64 (Hexanes/ether, 7:3; ×2); IR (neat): ν_{max} = 2971 (C–H), 1715 (C=O), 1416, 1267 (C–O), 982 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.94 (dt, *J* = 15.6 and 7.0 Hz, 1H, H-3),

6.18 (dt, J = 11.8 and 7.5 Hz, 1H, H-8), 5.81 (d, J = 15.6, 1H, H-2), 5.78 (d, J = 11.8 Hz, 1H, H-9), 4.79 (m, 2H, $CH(CH_2CH_3)_2$), 2.68–2.65 (m, 2H, H-4), 2.24–2.16 (m, 2H, H-7), 1.60–1.50 (4H, H-5 and H-6), 1.58 (q, J = 7.5 Hz, 8H, $CH(CH_2CH_3)_2$), 0.88 (t, J = 7.5 Hz, 12H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4 (s, C-1), 166.2 (s, C-10), 149.0 (d, C-3), 148.3 (d, C-8), 121.8 (t, C-2), 120.5 (t, C-9), 76.4 (d, $CH(CH_2CH_3)$), 76.3 (d, $CH(CH_2CH_3)$), 31.8 (t, C-4), 28.5 (2×t, C-5 and C-6), 27.6 (t, C-7), 26.4 (4×t, $CH(CH_2CH_3)_2$), 9.5 (4×q, $CH(CH_2CH_3)_2$) ppm; HRMS (EI): m/z (%): 251 (20), 198 (22), 181 (100), 182 (22), 135 25) 107 (30).

(*E*,*E*)-**1d**: R_f = 0.57 (Hexanes/ether, 7:3; ×2); IR (neat): ν_{max} = 2880 (C–H), 1727 (C=O), 1462, 1267 (C–O), 1034 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.93 (dt, J = 15.6 and 6.6 Hz, 2H, H-3 and H-8), 5.82 (d, J = 15.6 Hz, 1H, H-2 and H-9), 4.81 (q, J = 7.4 Hz, 2H, $CH(CH_2CH_3)_2$), 2.21 (m, 4H, H-4 and H-7), 1.55 (q, J = 7.4 Hz, 8H, $CH(CH_2CH_3)_2$), 1.50 (m, 4H, H-5 and H-6), 0.88 (t, J = 7.4 Hz, 12H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.0 (s, C-1 and C-10), 147.7 (d, C-3 and C-8), 122.0 (t, C-2 and C-9), 76.1 (2×d, $CH(CH_2CH_3)$), 31.6 (t, C-4 and C-7), 27.5 (2×t, C-5 and C-6), 26.4 (4×t, $CH(CH_2CH_3)_2$), 9.3 (4×q, $CH(CH_2CH_3)_2$). HRMS (ESI): m/z (M+H) calcd for $C_{20}H_{35}O_4$, 339.4880; found, 339.4877, Δ = 0.88 ppm.

4.6. (*R*,*E*)-7-(Benzyl((*R*)-1-phenylethyl)amino)-9-methoxy-9-oxonon-2-enoic acid 2[22b]

At first, 468 mg of **1a** (198.1 g/mol; 2.3 mmol) was dissolved in 10 mL of dry THF in a round bottom flask. The flask was sealed, purged with Ar, and cooled to −78 °C in a CO_2–acetone bath. In a second pear-shaped flask, 1.89 g of (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine (CAS: 38235-77-7, viscous light yellow oil, 211.3 g/mol, 8.9 mmol) was dissolved in 10 mL of dry THF. This one was also sealed, purged with Ar, and cooled to −78 °C. Once cooled, 5.3 mL of *n*BuLi (*n*-buthyllithium, CAS: 109-72-8, 64.1 g/mol, 8.51 mmol, 1.6 M solution) was added dropwise, turning the solution from colorless to a dark pink. The solution was stirred for 15 min at −78 °C, warmed to 0 °C in an ice bath along 30 min, and finally to −78 °C again for 15 min. The pink solution was added dropwise over the substrate solution and the resulting mixture turned orange. Once the addition was finished, the resulting mixture was magnetically stirred for 3 h before quenching with an excess of satd NH_4Cl. The solution turned from orange to yellow with precipitate. After 60 min, the yellow reaction mixture was extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). The AcOEt washed solution was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure affording a crude yellowish oil. This crude was redissolved in DCM, washed 3 times with a 10% citric acid (3 times), and dried again with anhydrous Na_2SO_4. Final filtration and solvent removal led to a viscous yellowish oil. Flash chromatography afforded 814 mg of product **3** (Hexanes/AcOEt 9:1, 84% yield). R_f = 0.61 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +4.6 (*c* 1.6, $CHCl_3$); IR (film): ν_{max} = 2926 (C–H), 1732 (C=O), 1688 (C=O, 1452 (C–N), 1299, 1145 (C–O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.26 (10H, $C_{ar}H$), 7.05 (dt, J = 15.5 7.1 Hz, 1H, H3), 5.83 (d, J = 15.7 Hz, 1H, H2), 3.84 (q, J = 7.0 Hz, 1H, $CH(CH_3)$), 3.80 (AB, J_{AB} = 15.0 Hz, 1H, NCH_AH), 3.57–3.50 (4H, CO_2CH_3 and $NCHH_B$), 3.35–3.25 (1H, m, H-7), 2.20–2.01 (6H, H-4, H-6 and H-8), 1.63–1.48 (2H, H-5), 1.35 (d, J = 7.0 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3 (s, C-1), 172.0 (s, C-9), 152.2 (d, C-3), 143.2 (s, C_{ipso}), 141.6 (s, C_{ipso}), 128.5 (d, C_{ar}), 128.4 (d, C_{ar}), 128.1 (d, C_{ar}), 127.3 (d, C_{ar}), 126.9 (d, C_{ar}), 121.0 (d, C-2), 58.3 (d, $CHCH_3$), 53.8 (d, C-7), 51.7 (s, CO_2CH_3), 50.2 (t, CH_2C_{ar}), 36.4 (t, C-8), 33.2 (t, C-4), 32.3 (t, C-6), 25.4 (t, C-5), 20.2 (q, $CHCH_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{25}H_{31}NO_4$, 410.2331; found, 410.2325, Δ = −0.98 ppm.

4.7. Dimethyl (*R*,*E*)-7-(benzyl((*R*)-1-phenylethyl)amino)non-2-enedioate 3[22b]

In a round bottom flask, 529 mg of acid **2** (410 g/mol; 1.29 mmol) was dissolved in 20 mL of toluene/MeOH 1:1. The flask was sealed and purged with Ar and cooled to 0 °C in an ice bath. Next, 0.97 mL of $TMSCHN_2$ ((trimethylsilyl)diazomethane solution, CAS: 18107-18-1, 114.2 g/mol, 1.9 mmol, 2.0 M solution) was added through syringe and the light yellow reaction solution was magnetically stirred for 5 min at 0 °C, after which it was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure, affording 508 mg of product **3**, 93% yield. R_f = 0.85 (Hexanes/AcOEt, 1:1) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.41–6.93 (10H, $C_{ar}H$), 6.97 (dt, J = 15.6 6.8 Hz, 1H, H-3), 5.83 (dt, J = 15.6 1.4 Hz, 1H, H-2), 3.89–3.81 (2H, $CHCH_3$ and NCH_AH), 3.76–3.72 (4H, $CHCO_2CH_3$ and $NCHH_B$), 3.56 (s, 3H, $CH_2CO_2CH_3$), 3.33 (m, 1H, H-7), 2.17–2.00 (6H, H-4, H-6 and H-8), 1.53 (2H, H-5), 1.34 (d, J = 7.1 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3 (s, C-1), 167.4 (s, C-9), 149.7 (d, C-3), 143.1 (s, C_{ipso}), 141.7 (s, C_{ipso}), 128.5 (d, C_{ar}), 128.4 (d, C_{ar}), 128.1 (d, C_{ar}), 127.3 (d, C_{ar}), 126.9 (d, C_{ar}), 121.0 (d, C-2), 58.1 (d, $CHCH_3$), 53.8 (d, C-7), 51.7 (q, CO_2CH_3), 51.6 (q, CO_2CH_3), 50.2 (t, CH_2C_{ar}), 36.4 (t, C-8), 33.2 (t, C-4), 32.3 (t, C-6), 25.6 (t, C-5), 20.2 (q, $CHCH_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{26}H_{34}NO_4$, 424.2487; found, 424.2475, Δ = 2.83 ppm. (M+Na) calcd for $C_{26}H_{33}NO_4Na$, 446.2307; found, 446.2287, Δ = 4.48 ppm.

4.8. Methyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-oxoheptanoate (4a) and (*R*)-5-(benzyl((*R*)-1-phenylethyl)amino)-7-methoxy-7-oxoheptanoic acid 4b

At first, 287 mg of diester **3** (424.4 g/mol; 0.68 mmol) was dissolved in 5 mL of dry DCM in a round bottom flask. Next, HCl gas (hydrogen chloride, CAS: 7647-01-0, 36.5 g/mol) was bubbled through a pipette for 10 min, while the reaction solution was cooled at −78 °C in a CO_2–acetone bath. Next, ozone (O_3, gas, generated in situ) was bubbled for 15 min until the solution turned light blue. Finally, 1.5 mL of H_2O_2 (hydrogen peroxide, CAS: 7722-84-1, 34.0 g/mol, 13.6 mmol, 30% solution) was added and the reaction was allowed to warm to room temperature. Next, 5 mL of 1 M NaOH was added, which caused the reaction mixture to turn white. After 15 min of stirring, the reaction was extracted with DCM (3 times). The organic solution was washed once with brine. Drying the solution over anhydrous Na_2SO_4, filtration and solvent removal under reduced pressure, afforded the acid. Flash chromatography afforded 72 mg of aldehyde **4a** (Hexanes/AcOEt 9:1, 29% yield), and 80 mg of acid **4b** (Hexanes/AcOEt 7:3, 31% yield).

Compound ***4a***:[22b] R_f = 0.83 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +12.5 (*c* 0.4, $CHCl_3$); IR (neat): ν_{max} = 2933 (C–H), 1734 (C=O, ester), 1701 (C=O, acid), 1201 (C–O), 1155 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 9.71 (t, J = 1.6 Hz, 1H, H-7), 7.43–7.21 (10H, $C_{ar}H$), 3.84–3.70 (2H, $CHCH_3$ and NCH_AH), 3.55–3.50 (4H, $NCHH_B$ and CO_2CH_3), 3.33 (m, 1H, H-5), 2.33 (td, J = 7.1 1.6 Hz, 2H, H-6), 2.08–1.92 (m, 2H, H-2), 1.67–1.47 (4H, H-3 and H-4), 1.36 (d, J = 6.9 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.8 (s, C-7), 173.4 (s, C-1), 143.2 (s, C_{ipso}), 141.7 (s, C_{ipso}), 128.5 (d, C_{ar}), 128.4 (d, C_{ar}), 128.3 (d, C_{ar}), 128.1 (d, C_{ar}), 127.3 (d, C_{ar}), 127.0 (d, C_{ar}), 58.2 (d, $CHCH_3$), 53.7 (d, C-5), 51.7 (q, CO_2CH_3), 50.2 (t, NCH_2), 43.8 (t, C-6), 36.2 (t, C-2), 33.1 (t, C-4), 20.2 (q, $CHCH_3$), 19.6 (t, C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{23}H_{29}NO_3Na$, 390.2045; found, 390.2039, Δ = 1.54 ppm.

