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Improved Auxiliary for the Synthesis of Medium-Sized Bis(lactams)

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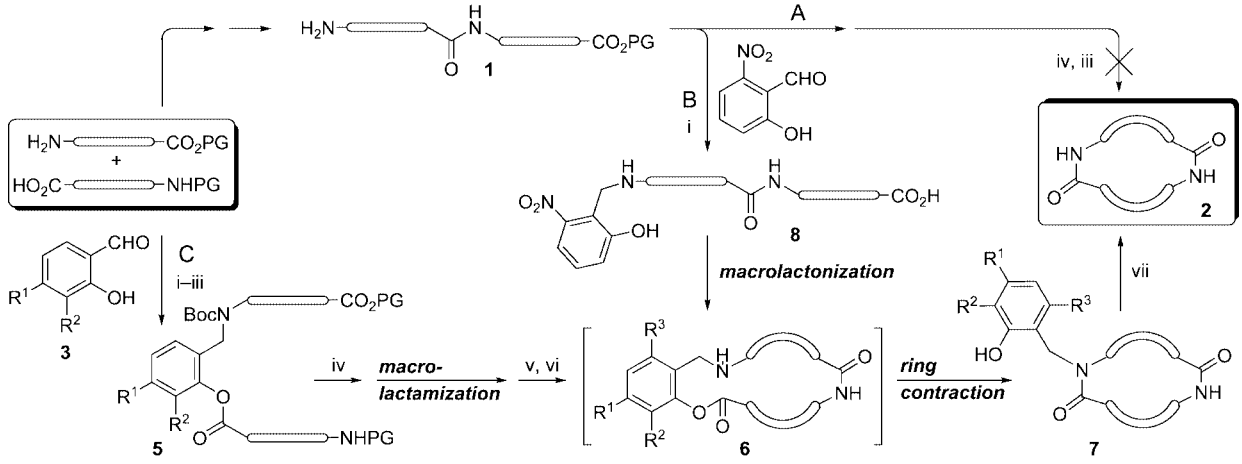
Our auxiliary-based method for the synthesis of bis(lactams) has been optimized. A novel auxiliary is described that is inserted in the backbone of a linear peptide facilitating the mutually reactive terminal groups to approach one another for a cyclization reaction. A subsequent ring contraction mechanism leads to the bis(lactams) with the remainings of the auxiliary still attached. Functionalized seven- and eight-membered bis(lactams) have been prepared that are difficult to access using traditional methods. Removal of the auxiliary from the bis(lactams) has been described with the possible side reactions that can occur.

Introduction

Small cyclic peptides constitute an important class of compounds.[1] Naturally occurring cyclic peptides often possess potent biological activities.[1d] Because of their restricted conformational flexibility they often show enhanced receptor selectivity.[2] Compared to their linear counterparts, cyclic peptides are more resistant against enzymatic degradation and show a better membrane permeability improving their bioavailability.[3] Besides pharmaceutical research, cyclic peptides find application in fields such as materials science[4] and catalysis.[5]

Despite their interesting properties, especially 7–15-membered cyclic peptides find limited application mainly because of their troublesome synthesis. Ring-closure is often hampered by the backbone amide bonds possessing a strong π-character with preferentially a *transoid* conformation leading to an extended structure with the mutually reactive terminal groups far apart.[6]



Scheme 1. General strategy for the synthesis of bis(lactams). Reaction conditions: (i) reductive amination; (ii) $(Boc)_2O$; (iii) coupling reaction; (iv) protecting group removal; (v) TFA; (vi) base; (vii) auxiliary removal.

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Synthetic strategies using peptide coupling reagents and high-dilution conditions often lead to low yields.[7] Other strategies are based on the use of auxiliaries,[8] cyclizations on solid phase,[9] intramolecular Staudinger ligation reactions,[10] chemoenzymatic cyclizations[11] and on the site-isolation effect exerted within dendrimeric nanoreactors.[12]

However, each application is still limited to specific sequences.