Compound ***4b***: R_f = 0.54 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +2.1 (*c* 3.36, $CHCl_3$); IR (neat): ν_{max} = 2933 (C–H), 1734 (C=O, ester), 1701 (C=O, acid), 1201 (C–O), 1155 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ = 7.44–7.22 (10H, CarH), 3.84 (q, J = 6.9 Hz, 1H, $CHCH_3$), 3.78 (AB, J_{AB} = 14.6 Hz, 1H, NCH_AH), 3.57–3.53 (4H, $NCHH_B$ and CO_2CH_3), 3.33 (m, 1H, H-5), 2.29 (m, 2H, H-6), 2.08–1.92 (2H, H-2), 1.74–1.53 (4H, H-3 and H-4), 1.36 (d, J = 6.9 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.3 (s, C-7), 173.1 (s, C-1), 142.8 (s, C_{ipso}), 141.3 (s, C_{ipso}), 128.2 (d, C_{ar}), 128.2 (d, C_{ar}), 128.1 (d, C_{ar}), 127.8 (d, C_{ar}), 126.9 (d, C_{ar}), 126.7 (d, C_{ar}), 57.7 (d, $CHCH_3$), 53.5 (d, C-5), 51.4 (q, CO_2CH_3), 49.9 (t, NCH_2), 36.3 (t, C-6), 33.8 (t, C-2), 32.8 (t, C-4), 22.1 (t, C-3), 19.6 (q, $CHCH_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{23}H_{30}NO_4$, 384.2175; found, 384.2190, Δ = −3.90 ppm.

4.9. (*R*)-5-(Benzyl((*R*)-1-phenylethyl)amino)-7-methoxy-7-oxoheptanoic acid 4b

At first, 72 mg of aldehyde **4a** (367.2 g/mol; 0.19 mmol) and 0.5 mL of 2-methyl-2-butene (CAS: 513-35-9, 70.1 g/mol, 5.9 mmol) were dissolved in 5 mL of *t*BuOH. The flask was sealed and purged with Ar. An aqueous solution consisting of 26 mg of $NaClO_2$ (sodium chlorite, CAS: 7758-19-2, 90.4 g/mol, 0.29 mmol) and 30 mg of $NaH_2PO_4{\cdot}H_2O$ (sodium phosphate monobasic monohydrate, CAS: 10049-21-5, 137.9 g/mol, 0.22 mmol) in 5 mL of H_2O was added, and the resulting solution was stirred for one hour. The solvent was removed under reduced pressure. Next, H_2O was added and the solution was acidulated until pH = 2. The aqueous solution was extracted with AcOEt (3 times). The organic solution was washed with H_2O 2 times. Drying the solution over anhydrous Na_2SO_4, filtration and forward solvent removal under reduced pressure, afforded 66 mg of acid **4b**, 88% yield.

4.10. 7-(*tert*-Butyl) 1-methyl (R)-3-(benzyl((*R*)-1-phenylethyl)-amino)heptanedioate 5

At first, 2.128 g of acid **4b** (383.7 g/mol; 5.55 mmol) was dissolved in 20 mL of *t*BuOH in a round bottom flask, together with 2.6 g of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.3 g/mol, 11.7 mmol). Next 204 mg of DMAP (4-(dimethylamino)pyridine, CAS: 1122-58-3, 122.2 g/mol, 1.7 mmol) was added and the reaction mixture was stirred at 30 °C for 2 d, with a $CaCl_2$ tube as desiccant seal. Solvent removal afforded the *tert*-butyl ester and flash chromatography afforded 1.99 g of ester **5** (Hexanes/AcOEt 95:5, 82% yield). R_f 0.83 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +9.8 (*c* 0.6, $CHCl_3$); IR (neat): ν_{max} = 2974 (C–H), 1730 (C=O), 1450, 1367, 1151 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.24 (10H, $C_{ar}H$), 3.86 (q, J = 7.0 Hz, 1H, $CHCH_3$), 3.80 (AB, J_{AB} = 14.7 Hz, 1H, NCH_AH), 3.57 (AB, J_{AB} = 14.7 Hz, 1H, $NCHH_B$), 3.55 (s, 3H, CO_2CH_3), 3.36–3.30 (m, 1H, H-3), 2.17 (td, J = 7.0 Hz and 1.9, 2H, H-2), 2.05 (t, J = 7.9 Hz, 2H, H-6), 1.69–1.51 (4H, H-4 and H-5), 1.46 (s, 9H, $CO_2C(CH_3)_3$), 1.37 (d, J = 7.0 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3 (s, C-7), 173.2 (s, C-1), 143.1 (s, C_{ipso}), 141.6 (s, C_{ipso}), 128.5 (d, C_{ar}), 128.3 (d, C_{ar}), 127.1 (d, C_{ar}), 126.9 (d, C_{ar}), 80.1 (s, $C(CH_3)_3$), 57.8 (d, $CHCH_3$), 53.8 (d, C-3), 51.6 (q, CO_2CH_3), 50.1 (t, NCH_2), 36.7 (t, C-2), 35.7 (t, C-6), 33.0 (t, C-4), 28.3 (q, $C(CH_3)_3$), 22.9 (q, $CHCH_3$), 19.6 (t, C-5) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{27}H_{38}NO_4$, 440.2801; found, 440.2805, Δ = −0.93 ppm.

4.11. 7-(*tert*-Butyl) 1-methyl (*R*)-3-((*tert*-butoxycarbonyl)-amino)heptanedioate 6

At first, 356 mg of protected substrate **5** (439.0 g/mol, 0.812 mmol) and 568 mg of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.3 g/mol, 2.6 mmol) were dissolved in 3 mL of dry AcOEt. Next, 120 mg of $Pd(OH)_2$ on carbon (palladium hydroxide on carbon 20% wet, Perlman's catalyst, CAS: 12135-22-7, 140.4 g/mol) were added, and the mixture was placed in a 5 mL pressure flask. The flask was connected to an H_2 gas line and the pressure was adjusted to 3.4 atm. The flask was mechanically stirred for 2 days. The flask was pressurized to atmospheric conditions and the mixture was filtered through a pad of Celite®, and washed with AcOEt and DCM. The solvents were removed under reduced pressure, affording 297 mg of carbamate **6** after flash chromatography (Hexanes/AcOEt 95:5, 83% yield). R_f = 0.90 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +15.3 (*c* 1.8, $CHCl_3$); IR (neat): ν_{max} = 3367 (N–H), 2978 (C–H), 1734 (C=O), 1367, 1165 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (d, J = 7.9 Hz, 1H, NH), 3.89 (1H, H-3), 3.67 (s, 3H, CO_2CH_3), 2.51 (d, J = 5.1 Hz, 2H, H-2), 2.22 (td, J = 7.1 and 2.7 Hz, 2H, H-6), 1.70–1.49 (4H, H-4 and H-5), 1.43 (9H, s, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (s, C-7), 172.2 (s, C-1), 155.5 (s, NCOO), 80.4 (s, $CO_2C(CH_3)_3$), 79.5 (s, $NCO_2C(CH_3)_3$), 51.8 (q, CO_2CH_3), 47.5 (d, C-3), 39.3 (t, C-2), 35.2 (t, C-6), 34.1 (t, C-4), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.8 (t, C-5) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{17}H_{31}NO_6Na$, 368.2043; found, 368.2025, Δ = −5.0 ppm.

4.12. tert-Butyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7-hydroxyheptanoate 7a

A 2 M solution of $LiBH_4$ was prepared in the next manner: 217.8 mg of $LiBH_4$ (lithium borohydride, CAS: 16949-15-8, 21.8 g/mol) was dissolved in 5 mL of dry THF in a 5 mL volumetric flask. The solution was shaken and sonicated for 5 min, until the solids were dissolved. Next 167 mg of ester **6** was dissolved in 2 mL of dry THF, sealed, and the atmosphere was replaced by inert gas. Next, 2 mL of 2 M lithium borohydride solution was added through a syringe, and the reaction mixture was stirred for 6 h after which 1 mL of a saturated solution of NH_4Cl was added, and stirring was continued until gas generation ceased. The reaction mixture was extracted with AcOEt 3 times. The organic layer was washed with brine (1 time) and dried over anhydrous Na_2SO_4. Filtration and solvent removal under reduced pressure, afforded 138 mg of alcohol **7a**, 90% yield. R_f = 0.64 (Hexanes/AcOEt, 4:1); $[\alpha]_D^{20}$ = +9.8 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} = 3367 (O-H), 2931 (C–H), 1707 (C=O), 1365, 1168 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (d, J = 9.1 Hz, 1H, NH), 3.81–3.69 (1H, H-5), 3.68–3.58 (2H, H-7), 2.23 (td, J = 7.5 and 4.8 Hz, 2H, H-2), 1.87–1.47 (6H, H-3, H-4 and H-6), 1.44 (9H, s, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0 (s, C-1), 157.4 (s, NCOO), 80.5 (s, $CO_2C(CH_3)_3$), 80.1 (s, $NCO_2C(CH_3)_3$), 58.9 (t, C-7), 47.3 (d, C-5), 39.3 (t, C-6), 35.3 (t, C-2), 35.1 (t, C-4), 28.6 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.7 (t, C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{16}H_{31}NO_5Na$, 340.2094; found, 340.2102, Δ = 2.22 ppm.

4.13. *tert*-Butyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7- ((methylsulfonyl)oxy)heptanoate 7b

At first, 74 μL of pyridine and 2.82 mg of DMAP (4-(dimethylamino)pyridine, CAS: 1122-58-3, 122.2 g/mol, 0.023 mmol) were added to a round bottom flask with 89 mg of alcohol **7a** (395.0 g/mol; 0.23 mmol) in 5 mL of dry DCM. The flask was sealed and the inner atmosphere was replaced with Ar. Next, 44 μL of MsCl (methanesulfonyl chloride, CAS: 124-63-0, 114.6 g/mol, 0.68 mmol) was added through syringe and the reaction mixture was magnetically stirred at room temperature for 12 h. An excess of satd K_2CO_3 was added dropwise with vigorous bubbling, and stirring was continued for an extra hour. The reaction mixture was extracted with AcOEt (3 times) and the organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution with anhydrous Na_2SO_4, filtration, and solvent removal under reduced pressure, afforded 102 mg of mesylate **7b**, 96% yield. R_f = 0.69 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −1.0 (*c* 2.2,

$CHCl_3$); IR (neat): ν_{max} = 3375 (N–H), 2976 (C–H), 1701 (C=O), 1174 (S=O), 974 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 4.39 (d, J = 8.0 Hz, 1H, NH), 4.27 (t, J = 6.4 Hz, 2H, H-7), 3.71 (1H, H-5), 3.03 (s, 3H, OSO_2CH_3), 2.23 (td, J = 6.9 and 1.8 Hz, 2H, H-2), 2.03–1.51 (6H, H-3, H-4 and H-6), 1.43 (s, 18H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8 (s, C-1), 155.8 (s, NCOO), 80.5 (s, $CO_2C(CH_3)_3$), 79.4 (s, $NCO_2C(CH_3)_3$), 67.4 (t, C-7), 47.5 (d, C-5), 37.4 (q, OSO_2CH_3), 35.2 (t, C-6), 35.1 (t, C-2), 35.0 (t, C-4), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.5 (t, C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{17}H_{33}NO_7NaS$, 418.1869; found, 418.1865, Δ = −1.18 ppm.