The smallest cyclic peptides that are difficult to address by classical direct lactamization (Scheme 1, route A) are the seven- and eight-membered bis(lactams) **2** (homodiketopiperazines), made up of α-, β- or γ-amino acids.[13] On the basis of pioneering studies by Meutermans et al.[8a,8c] (Scheme 1, route B) we have recently developed a general and sequence-independent methodology for the efficient synthesis of such bis(lactams) (Scheme 1, route C).[8b,8d]

In the strategy of Meutermans, which has been successfully applied in the synthesis of cyclic pentapeptides,[8a] the backbone amide bonds still hamper the macrolactonization step, thus leading to extensive epimerization. In addition, we have previously shown the sequence dependency of route B towards homodiketopiperazines.[8d]

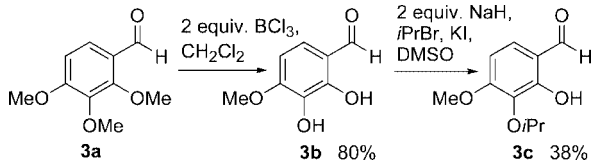
Results and Discussion

In our approach, a salicylaldehyde-derived auxiliary **3** is incorporated within the backbone of a linear peptide **5** (Scheme 1, route C). A macrolactamization reaction, facilitated by a combination of the templating effect of the auxiliary and an extension of the backbone by four atoms, results in the formation of lactam **6**. Liberation of the Boc-protected amine induces a ring-contractive O→N acyl shift providing the strained target lactam **7**. Final removal of the auxiliary residue liberates the lactam **2**.

In a previous study we found that introduction of a sterically demanding substituent flanking the aryl ester (Scheme 1; **3**: R^1 = H, R^2 = O*t*Bu) was necessary to prevent premature intermolecular aminolysis during the macrolactamization step.[8d] A drawback of this auxiliary, however, is the harsh conditions required for removal of its remainings after the final ring contraction step liberating the lactam **2**. More importantly, the sterically demanding O*t*Bu substituent prevented incorporation of two α-substituted amino acids flanking the auxiliary,[14] thereby severely limiting the synthetic scope of the target compounds. Herein, we present 2-hydroxy-3-isopropoxy-4-methoxybenzaldehyde (**3c**) as an improved auxiliary overcoming these problems as will be shown by the synthesis of several substituted seven- and eight-membered bis(lactams).

To avoid racemization in peptide synthesis, removal of protective groups is preferably done by treatment with strong acid.

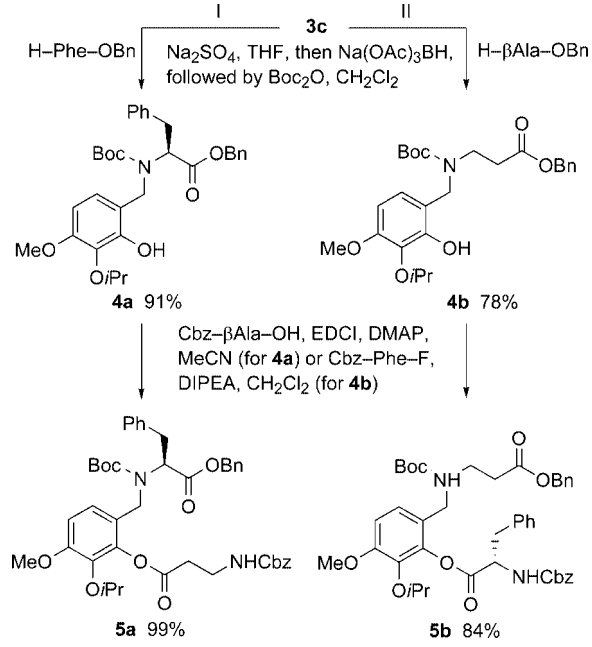
It was anticipated that incorporation of a methoxy substituent on the *para* position with respect to the aldehyde group on the auxiliary (Scheme 1; R^1 = OMe) should render the benzylic amide bond susceptible for acidolytic cleavage.[15] To reduce the steric hindrance of substituent R^2 such that it still prevents premature aminolysis of the phenolic ester during the macrolactamization step but allowing the introduction of two α-substituted amino acids, we chose to replace the *t*Bu group by an isopropyl group to give auxiliary **3c** (Scheme 2).



Scheme 2. Synthesis of the auxiliary.

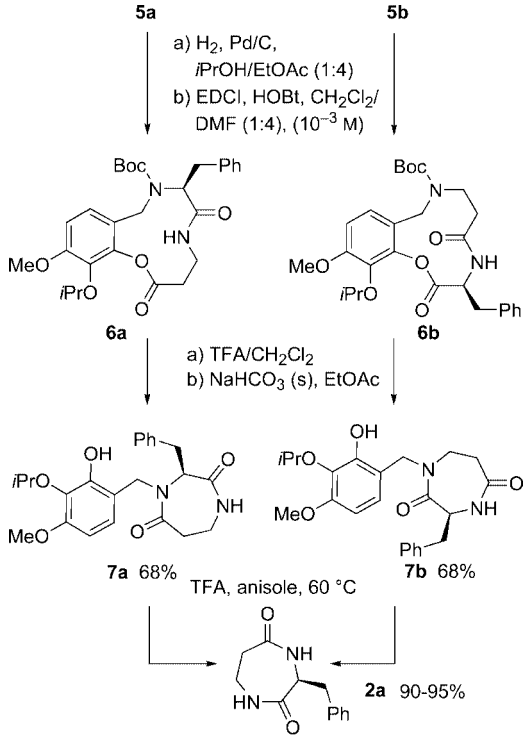
Auxiliary **3c** was obtained from commercially available 2,3,4-trimethoxybenzaldehyde (**3a**). Selective "BCl_3-mediated" demethylation of **3a**[16] was followed by alkylation with isopropyl bromide.[17] Besides **3c**, a mixture derived from alkylation on the *ortho* position and alkylation on both phenols was obtained. From this mixture **3c** could be isolated easily, although in a moderate 38% yield.

As a model compound to test the methodology (*S*)-3-benzyl-1,4-diazepine-2,5-dione (**2a**) was chosen (Schemes 3 and 4). To date, this seven-membered bis(lactam) could not be ring-closed by direct head-to-tail cyclization conditions from both linear precursors.[8d]



Scheme 3. Synthesis of the linear precursors.

The synthesis of the linear cyclization precursor peptides was accomplished by reductive amination of auxiliary **3c** with H–Phe–OBn or H–βAla–OBn (Scheme 3, routes I and II, respectively), followed by Boc protection of the resulting secondary amine to give the phenols **4a** and **4b** in yields of 91% and 78%, respectively. Consecutive "EDCI/DMAP-mediated" esterification of the phenol with Cbz–βAla–OH (route I) or acyl fluoride coupling[18] with Cbz–Phe–F in the presence of DIPEA (route II), provided the protected linear precursor peptides **5a** and **5b** in yields of 99% and 84%, respectively. These two coupling methods are complementary, although acyl fluoride couplings are preferred during sterically hindered couplings (vide infra).



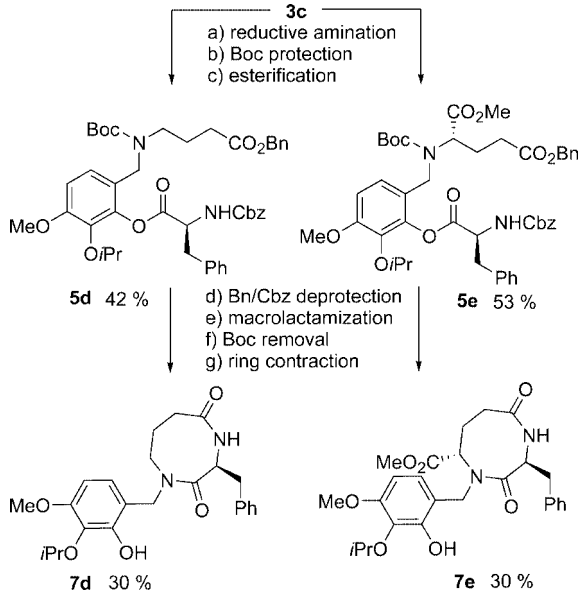
Scheme 4. Synthesis of the seven-membered bis(lactams).