4.14. Methyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-hydroxyheptanoate 8

At first, 1.48 g of **1b** (158.0 g/mol; 9.37 mmol) was dissolved in 60 mL of dry THF in a round bottom flask. The flask was sealed, purged with Ar, and cooled to −78 °C in am CO_2–acetone bath. In a second pear-shaped flask, 7.18 g of (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine (CAS: 38235-77-7, 211.3 g/mol, 34 mmol) was dissolved in 60 mL of dry THF. This one was also sealed, purged with Ar and cooled to −78 °C. Once cooled, 16 mL of *n*BuLi (*n*-buthyllithium, CAS: 109-72-8, 64.1 g/mol, 32 mmol, 1.6 M solution) was added dropwise, turning the solution from colorless to a dark pink. The solution was stirred for 15 min at −78 °C, warmed to 0 °C in an ice bath for 30 min and finally to −78 °C again for min. The pink solution was added dropwise over the substrate solution and the resulting mixture turned orange. Once the addition was finished, the resulting mixture was magnetically stirred for 3 h before quenching with an excess of satd NH_4Cl. The solution turned from orange to yellow with precipitate. After 60 min, the yellow reaction mixture was extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). The AcOEt washed solution was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure affording a crude yellowish oil. This crude was redissolved in DCM, washed 3 times with a 10% citric acid (3 times) ,and dried again with anhydrous Na_2SO_4. Final filtration and solvent removal lead to a viscous yellowish oil. Flash chromatography afforded 2.66 g of product **2** (Hexanes/AcOEt 9:1, 77% yield). R_f = 0.55 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +8.1 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} = 3431 (O-H), 2933 (C–H), 1730 (C=O), 1450, 1155 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.22 (10H, $C_{ar}H$), 3.85 (q, J = 6.9 Hz, 1H, $CHCH_3$), 3.79 (AB, J_{AB} = 14.9 Hz, 1H, NCH_AH), 3.62 (t, J = 6.3 Hz, 3H, H-7), 3.59–3.55 (1H, $NCHH_B$), 3.55 (s, 3H, CO_2CH_3), 3.31 (m, 1H, H-3), 2.09 (ABX, J_{ABX} = 14.7 4.6 Hz, 1H, H-2_A), 2.03 (ABX, J_{ABX} = 14.6 and 8.3 Hz, 1H, H-2_B), 1.64–1.37 (6H, H-4, H-5 and H-6), 1.35 (d, J = 7.0 Hz, 3H, $CHCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5 (s, CO_2CH_3), 143.3 (s, C_{ipso}), 141.8 (s, C_{ipso}), 128.5 (d, C_{ar}), 128.4 (d, C_{ar}), 128.3 (d, C_{ar}), 128.1 (d, C_{ar}), 127.1 (d, C_{ar}), 126.9 (d, C_{ar}), 63.1 (t, C-7), 58.1 (d, $CHCH_3$), 54.0 (d, C-3), 51.6 (q, CO_2CH_3), 50.1 (t, NCH_2), 36.6 (t, C-2), 33.4 (t, C-6), 32.8 (t, C-4), 23.3 (t, C-5), 19.8 (q, $CHCH_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{23}H_{32}NO_3$, 370.2376; found, 370.2374, Δ = −0.73 ppm.

4.15. (*R*)-5-(Benzyl((*R*)-1-phenylethyl)amino)-7-methoxy-7-oxoheptanoic acid 4b

In a round bottom flask, 1.0 g of **8** (369.3 g/mol; 2.7 mmol) was dissolved in 10 mL of acetone. Jones reagent was then added until a red persisted. The reaction mixture was stirred for 30 min after which 10 mL of 2-propanol were added, turning the solution from dark red to dark green. The reaction mixture was extracted with AcOEt (3 times) and the organic layers were combined and washed with water (6 times). Drying the ethyl acetate solution over anhydrous Na_2SO_4, filtration through a paper filter and solvent removal under reduced pressure afforded a crude oil. Flash chromatography afforded 942 mg of product **4b** (Hexanes/AcOEt 8:2, 91% yield).

4.16. *tert*-Butyl (3-hydroxypropyl)carbamate 9a

In a round bottom flask, 1.00 g of 3-amino-1-propanol (CAS: 156-87-6, 75.1 g/mol, 13.3 mmol) was dissolved together with 3.17 g of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.3 g/mol, 13.3 mmol) in 20 mL of dry DCM. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with AcOEt, and the organic layer was washed with water (2 times), 1 M HCl (2 times), and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration and forward solvent removal under reduced pressure, afforded 2.12 g of protected amine **9a**, 91% yield. ^1H NMR (200 MHz; $CHCl_3$): δ = 4.96 (br s, 1H, NH), 3.62 (t, J = 5.6 Hz, 2H, H-3), 3.23 (q, J = 6.2 Hz, 2H, H-1), 3.06 (br s, 1H, OH), 1.63 (quintet, J = 6.2 Hz, 2H, H-2), 1.40 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz; $CHCl_3$): δ = 157.3 (s, NCOO), 79.7 (s, $C(CH_3)_3$), 59.4 (t, C-3), 37.1 (t, C-1), 32.9 (t, C-2), 28.5 (q, $C(CH_3)_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_8H_{18}NO_3$, 176.1281; found, 176.1288, Δ = −1.0 ppm.

4.17. 3-((*tert*-Butoxycarbonyl)amino)propyl methanesulfonate 9b

At first, 186 mg of pyridine and 7 mg of DMAP (4-(dimethylamino)pyridine, CAS: 1122-58-3, 122.2 g/mol, 0.059 mmol) were added to a round bottom flask with 100 mg of alcohol **9a** (175.0 g/mol; 0.57 mmol) in 5 mL of dry DCM. The flask was sealed and the inner atmosphere was replaced with Ar. Next 170 mg of MsCl (methanesulfonyl chloride, CAS: 124-63-0, 114.6 g/mol, 1.8 mmol) were added through syringe and the reaction mixture was magnetically stirred at room temperature for 12 h. An excess of satd K_2CO_3 was added dropwise, with a vigorous bubbling, and stirring was continued for an hour. The reaction mixture was extracted with AcOEt (3 times) and the organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration and solvent removal under reduced pressure, afforded 110 mg of mesylate **9b**, 75% yield. ^1H NMR (200 MHz; $CHCl_3$): δ = 4.78 (br s, 1H, NH), 4.28 (t, J = 6.0 Hz, 2H, H-1), 3.23 (2H, H-3), 3.02 (s, 3H, SO_2CH_3), 1.92 (quintet, J = 6.2 Hz, 2H, H-2), 1.42 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz; $CHCl_3$): δ = 156.2 (s, NCOO), 79.6 (s, $C(CH_3)_3$), 67.7 (t, C-1), 37.5 (q, SO_2CH_3), 36.9 (t, C-3), 29.8 (t, C-2), 28.5 (q, $C(CH_3)_3$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_9H_{19}NSO_5$, 254.1062; found, 254.1073, Δ = −4.33 ppm.

4.18. 1,3-Oxazinan-2-one 10c, Table 1-entry 1.3

In a round bottom flask, 90 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.652 mmol) was suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 80 mg of mesylate **9b** (253.0 g/mol; 0.32 mmol) and 39 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.097 mmol), were dissolved in 3 mL of dry DMF in round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. An excess of water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 9 mg of cyclic carbamate **10c**[32] (Hexanes/AcOEt 95:5, 29% yield) and 12 mg of starting material **9b** (Hexanes/AcOEt 9:1).

4.19. *tert*-Butyl (3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propyl)carbamate 10a, Table 1-entry 2

In a round bottom flask, 86 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.68 mmol) and 63 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.456 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 56 mg of mesylate **9b** (253.0 g/mol; 0.22 mmol) and 27 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.067 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 4 mg of cyclic carbamate **10c** (Hexanes/AcOEt 95:5, 18% yield) and 17 mg of product **10a** (Hexanes/AcOEt 9:1, 27%). R_f = 0.44 (Hexanes/AcOEt, 1:1) cm^{-1}; ^1H NMR (200 MHz; $CHCl_3$): δ = 9.15 (1H, br s, CONHCO), 7.04 (br s, 1H, NCH), 5.04 (br s, 1H, NH), 3.77 (t, J = 6.6 Hz, 2H, H-3), 3.23 (q, J = 6.1 Hz, 2H, H-1), 1.92 (s, 3H, CCH_3), 1.84 (quintet, J = 6.4 Hz, 2H, H-2), 1.43 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz; $CHCl_3$): δ = 164.5 (s, HNCOC), 156.3 (s, NCOO), 151.4 (s, NCON), 140.6 (d, CH), 111.2 (s, CCH_3), 79.7 (s, $C(CH_3)_3$), 45.9 (t, C-3), 37.2 (t, C-1), 29.7 (t, C-2), 28.6 (q, $C(CH_3)_3$), 12.5 (q, CCH_3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{13}H_{21}N_3O_4Na$, 306.1424; found, 306.1429, Δ = 1.5 ppm.

4.20. *tert*-Butyl (3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propyl)carbamate 10a, Table 1-entry 3

In a round bottom flask, 99 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.79 mmol) and 72 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.524 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 65 mg of mesylate **9b** (253.0 g/mol; 0.25 mmol) and 31 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.079 mmol), were dissolved in 3 mL of dry DMF in round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 2 mg of cyclic carbamate **10c** (Hexanes/AcOEt 95:5, 7% yield) and 9 mg of product **10a** (Hexanes/AcOEt 9:1, 12%).

4.21. *tert*-Butyl (3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propyl)carbamate 10a, Table 1-entry 4

In a round bottom flask, 71 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.56 mmol) and 52 mg of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, CAS: 6674-22-2, 152.2 g/mol, 0.341 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 46 mg of mesylate **9b** (253.0 g/mol; 0.18 mmol) and 22 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.056 mmol), were dissolved in 3 mL of dry DMF in round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 3.5 mg of cyclic carbamate **10c** (Hexanes/AcOEt 95:5, 19% yield) and 17 mg of product **10a** (Hexanes/AcOEt 9:1, 33%).