Hydrogenolytic removal of the Bn and Cbz groups from **5a** and **5b** provided the precursors for the tethered macrolactamization step (Scheme 4). Activation of the carboxylic acid by EDCI/HOBt under diluted conditions (10^{-3} M) smoothly gave the medium-sized lactams **6a** and **6b**, respectively, without the detectable formation of dimers or oligomers. Also, no premature intermolecular aminolysis was observed, indicating that the isopropyl group exerts sufficient steric bulk to shield the ester.

The obtained lactams **6a** and **6b** were not purified, as this led to inevitable loss of the products, so the crude mixture was carried on in further reactions. "TFA-mediated" removal of the Boc group from both crude **6a** and **6b** was followed by "$NaHCO_3$-mediated" neutralization inducing the final ring contraction providing the *N*-benzyl-substituted 1,4-diazepine-2,5-diones **7a** and **7b** in overall yields of 72% and 85%, respectively, over four steps.

We then turned our attention to the eight-membered bis(lactam) series. Only a few examples of substituted 1,4-diazocane-3,8-diones are known which show interesting biological activities.[19] Herein it has been described that the cyclizations of the linear precursors gave low yields only. To show the applicability of the method, two substituted 1,4-diazocane-3,8-diones **7d** and **7e** were addressed. The latter example also bears substituents next to the amine and carboxyl auxiliary connecting groups, a sequence that was inaccessible using the previously described auxiliary **3** (R^1 = H, R^2 = O*t*Bu).

The reductive amination of γ-Abu–OBn and Glu(OMe)–OBn with the auxiliary and subsequent Boc protection smoothly gave the phenols in good yields of 69% and 54%, respectively (Scheme 5). For these two examples esterification using the coupling reagents EDCI and DMAP only gave low yields. To our delight the more powerful acyl fluoride coupling using Cbz–Phe–F and DIPEA gave the esters **5d** and **5e** in good yields of 61% and 99%, respectively, for these very hindered couplings.



Scheme 5. Synthesis of the eight-membered bis(lactams).

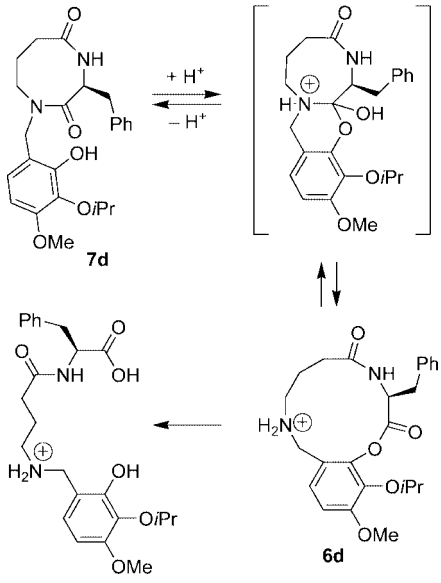
The rest of the sequence was continued using the optimized conditions resulting in the formation of the products **7d** and **7e** in yields of 30% over four steps. Macrolactamization reactions were run at a concentration of 10^{-3} M to avoid any oligomerization. These two examples have shown the efficiency of our method for substituted eight-membered bis(lactams) giving the products in acceptable overall yields.

Evaluation of the enantiomeric purity of the products **7d** and **7e** was performed by hydrolysis of the products in strong acidic media and subsequent GC-MS analysis for the presence of L-Phe and D-Phe. This revealed an enantiomeric excess of 80% for **7d** and 97% for **7e**, indicating that no extensive racemization had occurred.

In the case of the seven-membered bis(lactams) the auxiliary remainings were removed by treatment of both **7a** and **7b** with TFA in the presence of anisole at 60 °C liberating the target (*S*)-3-benzyl-1,4-diazepine-2,5-dione **2a**[8d,10] in nearly quantitative yields after precipitation with diethyl ether/pentane (Scheme 4).

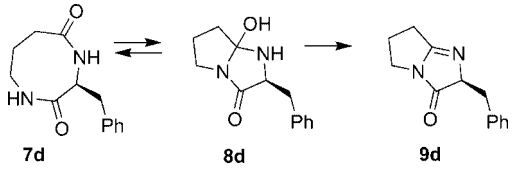
Evaluation of the enantiomeric purity of the product **2a** by chiral HPLC showed that no extensive racemization had occurred, especially during the coupling of the α-substituted amino acid in route II (Scheme 3; route I: *ee* = 97%; route II: *ee* = 90%). Compared to experiments using more hindered templates (R^2 = O*t*Bu, OTIPS; data not shown) giving extensive epimerization due to slow esterification reactions (*ee* values only up to ca. 60%), the enantiomeric purity had greatly improved especially during the hindered coupling along route II.

Unexpectedly, removal of the auxiliaries from both the eight-membered bis(lactams) **7d** and **7e** only led to side reactions. Treatment of **7d** and **7e** with TFA in the presence of anisole at 60 °C resulted, as became clear by careful LC-MS and MS-MS analysis, in re-attack of the phenol to the tertiary amide forming back the ester and the amine as it's TFA salt (Scheme 6; **7d** shown). Most probably this is due to the unfavored eight-membered ring as becomes apparent from the amide carbonyl IR absorptions of **7e** (1731 and 1664 cm^{-1}) showing the ketone character of the tertiary amide carbonyl moiety due to loss of planarity of this amide to relief ring-strain. To prevent these side reactions it was tried to methylate the phenolic hydroxy group, but all attempts were unsuccessful (not shown).[20]



Scheme 6. Possible auxiliary-mediated side reactions from **7**.

Furthermore, by LC-MS imidazolone **9d** was characterized. The formation of **9d** can be envisioned by an equilibrium of **7d** with the bicyclic hemiaminal **8d** by transannular attack of the γ-amino acid amide nitrogen atom on the opposite amide carbonyl moiety followed by loss of water (Scheme 7).[21] This may also explain the difficulties in the removal of the template from both products **7d** and **7e** by treatment with TFA.



Scheme 7. Possible transannulation process providing **9d**.

Conclusions

We have optimized our auxiliary-based approach towards medium-sized bis(lactams) that are difficult to access using traditional methodologies. Auxiliary **3c** allows straightforward synthesis of the cyclization precursors and can be efficiently removed from the seven-membered bis(lactams). However, removal of the auxiliary from the eight-membered bis(lactms) is hindered by unwanted side reactions and possible product instability. Currently, auxiliary **3c** is developed further to allow solid-phase combinatorial access towards a library of medium-sized bis(lactams)[22] as well as the use of auxiliary **3c** in the synthesis of cyclic tetrapeptides with all-L configuration.[23]

Experimental Section

General: All reactions were conducted under nitrogen unless stated otherwise and monitored by TLC on silica gel coated aluminium sheets. Flash column chromatography was performed on silica gel 300–400 mesh using the indicated solvent mixtures. All solvents were distilled from sodium/benzophenone ketyl (THF, Et_2O) or CaH_2 (DMF, CH_2Cl_2). The NMR spectra were determined in $CDCl_3$ solutions, using a Bruker ARX 400 and a Varian Inova 500 spectrometer unless indicated otherwise. Spectra are reported in δ units (ppm) and J values (Hz) with Me_4Si as the internal standard. HRMS data (FAB^+) were recorded with a JEOL JMS SX/SX 102A four-sector mass spectrometer. The LC-MS experiments were performed with the use of a Finnigan LXQ Ion Trap apparatus. LC was carried out with an ODS-3 column using gradients between H_2O/0.1% HCOOH (solvent A) and CH_3CN/0.1% HCOOH (solvent B). The electronspray ionization mass spectra (positive ions) were recorded in full scan mode (m/z = 100–2000). The MS-MS experiments were performed by collision-induced dissociation with an indicated collision energy of 30 eV. Infrared (IR) spectra were obtained with a Bruker IFS 28 FTIR spectrometer and are reported in wave numbers [cm^{-1}]. Melting points were recorded with a Büchi melting point apparatus B-545 and are uncorrected. HPLC analyses were measured with an Agilent HPLC system equipped with a C-18 column (Varian-Chrompack, inertsil-ODS-3, 3μ, 50 × 4.6 mm), a maximum flowspeed of 2.0 mL/min, the UV/Vis detector at λ = 220 or 254 nm as indicated, and a gradient of 100% A to 100% B [A: H_2O/CH_3CN/HCOOH (95:5:0.04); B: H_2O/CH_3CN/HCOOH (5:95:0.04)] as the eluent in 5 min. The enantiomeric excess values of compounds **2a** were determined at DSM Pharma Chemicals and obtained from chiral HPLC analyses. Measurements were taken on I.D. Chiralpack AD column (25 × 0.46 cm), a flowspeed of 1 mL/min, the UV/Vis detector at λ = 210 nm, and *n*-heptane/*i*PrOH (55:45%v/v) as the eluent.