4.22. *tert*-Butyl (3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propyl)carbamate 10a, Table 1-entry 5

In a round bottom flask, 99 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.79 mmol) and 28 mg of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, CAS: 6674-22-2, 152.2 g/mol, 0.183 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 27 mg of mesylate **9b** (253.0 g/mol; 0.11 mmol) and 12 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.03 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 2 mg of product **10a** (Hexanes/AcOEt 9:1, 6%).

4.23. *tert*-Butyl (3-(6-chloro-9*H*-purin-9-yl)propyl)carbamate 10b, Table 1-entry 6

In a round bottom flask, 45 mg of 6-chloropurine (CAS: 87-42-3, 154.5 g/mol, 0.292 mmol) and 40 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.292 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 60 mg of mesylate **9b** (253.0 g/mol; 0.24 mmol) and 29 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.072 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 2 mg of cyclic carbamate **10c** (Hexanes/AcOEt 95:5, 9% yield) and 18 mg of product **10b** (Hexanes/AcOEt 7:3, 25%). R_f = 0.09 (Hexanes/AcOEt, 1:1); IR (neat): ν_{max} = 3329 (N–H), 2976 (C–H), 1695 (C=O), 1654, 1595, 1170 (C–O) cm^{-1}; ^1H NMR (200 MHz; $CHCl_3$): δ = 8.77 (s, 1H, CH_2NCHN), 8.26 (1H, br s, NCHNCCl), 5.00 (br s, 1H, NH), 4.37 (t, J = 6.7 Hz, 2H, H-3), 3.13 (q, J = 6.0 Hz, 2H, H-1), 2.10 (quintet, J = 6.4 Hz, 2H, H-2), 1.45 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz; $CHCl_3$): δ = 156.3 (NCOO), 152.1 (CCl), 152.0 (NCHNCCl), 151.3 (CH_2NCN), 145.8 (CH_2NCHN), 131.8 (NCCCl), 79.9 ($C(CH_3)_3$), 42.0 (C-3), 37.4 (C-1), 30.7 (C-2), 28.5 ($C(CH_3)_3$) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{13}H_{18}N_5O_2ClNa$, 334.1041; found, 334.1046, Δ = 1.4 ppm.

4.24. *tert*-Butyl (3-(6-chloro-9*H*-purin-9-yl)propyl)carbamate 10b, Table 1-entry 7

In a round bottom flask, 86 mg of 6-chloropurine (CAS: 87-42-3, 154.5 g/mol, 0.558 mmol) and 51 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.372 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 46 mg of mesylate **9b** (253.0 g/mol; 0.18 mmol) and 22 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.055 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5

times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 2 mg of cyclic carbamate **10c** (Hexanes/AcOEt 95:5, 11% yield) and 11 mg of product **10b** (Hexanes/AcOEt 7:3, 20%).

4.25. *tert*-Butyl (3-(6-chloro-9*H*-purin-9-yl)propyl)carbamate 10b, Table 1-entry 8

In a round bottom flask, 100 mg of alcohol **9a** (175.0 g/mol; 0.57 mmol), 143 mg of PBu_3 (tributylphosphine, CAS: 998-40-3, 202.3 g/mol, 0.71 mmol), 143 mg of DIAD (diisopropyl azodicarboxylate, CAS: 2446-83-5, 202.2 g/mol) and 109 mg of 6-chloropurine (CAS: 87-42-3, 154.5 g/mol, 0.71 mmol) were dissolved in 4 mL of dry THF. After sealing the flask and replacing the inner atmosphere with Ar, the reaction mixture was magnetically stirred at room temperature 48 h. Excess water was added to the reaction mixture and then extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration, and solvent removal under reduced pressure, afforded a crude oil. Flash chromatography afforded 101 mg of product **10b** (Hexanes/AcOEt 7:3, 68% yield).

4.26. Mixture of 11e regioisomers N^1/N^3-11e, Table 2-entry 1

In a round bottom flask, 98 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.77 mmol) and 72 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.518 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred for 1 h at 70 °C. Separately, 102 mg of mesylate **7b** (395.0 g/mol; 0.26 mmol) and 31 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.078 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 23 mg of cyclic carbamate **11c** (Hexanes/AcOEt 9:1, 37%) and 38 mg of a 1:1 PNA regioisomers mixture N^1/N^3-**11d** (Hexanes/AcOEt 7:3, 35%).

Compound ***11c****:* R_f = 0.90 (Hexanes/AcOEt, 1:1); IR (neat): ν_{max} = 3253 (N–H), 2927 (C–H), 1718 (C=O), 1363, 1153 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.43 (s, 1H, NH), 4.33 (dt, J = 11.2 4.3 Hz, 1H, CH_AHO), 4.33 (td, J = 11.2 and 2.7 Hz, 1H, CHH_BO), 3.47 (quintet, J = 5.6 Hz, 1H, CHN), 2.25 (td, J = 6.8 2.8 Hz, 2H, H-2), 2.02 (1H, CH_AHCH_2O), 1.75–1.49 (5H, H-3, H-4 and CHH_BCH_2O), 1.44 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (C-1), 154.2 (NCOO), 80.9 ($C(CH_3)_3$), 65.8 (CH_2O), 50.9 (CHN), 36.1 (C-2), 35.2 (C-4), 28.4 ($C(CH_3)_3$), 27.5 (t, CH_2CH_2O), 20.9 (C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{12}H_{21}NO_4Na$, 266.1362; found, 266.1356, Δ = −2.55 ppm.

4.27. *tert*-Butyl (*R*)-7-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((*tert*-butoxycarbonyl)amino)-heptanoate 11d, Table 2-entry 2

In a round bottom flask, 113 mg of N^3-benzoyl-thymine[31] (230.2 g/mol, 0.492 mmol)2 and 45 mg of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, CAS: 6674-22-2, 152.2 g/mol, 0.328 mmol) were suspended in 5 mL of dry DMF. This mixture was stirred 1 h at 70 °C. Separately, 64 mg of mesylate **7b** (395.0 g/mol; 0.164 mmol) and 19 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.37 g/mol, 0.049 mmol), were dissolved in 3 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 12 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 20 mg of product **11d** (Hexanes/AcOEt 75:25, 23%). R_f = 0.55 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −16.8 (c 1.0, MeOH); IR (neat): ν_{max} = 3354 (N–H), 2976 (C–H), 1701 (C=O), 1647, 1251 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, J = 8.5 and 1.2 Hz, 2H, o-$C_{ar}H$), 7.63 (tt, J = 7.4 and 1.6 Hz, 1H, p-$C_{ar}H$), 7.63 (t, J = 7.4 Hz, 1H, m-$C_{ar}H$), 7.23 (br s, 1H, NCH), 4.43 (d, J = 9.1 Hz, 1H, NH), 3.93 (1H, H-7_A), 3.61 (2H, H-5 and H-7_B), 2.21 (q, J = 6.3 Hz, 2H, H2), 1.95 (s, 3H, CCH_3), 1.91 (1H, H-4_A), 1.74–1.37 (5H, H-3, H-4_B and H-6), 1.44 (s, 18H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8 (s, C-1), 169.3 ($NCOC_{ar}$), 163.4 (s, NCO), 156.0 (s, NCOO), 150.0 (s, NCON), 141.0 (d, NCH), 135.1 (d, p-C_{ar}), 131.9 (s, C_{ipso}), 130.6 (d, o-C_{ar}), 129.3 (d, m-C_{ar}), 110.8 (s, CCH_3), 80.5 (s, $CO_2C(CH_3)_3$), 79.8 (s, $NCO_2C(CH_3)_3$), 48.4 (d, C-5), 46.8 (t, C-7), 35.2 (t, C-2), 35.1 (t, C-4), 34.9 (t, C-6), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.5 (t, C-3), 12.6 (q, CCH3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{28}H_{39}N_3O_7Na$, 552.2680; found, 552.2695, Δ = 2.67 ppm.

4.28. *tert*-Butyl (*R*)-7-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((*tert*-butoxycarbonyl)amino)-heptanoate 11d, Table 2-entry 3

In a round bottom flask, 46 mg of alcohol **7a** (395.0 g/mol; 0.118 mmol), 52 mg of PBu_3 (tributylphosphine, CAS: 998-40-3, 202.3 g/mol, 0.261 mmol), 52 mg of DIAD (diisopropyl azodicarboxylate, CAS: 2446-83-5, 202.2 g/mol, 0.261 mmol), and 60 mg of N^3-benzoyl-thymine[31] (230.2 g/mol, 0.261 mmol)2 were dissolved in 4 mL of dry THF. After sealing the flask and replacing the inner atmosphere with Ar, the reaction mixture was magnetically stirred at room temperature 48 h. Excess water was added to the reaction mixture and then extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration, and solvent removal under reduced pressure, afforded a crude oil. Flash chromatography afforded 47 mg of product **11d** (Hexanes/AcOEt 75:25, 75% yield).

4.29. *tert*-Butyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7-(6-chloro-9*H*-purin-9-yl)heptanoate 11a, Table 2-entry 4

In a round bottom flask, 39 mg of alcohol **7a** (395.0 g/mol; 0.099 mmol), 44 mg of PBu_3 (tributylphosphine, CAS: 998-40-3, 202.3 g/mol, 0.22 mmol), 44 mg of DIAD (diisopropyl azodicarboxylate, CAS: 2446-83-5, 202.2 g/mol, 0.22 mmol), and 34 mg of 6-chloropurine (CAS: 87-42-3, 154.5 g/mol, 0.22 mmol) were dissolved in 4 mL of dry THF. After sealing the flask and replacing the inner atmosphere with Ar, the reaction mixture was magnetically stirred at room temperature for 48 h. Excess water was added to the reaction mixture and then extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration and forward solvent removal under reduced pressure, afforded a crude oil. Flash chromatography afforded 26 mg of product **11a** (Hexanes/AcOEt 75:25, 61% yield). R_f = 0.47 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −10.5 (c 1.4, MeOH); IR (neat): ν_{max} = 3329 (N–H), 2978 (C–H), 1701 (C=O, ester), 1593, 1251 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1H, NCHNCCl), 8.73 (s, rotamer, 1H, NCHNCCl), 8.33 (s, 1H, CH_2NCHN), 8.30 (s, rot-

amer, 1H, CH_2NCHN), 4.49 (d, J = 8.0 Hz, 1H, NH), 4.40 (ABXY, J_{ABXY} = 14.1 7.2 and 5.2 Hz, 1H, H-7_A), 4.33 (quintet, J = 7.2 Hz, 1H, H-7_B), 3.61 (1H, H-5), 2.18 (m, 2H, H2), 1.91–1.84 (2H, H-6), 166–1.40 (2H, H-3 and H-4), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.40 (s, 9H, $NCO_2C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7 (s, C-1), 156.1 (s, NCOO), 152.1 (d, ClCNCH), 152.0 (s, CCl), 151.2 (s, ClCCC), 146.2 (d, CNCHNC), 131.9 (s, ClCC), 80.5 (s, $CO_2C(CH_3)_3$), 80.0 (s, $NCO_2C(CH_3)_3$), 48.3 (d, C-5), 42.0 (t, C-7), 36.1 (t, C-6), 35.1 (t, C-2), 35.0 (t, C-4), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.4 (t, C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{21}H_{32}N_5O_4NaCl$, 476.2035; found, 476.2040, Δ = 1.04 ppm.

4.30. *tert*-Butyl (*R*)-7-(2-amino-6-chloro-9*H*-purin-9-yl)-5-((*tert*-butoxycarbonyl)amino)heptanoate 11b, Table 2-entry 5

In a round bottom flask, 35 mg of alcohol **7a** (395.0 g/mol; 0.103 mmol), 63 mg of PBu_3 (tributylphosphine, CAS: 998-40-3, 202.3 g/mol, 0.311 mmol), 63 mg of DIAD (diisopropyl azodicarboxylate, CAS: 2446-83-5, 202.21 g/mol, 0.311 mmol), and 53 mg of 2-amino-6-chloropurine (CAS: 10310-21-1, 169.5 g/mol, 0.311 mmol) were dissolved in 4 mL of dry THF. After sealing the flask and replacing the inner atmosphere with Ar, the reaction mixture was magnetically stirred at room temperature for 48 h. Water excess was added to the reaction mixture and later was extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration, and forward solvent removal under reduced pressure, afforded a crude oil. Flash chromatography afforded 22 mg of product **11b** (Hexanes/AcOEt 75:25, 53% yield). R_f = 0.35 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −15.7 (*c* 1.2, MeOH); IR (neat): ν_{max} = 3329 (N–H), 2976 (C–H), 1701 (C=O, ester), 1610 (C=O, carbamate), 1251 (C–O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (s, 1H, NCHN), 5.23 (br s, 2H, NH_2), 4.56 (d, J = 8 Hz, 1H, NH), 4.13 (2H, H-7), 3.62 (br s, 1H, H-5), 2.21 (t, J = 7.0 Hz, 2H, H-2), 2.03–1.46 (6H, H-3, H-4 and H-6), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.42 (s, 9H, $NCO_2C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (s, C-1), 159.2 (s, CNH_2), 155.9 (s, NCOO), 153.9 (s, CCl), 151.4 (s, ClCCC), 143.0 (d, NCH), 125.6 (s, ClCC), 80.5 (s, $CO_2C(CH_3)_3$), 79.8 (s, $NCO_2C(CH_3)_3$), 48.5 (d, C-5), 41.3 (t, C-7), 35.7 (t, C-2), 35.1 (t, C-4), 35.0 (t, C-6), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.4 (t, C-3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{21}H_{33}N_6O_4NaCl$, 491.2144; found, 491.2150, Δ = 1.21 ppm.

4.31. *tert*-Butyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)heptanoate 11e

At first, 9 mg of **11d** (529.2 g/mol; 0.058 mmol) was dissolved in 2 mL of MeOH/THF/H_2O 3:3:1 in a round bottom flask. 5 mg of $LiOH{\cdot}H_2O$ (lithium hydroxide monohydrate, CAS: 1310-66-3, 41.9 g/mol, 0.13 mmol) was added and the resulting solution was stirred at room temperature for 5 h. The pH of the solution was checked (basic) and AcOEt was added. The mixture was partitioned between water and AcOEt and the aqueous solution was extracted again with AcOEt. The aqueous solution was acidified with HCl 1 M and extracted three times with DCM. This organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to dryness. Flash chromatography afforded 7 mg of product **11e** (Hexanes/AcOEt 7:3, 97% yield). R_f = 0.40 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −15.4 (*c* 0.7, MeOH); IR (neat): ν_{max} = 3327 (N–H), 2976 (C–H), 1701 (C=O), 1670, 1166 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1H, CONHCO), 7.12 (s, 1H, NCH), 4.47 (d, J = 9.2 Hz, 1H, NHCO), 3.88 (quintet, J = 6.6 Hz, 1H, H-7_A), 3.59 (m, 2H, H-5 and H-7_B), 2.23 (td, J = 7.1 and 4.3 Hz, 2H, H-2), 1.91 (s, 3H, CCH_3), 1.72–1.41 (6H, H-3, H-4 and H-6), 1.44 (s, 18H, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (s, C-1), 164.2 (s, NCO), 156.0 (s, NCOO), 150.9 (s, NCON), 141.3 (d, NCH), 110.7 (s, CCH_3), 80.5 (s, $CO_2C(CH_3)_3$), 79.8 (s, $NCO_2C(CH_3)_3$), 48.3 (d, C-5), 46.4 (t, C-7), 35.3 (t, C-2), 35.1 (t, C-4), 34.9 (t, C-6), 28.5 (q, $CO_2C(CH_3)_3$), 28.3 (q, $NCO_2C(CH_3)_3$), 21.4 (t, C-3), 12.5 (q, CCH_3) ppm; HRMS (ESI): m/z (M+Na) calcd for $C_{21}H_{35}N_3O_6Na$, 448.2418; found, 448.2420, Δ = 0.42 ppm.

4.32. Ethyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)heptanoate 11f

At first, 4.8 mg of **11e** (425.2 g/mol, 0.073 mmol) were dissolved in 3 mL of dry EtOH. Next, HCl gas (hydrogen chloride, CAS: 7647-01-0, 36.4 g/mol) was bubbled for 5 min. The solvent was removed under reduced pressure and the crude was dissolved in 2 mL of dry DCM. Next, 8 mg of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.2 g/mol, 0.038 mmol) and 9 mg of DMAP (4-(dimethylamino)pyridine, CAS: 1122-58-3, 122.1 g/mol, 0.073 mmol). The solution was magnetically stirred at room temperature for 12 h. Next, 10 mL of DCM were added and the mixture was washed with water (2 times), 1 M HCl (2 times) and brine (1 time). The solution was dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. Flash chromatography afforded 2.4 mg of product **11f** (Hexanes/AcOEt 7:3, 54% yield). R_f = 0.45 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −11.2 (*c* 0.24, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H, CONHCO), 7.12 (s, 1H, NCH), 4.41 (d, J = 7.4 Hz, 1H, NHCO), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.82 (m, 1H, H-7_A), 3.60 (m, 2H, H-5 and H-7_B), 2.30 (2H, H-2), 1.92 (s, 3H, CCH_3), 1.69–1.45 (6H, H-3, H-4 and H-6), 1.45 (s, 9H, $C(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1 (s, C-1), 163.5 (s, NCO), 156.0 (s, NCOO), 150.2 (s, NCON), 140.9 (d, NCH), 110.2 (s, CCH_3), 79.2 (s, $CO_2C(CH_3)_3$), 60.6 (t, OCH_2CH_3), 48.8 (d, C-5), 46.7 (t, C-7), 33.9 (t, C-2), 35.1 (t, C-4), 33.8 (t, C-6), 28.5 (q, $C(CH_3)_3$), 21.4 (t, C-3), 14.3 (q, OCH_2CH_3), 12.4 (q, CCH_3) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{19}H_{32}N_3O_6$, 398.2285; found, 398.2287, Δ = 0.34 ppm.

4.33. Di(pentan-3-yl) (*R*,*E*)-8-(benzyl((*R*)-1-phenylethyl)amino)-dec-3-enedioate 12a

At first, 76 mg of **1c** (338.2 g/mol; 0.22 mmol) were dissolved in 1 mL of dry THF in a round bottom flask. The flask was sealed, purged with Ar, and cooled to −78 °C in a CO_2–acetone bath. In a second pear-shaped flask, 145 mg of (*R*)-(+)-N-benzyl-α-methylbenzylamine (CAS: 38235-77-7, 211.3 g/mol, 0.69 mmol) were dissolved in 3 mL of dry THF. This one was also sealed, purged with Ar and cooled to −78 °C. Once cooled, 0.41 mL of *n*BuLi (*n*-buthyllithium, CAS: 109-72-8, 64.1 g/mol, 0.66 mmol, 1.6 M solution) were added dropwise, turning the solution from colorless to a dark pink. The solution was stirred for 15 min at −78 °C, warmed to 0 °C in an ice bath for 30 min and finally to −78 °C for 15 min. The pink solution was added dropwise over the substrate solution and the resulting mixture turned orange. Once the addition was finished, the resulting mixture was magnetically stirred for 3 h before quenching with an excess of satd NH_4Cl. The solution turned from orange to yellow with precipitate. After 60 min, the yellow reaction mixture was extracted with AcOEt (3 times). The organic layers were combined and washed with water (3 times) and brine (1 time). The AcOEt washed solution was dried with anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure affording a crude yellowish oil. This crude was redissolved in DCM, washed 3 times with a 10% citric acid (3 times) and dried over anhydrous Na_2SO_4. Final filtration and solvent removal gave a viscous yellowish oil. Flash chromatography afforded 85 mg of product **12a** (Hexanes/AcOEt 95:5, 70% yield). R_f = 0.66 (Hexanes/AcOEt, 9:1); $[\alpha]_D^{20}$ = +6.9 (*c* 0.93, $CHCl_3$); IR (film): ν_{max} = 2971 (C–H), 1732 (C=O), 1688 (C=O), 1458 (C–N), 1260, 1157 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.2 (10H, $C_{ar}H$), 5.54 (m, 2H,

H-7 and H-8), 4.77 (q, J = 5.4 Hz, 1H, $CH(CH_2CH_3)$), 4.68 (q, J = 5.4 Hz, 1H, $CH(CH_2CH_3)$), 3.82 (q, J = 7.0 Hz, 1H, $CH(CH_3)$), 3.81 (d, J = 13.9 Hz, 1H, NCH_AH), 3.49 (d, J = 13.9 Hz, 1H, $NCHH_B$), 3.36 (m, 1H, H-3), 3.01 (d, J = 5.1 Hz, 2H, H-9), 1.98 (m, 1H, H-2 and H-6), 1.57 (m, 8H, $CH(CH_2CH_3)_2$), 1.50 (4H, H-4 and H-5), 1.34 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.89 (t, J = 7.5 Hz, 6H, $CH(CH_2CH_3)_2$), 0.84 (t, J = 7.5 Hz, 6H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (2×s, C-1 and C-10), 142.9 (s, C_{ipso}), 141.8 (s, C_{ipso}), 128.2–126.6 (10×d, C_{ar}), 134.4 (d, C-8), 122.0 (d, C-7), 77.0 (d, $CH(CH_2CH_3)$), 76.6 (d, $CH(CH_2CH_3)$), 58.3 (d, $CHCH_3$), 53.7 (d, C-3), 50.1 (t, CH_2C_{ar}), 38.5 (t, C-9), 36.7 (t, C-2), 33.2 (t, C-6), 32.4 (t, C-4), 26.6 (t, C-5), 26.5 (2×t, $CH(CH_2CH_3)_2$), 26.3 (2×t, $CH(CH_2CH_3)_2$), 20.5 (q, $CHCH_3$), 9.5 (4×q, $CH(CH_2CH_3)_2$) ppm; HRMS (EI): m/z (M+) calcd for $C_{35}H_{51}NO_4$, 549.3818; found, 549.3829, Δ = −2.00 ppm.

4.34. Di(pentan-3-yl) (*R*,*E*)-8-(benzyl((*R*)-1-phenylethyl)amino)-dec-2-enedioate 12b

See literature for complete procedure.[21] R_f = 0.57 (Hexanes/AcOEt, 9:1); $[\alpha]_D^{20}$ = +6.2 (c 2.62, $CHCl_3$); IR (film): ν_{max} = 3000 (C–H), 1714 (C=O), 1640 (C=O), 1500 (C–N), 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.2 (10H, $C_{ar}H$), 6.95 (dt, J = 15.6 6.9 Hz, 1H, H-8), 5.81 (d, J = 15.6 Hz, 1H, H-9), 4.82 (q, J = 6.8 Hz, 1H, $CH(CH_2CH_3)$), 4.67 (q, J = 6.8 Hz, 1H, $CH(CH_2CH_3)$), 3.81 (q, J = 7.0 Hz, 1H, $CH(CH_3)$), 3.81 (d, J = 15.0 Hz, 1H, NCH_AH), 3.50 (d, J = 15.0 Hz, 1H, $NCHH_B$), 3.33 (m, 1H, H-3), 2.17 (q, J = 6.9 Hz, 2H, H-7), 2.04 (dd, J = 14.6 and 6.0 Hz, 1H, H-2$_B$), 1.96 (dd, J = 14.6 and 3.0 Hz, 1H, H-2$_A$), 1.60 (m, 4H, H-4, H-5 and H-6), 1.50 (m, 8H, $CH(CH_2CH_3)_2$), 1.33 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.89 (t, J = 7.4 Hz, 6H, $CH(CH_2CH_3)_2$), 0.85 (t, J = 7.4 Hz, 3H, $CH(CH_2CH_3)$), 0.81 (t, J = 7.4 Hz, 3H, $CH(CH_2CH_3)$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (s, C-1), 166.6 (s, C-10), 148.8 (d, C-8), 143.2 (s, C_{ipso}), 141.9 (s, C_{ipso}), 128.2–126.6 (10×d, C_{ar}), 121.7 (d, C-9), 76.4 (2×d, $CH(CH_2CH_3)_2$), 58.6 (d, $CHCH_3$), 53.9 (d, C-3), 50.2 (t, CH_2C_{ar}), 36.6 (t, C-2), 33.6 (t, C-7), 33.4 (t, C-4), 32.1 (t, C-6), 27.8 (t, C-5), 26.5 (2×t, $CH(CH_2CH_3)_2$), 26.3 (2×t, $CH(CH_2CH_3)_2$), 20.7 (q, $CHCH_3$), 9.5 (4×q, $CH(CH_2CH_3)_2$) ppm; HRMS (EI): m/z (M+) calcd for $C_{35}H_{51}NO_4$, 549.3818; found, 549.3837, Δ = −3.46 ppm.

4.35. 3-Pentyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-oxo-heptanoate 13a

At first, 83 mg of diester **12a** (549.3 g/mol; 0.15 mmol) was dissolved in 5 mL of dry DCM in a round bottom flask. Next, HCl gas (hydrogen chloride, CAS: 7647-01-0, 36.5 g/mol) was bubbled through a pipette for 10 min, while the reaction solution was cooled at −78 °C in a CO_2–acetone bath. Next, ozone (O_3, gas, generated in situ) was bubbled for 15 min until the solution was light blue. Finally, 0.2 mL of Me_2S (dimethyl sulfide, CAS: 75-18-3, 62.1 g/mol, 2.7 mmol) was added and the reaction was allowed to warm to room temperature. Next, 5 mL of 1 M KOH was added, turning the reaction mixture white. After 30 min of stirring, the reaction was extracted with DCM (3 times). The organic solution was washed with brine 1 time. Drying the solution over anhydrous Na_2SO_4, filtration and forward solvent removal under reduced pressure, afforded 58 mg of aldehyde **13a**, 92% yield. R_f = 0.53 (Hexanes/AcOEt, 8:2); IR (neat): ν_{max} = 2969 (C–H), 1726 (C=O), 1454 (C–N), 1260 (C–O), 1155 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.7 (s, 1H, H-7), 7.4–7.2 (10H, $C_{ar}H$), 4.70 (q, J = 6.0 Hz, 1H, $CH(CH_2CH_3)$), 3.82 (d, J = 14.5 Hz, 1H, NCH_AH), 3.8 (q, J = 7.0 Hz, 1H, $CH(CH_3)$), 3.55 (d, J = 14.5 Hz, 1H, $NCHH_B$), 3.4 (1H, m, H-3), 2.32 (t, J = 4.7 Hz, 2H, H6), 2.0 (m, 2H, H-2), 1.7–1.5 (m, 4H, $CH(CH_2CH_3)_2$), 1.34 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.84 (t, J = 7.4 Hz, 6H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.3 (s, C-7), 172.5 (s, C-1), 143.0 (s, C_{ipso}), 141.6 (s, C_{ipso}), 128.2-126.6 (10×d, C_{ar}), 76.4 (d, $CH(CH_2CH_3)_2$), 58.5 (d, $CHCH_3$), 53.5 (d, C-3), 50.2 (t, CH_2C_{ar}), 43.6 (t, C-6), 36.3 (t, C-2), 33.0 (t, C-4), 26.3 (2×t, $CH(CH_2CH_3)_2$), 20.7 (q, $CHCH_3$), 19.5 (t, C-5), 9.5 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{27}H_{38}NO_3$, 424.2852; found, 424.2845, Δ = 1.65 ppm.

4.36. 3-Pentyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-8-oxo-octanoate 13b

At first, 97 mg of diester **12b** (549.3 g/mol; 0.18 mmol) was dissolved in 6 mL of dry DCM in a round bottom flask. Next, HCl gas (hydrogen chloride, CAS: 7647-01-0, gas, 36.5 g/mol) was bubbled through a pipette for 10 min, while the reaction solution was cooled at −78 °C in a CO_2–acetone bath. Next, ozone (O_3, gas, generated in situ) was bubbled for 15 min until the solution was light blue. Finally, 0.2 mL of Me_2S (dimethyl sulfide, CAS: 75-18-3, 62.1 g/mol, 2.7 mmol) was added and the reaction was allowed to warm to room temperature. Next 10 mL of 1 M KOH was added, turning the reaction mixture white. After 30 min of stirring, the reaction was extracted with DCM (3 times). The organic solution was washed with brine 1 time. The solution was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 75 mg of product **13b** (Hexanes/AcOEt 95:5, 98% yield). R_f = 0.67 (Hexanes/AcOEt, 8:2); $[\alpha]_D^{20}$ = +6.8 (c 1.28, $CHCl_3$); IR (neat): ν_{max} = 2971 (C–H), 1724 (C=O), 1456 (C–N), 1277 (C–O), 1202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (t, J = 1.8 Hz, 1H, H-8), 7.4–7.2 (10H, $C_{ar}H$), 5.67 (m, 1H, $CH(CH_2CH_3)$), 3.8 (m, 1H, $CH(CH_3)$), 3.82 (d, J = 7.5 Hz, 1H, NCH_AH), 3.50 (d, J = 7.5 Hz, 1H, $NCHH_B$), 3.35 (m, 1H, H3), 2.38 (m, 2H, H7), 2.0 (m, 2H, H2), 1.75–1.35 (10H, H-4, H-5, H-6 and $CH(CH_2CH_3)_2$), 1.33 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.84 (t, J = 7.4 Hz, 3H, $CH(CH_2CH_3)$), 0.81 (t, J = 7.4 Hz, 3H, $CH(CH_2CH_3)$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.3 (d, C-8), 172.6 (s, C-1), 142.8 (s, C_{ipso}), 141.7 (s, C_{ipso}), 128.3–126.6 (10×d, C_{ar}), 76.6 (d, $CH(CH_2CH_3)_2$), 58.3 (d, $CHCH_3$), 53.5 (d, C-3), 50.0 (t, C-7), 50.0 (t, CH_2C_{ar}), 36.4 (t, C-2), 33.3 (t, C-4), 26.4 (2×t, $CH(CH_2CH_3)_2$), 21.9 (t, C-5), 20.6 (q, $CHCH_3$), 20.5 (t, C-6), 9.5 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (ESI): m/z (M+H) calcd for $C_{28}H_{40}NO_3$, 438.3008; found, 438.2993, Δ = 3.42 ppm.

4.37. 3-Pentyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-6-(1,3-dioxolan-2-yl)hexanoate 14a

At first, 420 mg of ester **13a** (423.3 g/mol; 0.99 mmol) was dissolved in 10 mL of dry benzene in a round bottom flask. Next, 40 mg of pTsOH·H_2O (p-toluenesulfonic acid monohydrate, CAS: 6192-52-5, 190.2 g/mol, 0.21 mmol) followed by 3 mL of ethylene glycol (CAS: 107-21-1, 62.1 g/mol, 53 mmol) were added, and the reaction solution was heated at reflux overnight. The solution was cooled and 5 mL of water was added. After 30 min of stirring, the reaction was extracted with ether (3 times). The organic solution was washed with 5% $NaHCO_3$ solution (1 time) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration, and solvent removal under reduced pressure, afforded a reaction crude. Flash chromatography afforded 344 mg of product **14a** (Hexanes/AcOEt 95:5, 82% yield). R_f = 0.55 (Hexanes/AcOEt, 8:2); $[\alpha]_D^{20}$ = +11.9 (c 0.7, $CHCl_3$); IR (neat): ν_{max} = 2969 (C–H), 1724 (C=O), 1493 (C–N), 1140 (C–O), 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.2 (10H, $C_{ar}H$), 4.85 (t, J = 4.7 Hz, 1H, H-7), 4.68 (q, J = 5.5 Hz, 1H, $CH(CH_2CH_3)$), 3.96 (m, 2H, OCH_2CH_2O), 3.84 (m, 2H, OCH_2CH_2O), 3.82 (q, J = 7.0 Hz, 1H, $CH(CH_3)$), 3.81 (d, J = 14.9 Hz, 1H, NCH_AH), 3.50 (d, J = 14.9 Hz, 1H, $NCHH_B$), 3.39 (m, 1H, H-3), 1.98 (m, 2H, H-2), 1.8–1.4 (m, 6H, H-4, H-5 and H-6), 1.50 (q, J = 7.5 Hz, 2H, $CH(CH_2CH_3)$), 1.51 (q, J = 7.5 Hz, 2H, $CH(CH_2CH_3)$), 1.35 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.85 (t, J = 7.5 Hz, 3H, $CH(CH_2CH_3)$), 0.83 (t, J = 7.5 Hz, 3H, $CH(CH_2CH_3)$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 (s, C-1),

142.9 (s, C_{ipso}), 141.8 (s, C_{ipso}), 128.9–126.5 (10×d, C_{ar}), 104.7 (d, C-7), 76.3 (d, $CH(CH_2CH_3)_2$), 64.9 (2×t, OCH_2CH_2O), 58.3 (d, $CHCH_3$), 53.9 (d, C-3), 50.2 (t, CH_2C_{ar}), 36.8 (t, C-2), 33.8 (t, C-6), 33.6 (t, C-4), 26.3 (2×t, $CH(CH_2CH_3)_2$), 21.5 (t, C-5), 20.4 (q, $CHCH_3$), 9.5 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (EI): *m*/*z* (M+) calcd for $C_{29}H_{41}NO_4$, 467.3035; found, 467.3038, Δ = −0.64 ppm.

4.38. 3-Pentyl (*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-(1,3-dioxolan-2-yl)heptanoate 14b

At first, 200 mg of ester **13b** (437.3 g/mol; 0.46 mmol) was dissolved in 12 mL of dry benzene in a round bottom flask. Next 15 mg of *p*TsOH·H_2O (p-toluenesulfonic acid monohydrate, CAS: 6192-52-5, 190.2 g/mol, 0.07 mmol) followed by 1.2 mL of ethylene glycol (CAS: 107-21-1, 62.1 g/mol, 21.2 mmol) were added, and the reaction solution was heated at reflux overnight. The solution was cooled and 5 mL of water was added. After 30 min of stirring, the reaction was extracted with ether (3 times). The organic solution was washed with 5% $NaHCO_3$ solution (1 time) and brine (1 time). Drying the solution over anhydrous Na_2SO_4, filtration, and forward solvent removal under reduced pressure, afforded a crude. Flash chromatography afforded 196 mg of product **14b** (Hexanes/AcOEt 95:5, 89% yield). R_f = 0.24 (Hexanes/AcOEt, 9:1); $[\alpha]_D^{20}$ = +9.0 (*c* 1.30, $CHCl_3$); IR (neat): ν_{max} = 2971 (C–H), 1724 (C=O), 1493 (C–N), 1028, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.2 (10H, $C_{ar}H$), 4.83 (t, *J* = 4.7, 1H, H-8), 4.67 (q, *J* = 6.7, 1H, $CH(CH_2CH_3)$), 3.96 (m, 2H, OCH_2CH_2O), 3.84 (m, 2H, OCH_2CH_2O), 3.82 (q, *J* = 7.0 Hz, 1H, $CH(CH_3)$), 3.81 (d, *J* = 15.0 Hz, 1H, NCH_AH), 3.48 (d, *J* = 15.0 Hz, 1H, $NCHH_B$), 3.36 (1H, m, H-3), 1.96 (m, 2H, H-2), 1.65 (m, 2H, H-7), 1.60–1.30 (m, 6H, H-4, H-5 and H-6), 1.55–1.40 (m, 4H, $CH(CH_2CH_3)_2$), 1.32 (d, *J* = 7.0 Hz, 3H, $CHCH_3$), 0.84 (t, *J* = 7.4 Hz, 3H, $CH(CH_2CH_3)$), 0.81 (t, *J* = 7.4 Hz, 3H, $CH(CH_2CH_3)$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (s, C-1), 143.0 (s, C_{ipso}), 141.8 (s, C_{ipso}), 128.1–126.5 (10×d, C_{ar}), 104.7 (d, C-8), 76.4 (d, $CH(CH_2CH_3)_2$), 64.8 (2×t, OCH_2CH_2O), 58.3 (d, $CHCH_3$), 53.9 (d, C-3), 50.1 (t, CH_2C_{ar}), 33.9 (t, C-2), 33.6 (t, C-7), 26.9 (t, C-4), 26.3 (t, C-5), 26.3 (2×t, $CH(CH_2CH_3)_2$), 24.0 (t, C-6), 20.4 (q, $CHCH_3$), 9.5 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{30}H_{43}NO_4$, 482.3270; found, 482.3258, Δ = 2.49 ppm.

4.39. 3-Pentyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-6-(1,3-dioxolan-2-yl)hexanoate 15a

At first, 270 mg of protected substrate **5** (467.3 g/mol, 0.57 mmol) and 460 mg of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.3 g/mol, 2.11 mmol) were dissolved in 2 mL of dry AcOEt. 100 mg of $Pd(OH)_2$ on carbon (palladium hydroxide on carbon 20% wet, Perlman's catalyst, CAS: 12135-22-7, 140.4 g/mol) were added, and the mixture was placed in a 5 mL pressure flask. The flask was connected to an H_2 gas line and the pressure was adjusted to 3.4 atm. The flask was mechanically stirred for 2 days. The flask was pressurized to atmospheric conditions and the mixture was filtered through a pad of Celite®, and washed with AcOEt and DCM. The excess Boc_2O was removed through Kugelrohr distillation, affording 206 mg of carbamate **15a**, 98% yield. R_f = 0.52 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = +11.2 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} = 2972 (C–H), 1715 (C=O), 1460 (C–NC–N), 1248 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.94 (m, 1H, NH), 4.84 (t, *J* = 4.6 Hz, 1H, H-7), 4.76 (q, *J* = 6.7 Hz, 1H, $CH(CH_2CH_3)_2$), 3.94 (m, 2H, OCH_2CH_2O), 3.90 (m, 1H, H-3), 3.83 (m, 2H, OCH_2CH_2O), 2.50 (m, 2H, H-2), 1.66 (m, 2H, H-6), 1.58-1.52 (m, 8H, H-4, H-5 and $CH(CH_2CH_3)_2$), 1.43 (s, 9H, $CH(CH_3)_3$), 0.88 (t, *J* = 7.5 Hz, 3H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3 (s, C-1). 155.2 (s, NCO), 104.3 (d, C-7), 78.9 (s, $C(CH_3)_3$), 76.9 (d, $CH(CH_2CH_3)_2$), 64.7 (2×t, OCH_2CH_2O), 47.8 (d, C-3), 39.4 (t, C-2), 34.5 (t, C-6), 33.5 (t, C-4), 28.3 (q, $C(CH_3)_3$), 26.3 (2×t, $CH(CH_2CH_3)_2$), 20.5 (t, C-5), 9.4 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{19}H_{36}NO_6$, 374.2543; found, 374.2560, Δ = −4.54 ppm.

4.40. 3-Pentyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-7-(1,3-dioxolan-2-yl)heptanoate 15b

At first, 338 mg of protected substrate **14b** (481.3 g/mol, 0.70 mmol) and 567 mg of Boc_2O (di-*tert*-butyl dicarbonate, CAS: 24424-99-5, 218.3 g/mol, 2.60 mmol) were dissolved in 3 mL of dry AcOEt. 135 mg of $Pd(OH)_2$ on carbon (palladium hydroxide on carbon 20% wet, Perlman's catalyst, CAS: 12135-22-7, 140.4 g/mol) were added, and the mixture was placed in a 5 mL pressure flask. The flask was connected to a H_2 gas line and the pressure was adjusted to 3.4 atm. The flask was mechanically stirred for 2 days. The flask was pressurized to atmospheric conditions and the mixture was filtered through a pad of Celite®, and washed with AcOEt and DCM. The excess Boc_2O was removed through Kugel Rohr distillation, affording 250 mg of carbamate **15b**, 93% yield. R_f = 0.73 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{20}$ = +10.4 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} = 2938 (C–H), 1717 (C=O), 1366 (C–N), 1246 (C–O), 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.95 (d, *J* = 9.2 Hz, 1H, NH), 4.83 (t, *J* = 4.8 Hz, 1H, H-7), 4.76 (q, *J* = 6.6, 1H, $CH(CH_2CH_3)_2$), 3.94 (m, 2H, OCH_2CH_2O), 3.88 (m, 1H, H-3), 3.84 (m, 2H, OCH_2CH_2O), 2.51 (m, 2H, H-2), 1.63 (m, 8H, H-4, H-5, H-6 and H-7), 1.53 (m, 4H, $CH(CH_2CH_3)_2$), 1.42 (s, 9H, $CH(CH_3)_3$), 0.87 (t, *J* = 7.5 Hz, 3H, $CH(CH_2CH_3)_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4 (s, C-1). 155.3 (s, NCO), 104.6 (d, C-8), 79.1 (s, $C(CH_3)_3$), 77.0 (d, $CH(CH_2CH_3)_2$), 64.8 (2×t, OCH_2CH_2O), 48.0 (d, C-3), 39.6 (t, C-2), 34.7 (t, C-7), 33.8 (t, C-4), 28.4 (q, $C(CH_3)_3$), 26.4 (2×t, $CH(CH_2CH_3)_2$), 26.0 (t, C-5), 23.8 (t, C-6), 9.5 (2×q, $CH(CH_2CH_3)_2$) ppm; HRMS (ESI): *m*/*z* (M+) calcd for $C_{20}H_{37}NO_6$, 387.2621; found, 387.2627, Δ = −1.54 ppm.

4.41. *tert*-Butyl (*R*)-(6-(1,3-dioxolan-2-yl)-1-hydroxyhexan-3-yl)carbamate 16a

In a round bottom flask, 30 mg of ester **15a** (373.3 g/mol, 0.08 mmol) was added and dissolved in 1 mL of dry DCM. The flask was sealed, purged with Ar, and cooled to −78 °C in a CO_2–acetone bath. Once cooled, 0.34 mL of DIBAL-H (diisobutylaluminum hydride, CAS: 1191-15-7, 142.2 g/mol, 2.07 mmol, 1.5 M toluene solution) was added dropwise via syringe. Stirring was continued until TLC monitoring showed the consumption of starting material. Excess water was added and the reaction mixture was allowed to warm to room temperature. The reaction solution was poured into an Erlenmeyer flask with 5 mL of AcOEt where 1 g of Na_2SO_4 and 1 g of $NaHCO_3$ were suspended. This mixture was stirred vigorously for 1 h. Finally, the solids were filtered through a pad of Celite® and the solvent were removed under reduced pressure. Flash chromatography afforded 22 mg of product **16a** (Hexanes/AcOEt 7:3, 90% yield). R_f = 0.29 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −2.1 (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} = 3600 (O–H), 2949 (C–H), 1688 (C=O), 1456 (C–N), 1171 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (t, *J* = 4.6 Hz, 1H, H-7), 4.38 (m, 1H, NH), 3.95 (m, 2H, OCH_2CH_2O), 3.83 (m, 2H, OCH_2CH_2O), 3.90 (m, 1H, H-3), 3.62 (m, 2H, H-1), 1.8–1.5 (m, 8H, H-2, H-4, H-5 and H-6), 1.44 (s, 9H, $CH(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.9 (s, NCO), 104.4 (d, C-7), 79.7 (s, $C(CH_3)_3$), 64.6 (2×t, OCH_2CH_2O), 58.9 (t, C-1), 47.5 (d, C-3), 39.0 (t, C-2), 35.5 (t, C-6), 33.6 (t, C-4), 28.3 (q, $C(CH_3)_3$), 20.6 (t, C-5) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{14}H_{28}NO_5$, 290.1967; found, 290.1965, Δ = 0.69 ppm.

4.42. *tert*-Butyl (*R*)-(7-(1,3-dioxolan-2-yl)-1-hydroxyheptan-3-yl)carbamate 16b

In a round bottom flask, 400 mg of ester **15b** (387.3 g/mol, 1.0 mmol) was placed and dissolved in 10 mL of dry DCM. The flask was sealed, purged with Ar, and cooled to −78 °C in a CO_2–acetone bath. Once cooled, 2.2 mL of DIBAL-H (diisobutylaluminum hydride, CAS: 1191-15-7, 142.2 g/mol, 13.6 mmol, 1.5 M toluene solution) was added dropwise via syringe. Stirring was continued until TLC monitoring showed consumption of the starting material. Excess water was added and the reaction mixture was allowed to warm to room temperature. The reaction solution was poured into an Erlenmeyer flask with 20 mL of AcOEt where 5 g of Na_2SO_4 and 5 g of $NaHCO_3$ were suspended. This mixture was stirred vigorously for 1 h. Finally, the solids were filtered through a pad of Celite® and the solvent was removed under reduced pressure. Flash chromatography afforded 304 mg of product **16b** (Hexanes/AcOEt 8:2, 98% yield). R_f = 0.27 ($CHCl_3$/MeOH, 95:5); $[\alpha]_D^{20}$ = −1.8 (*c* 0.91, $CHCl_3$); IR (neat): ν_{max} = 3500 (O-H), 2950 (C–H), 1688 (C=O), 1526 (C–N), 1250 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.82 (t, *J* = 4.7 Hz, 1H, H-8), 4.38 (d, *J* = 8.7 Hz, 1H, NH), 3.94 (m, 2H, OCH_2CH_2O), 3.83 (m, 2H, OCH_2CH_2O), 3.75 (m, 1H, H-3), 3.61 (m, 2H, H-1), 1.85 (m, 2H, H-2), 1.65 (m, 2H, H-7), 1.43 (s, 9H, $CH(CH_3)_3$), 1.5–1.4 (m, 6H, H-4, H-5 and H-6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.1 (s, NCO), 104.5 (d, C-8), 79.8 (s, $C(CH_3)_3$), 64.8 (2×t, OCH_2CH_2O), 58.9 (t, C-1), 47.4 (d, C-3), 39.1 (t, C-2), 35.8 (t, C-7), 33.7 (t, C-4), 28.4 (q, $C(CH_3)_3$), 26.0 (t, C-5), 23.8 (t, C-6) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{15}H_{30}NO_5$, 304.2124; found, 304.2135, Δ = −3.61 ppm.

4.43. *tert*-Butyl (*R*)-(7-(1,3-dioxolan-2-yl)-1-bromoheptan-3-yl)-carbamate 17

In a round bottom flask, 230 mg of alcohol **16b** (303.2 g/mol; 0.76 mmol), 239 mg of PBu_3 (triphenylphosphine, CAS: 603-35-0, 262.3 g/mol, 0.91 mmol), and 360 mg of CBr_4 (tetrabromomethane, CAS: 558-13-4, 331.6 g/mol, 0.91 mmol) were dissolved in 4 mL of dry DCM. After sealing the flask and replacing the inner atmosphere with Ar, the reaction mixture was magnetically stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residue was dissolved in ether. Cooling the solution in an ice bath promoted the precipitation of the phosphine oxide. Filtration and solvent removal under reduced pressure afforded a crude oil. Flash chromatography afforded 249 mg of product **17** (Hexanes/AcOEt 9:1, 79% yield). R_f = 0.48 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −8.7 (*c* 1.9, $CHCl_3$); IR (neat): ν_{max} = 2947 (C–HC–H), 1697 (C=O), 1522 (C–N), 1246 (C–O), 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (t, *J* = 4.7 Hz, 1H, H-8), 4.32 (m, 1H, NH), 3.94 (m, 2H, OCH_2CH_2O), 3.82 (m, 2H, OCH_2CH_2O), 3.65 (m, 1H, H-3), 3.40 (t, *J* = 7.5 Hz, 2H, H-1), 2.00 (m, 2H, H-2), 1.65 (m, 2H, H-7), 1.42 (s, 9H, $CH(CH_3)_3$), 1.4–1.3 (6H, m, H-4, H-5 and H-6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.6 (s, NCO), 104.5 (d, C-8), 79.3 (s, $C(CH_3)_3$), 64.8 (2×t, OCH_2CH_2O), 50.0 (t, C-3), 39.2 (d, C-2), 35.2 (t, C-7), 33.6 (t, C-4), 29.7 (t, C-1), 28.3 (q, $C(CH_3)_3$), 25.7 (t, C-5), 23.8 (t, C-6) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{15}H_{29}BrNO_4$, 366.1280; found, 366.1297, Δ = −4.64 ppm.

4.44. *tert*-Butyl (*R*)-(7-(1,3-dioxolan-2-yl)-1-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)heptan-3-yl)carbamate 18

In a round bottom flask, 32 mg of thymine (CAS: 65-71-4, 126.1 g/mol, 0.03 mmol) and 15.2 mg of K_2CO_3 (potassium carbonate, CAS: 584-08-7, 138.2 g/mol, 0.11 mmol) were suspended in 2 mL of dry DMF. This mixture was stirred 1 h at 70 °C. Separately, 27 mg of bromide **17** (366.3 g/mol; 0.07 mmol) and 6.0 mg of TBAI (tetrabutylammonium iodide, CAS: 311-28-4, 396.4 g/mol, 0.02 mmol), were dissolved in 2 mL of dry DMF in a round bottom flask. This mixture was added to the initial mixture, and the reaction was stirred for 6 h at 70 °C. Excess water was added to the reaction mixture, which was later extracted with AcOEt (3 times). The organic extract was washed with water (5 times). The organic extract was washed with water (5 times), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 10.8 mg of product **18** (Hexanes/AcOEt 4:6, 38%). R_f = 0.36 (Hexanes/AcOEt, 1:4); $[\alpha]_D^{20}$ = −17.5 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} = 3352 (N–H), 2947 (C–H), 1684 (C=O), 1422 (C–N), 1169 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1H, CONHCO), 7.13 (br s, 1H, NCH), 4.82 (t, *J* = 4.7 Hz, 1H, H-8), 4.43 (d, *J* = 8.7 Hz, 1H, HNCOO), 3.98 (m, 2H, OCH_2CH_2O), 3.90 (m, 1H, H-3), 3.84 (m, 2H, OCH_2CH_2O), 3.57 (m, 2H, H-1), 1.91 (s, 3H, CCH_3), 1.6–1.4 (m, 8H, H-2, H-4, H-5 and H-6), 1.43 (s, 9H, $CH(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.9 (s, NCO), 155.9 (s, NCOO), 150.7 (s, NCON), 141.0 (d, NCH), 110.5 (s, CCH_3), 104.4 (s, C-8), 79.5 (s, $C(CH_3)_3$), 64.8 (2×t, OCH_2CH_2O), 48.5 (d, C-3), 46.2 (t, C-1), 35.8 (t, C-7), 34.8 (t, C-2), 33.6 (t, C-4), 28.4 (q, $C(CH_3)_3$), 25.7 (t, C-5), 23.8 (t, C-6), 12.2 (q, CCH_3) ppm; HRMS (ESI): *m*/*z* (M+) calcd for $C_{20}H_{33}N_3O_6$, 411.2369; found, 411.2364, Δ = 1.21 ppm.

4.45. (*R*)-3-((*tert*-Butoxycarbonyl)amino)-6-(1,3-dioxolan-2-yl)-hexyl acetate 19

In a round bottom flask, 23 mg of alcohol **16a** (289.2 g/mol, 0.08 mmol) was placed and dissolved in 1 mL of recently distilled pyridine. The flask was sealed and purged with Ar and cooled to 0 °C. Once cooled, 0.5 mL of Ac_2O (acetic anhydride, CAS: 108-24-7, 102.1 g/mol) was added dropwise via syringe. Stirring was continued for 6 h. Crushed iced was then added, and the reaction mixture was extracted with AcOEt (3 times). The organic extract was washed with 20% $CuSO_4$ (3 times), brine (1 time), dried with anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography afforded 15 mg of product **19** (Hexanes/AcOEt 95:5, 56%). R_f = 0.39 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −4.0 (*c* 0.59 $CHCl_3$); IR (neat): ν_{max} = 3362 (N–H), 2955 (C–H), 1740 (C=O), 1458 (C–N), 1244 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.84 (t, *J* = 4.7 Hz, 1H, H-7), 4.27 (1H, NH), 4.12 (t, *J* = 7.0 Hz, 2H, H-1), 3.96 (m, 2H, OCH_2CH_2O), 3.84 (m, 2H, OCH_2CH_2O), 3.67 (m, 1H, H-3), 2.04 (s, 3H, CH_3COO), 1.8–1.5 (m, 6H, H-2, H-4, H-5 and H-6), 1.43 (s, 9H, $CH(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0 (s, CH_3COO), 155.5 (s, NCO), 104.3 (d, C-7), 79.1 (s, $C(CH_3)_3$), 64.8 (2×t, OCH_2CH_2O), 61.6 (t, C-1), 48.0 (d, C-3), 35.2 (t, C-4), 34.0 (t, C-2), 33.6 (t, C-6), 28.3 (q, $C(CH_3)_3$), 20.9 (t, C-5), 20.2 (q, CH_3COO) ppm; HRMS (ESI): *m*/*z* (M+) calcd for $C_{16}H_{29}NO_6$, 331.1994; found, 331.2002, Δ = −2.41 ppm.

4.46. 2-Hydroxyethyl (*R*)-7-acetoxy-5-((*tert*-butoxycarbonyl)-amino)heptanoate 20

At first, 10 mg of compound **19** (331.4 g/mol; 0.03 mmol) was dissolved in 3 mL of dry DCM in a round bottom flask. Ozone (O_3, gas, generated in situ) was bubbled for 15 min until the solution was light blue. Finally, an Ar flow was bubbled for 5 min. Solvent removal under reduced pressure, afforded 9 mg of ester **20**, 86% yield. R_f = 0.25 (Hexanes/AcOEt, 1:1); $[\alpha]_D^{20}$ = −4.0 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} = 3500 (O-H), 2930 (C–H), 1738 (C=O), 1460 (C–N), 1246 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.42 (1H, NH), 4.21 (t, *J* = 4.0 Hz, 2H, OCH_2CH_2OH), 4.12 (t, *J* = 6.3 Hz, 2H, H-7), 3.82 (t, *J* = 4.5 Hz, 2H, OCH_2CH_2OH), 3.67 (m, 1H, H-5), 2.38 (m, 2H, H-2), 2.05 (s, 3H, CH_3COO), 1.82 (2H, m, H-6), 1.8–1.6 (m, 4H, H-3 and H-4), 1.43 (s, 9H, $CH(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5 (s, C-7), 171.0 (s, CH_3COO), 155.5 (s, NCO), 79.3 (s, $C(CH_3)_3$), 66.0 (t, OCH_2CH_2OH), 61.4 (t, OCH_2CH_2OH), 61.1 (t,

C-7), 47.7 (d, C-5), 34.5 (t, C-2), 33.9 (t, C-4), 33.6 (t, C-6), 28.3 (q, $C(CH_3)_3$), 21.1 (t, C-3), 20.9 (q, CH_3COO) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{16}H_{30}NO_7$, 348.2022; found, 348.2031, Δ = −2.58 ppm.

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