2-Hydroxy-3-isopropoxy-4-methoxybenzaldehyde (3c): Compound **3b** (0.5 g, 3 mmol) was added in small portions to a solution of sodium hydride (0.240 g, 60% w/w in mineral oil, 6 mmol) in dry DMSO (8 mL). The solution was stirred for 20 min, after which potassium iodide (0.498 g, 3 mmol) and 2-bromopropane (0.282 mL, 3 mmol) were added. The reaction mixture was stirred at room temperature for 16 h after which it was diluted with EtOAc (30 mL) and washed with water (2 × 40 mL). The organic phase was then washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:9] to give aldehyde **1c** as yellowish needles (0.193 g, 0.92 mmol, 31%). M.p. 81–83 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.14 (s, 1 H), 9.74 (s, 1 H), 7.27 (d, J = 8.4 Hz, 1 H), 6.59 (d, J = 8.8 Hz, 1 H), 4.46 (sept, J = 6.4 Hz, 1 H), 3.92 (s, 3 H), 1.32 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 160.0, 156.3, 134.1, 129.9, 116.5, 103.9, 75.3, 56.2, 22.5 ppm. IR (neat): $\tilde{\nu}$ = 1639, 1502, 1439 cm^{-1}.

General Procedure for Reductive Amination and Boc Protection: The appropriate amine (1.1 equiv.) and Na_2SO_4 (excess) was added to a solution of the aldehyde in THF. The reaction mixture was then stirred at room temperature for 3–5 h after which $Na(OAc)_3BH$ (4 equiv.) was added and stirring was continued for 16 h. The reaction mixture was then quenched by pouring it into saturated ammonium chloride solution and stirring for 30 min. The remaining mixture was quenched with saturated sodium hydrogen carbonate solution and extracted with EtOAc. The organic phase was then washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was used without purification in the next step. If necessary the resulting oil can be purified by flash column chromatography [silica gel, ethyl acetate/petroleum ether (40:65), 1:3]. To a solution of the amine in dry CH_2Cl_2 was added $(Boc)_2O$ (1.1–1.5 equiv.), and the reaction mixture was stirred at room temperature until completed. The reaction mixture was then washed with $NaHCO_3$ (sat.) and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:9, then 1:4].

Benzyl 2-[*tert*-Butoxycarbonyl(2-hydroxy-3-isopropoxy-4-methoxybenzyl)amino]-3-phenylpropionate (4a): According to the general procedure, using aldehyde **3c** (0.070 g, 0.33 mmol) and H_2N–Phe–OBn (0.084 g, 0.33 mmol), the product **4a** (0.164 g, 0.30 mmol, 91%) was obtained as a colorless oil. ^{1}H NMR (125 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 10 H), 6.76 (d, J = 8.5 Hz, 1 H), 6.27 (d, J = 8.3 Hz, 1 H), 5.85 (br. s, 1 H), 5.07–4.95 (m, 2 H), 4.60–4.24 (m, 3 H), 3.79 (s, 3 H), 3.70 (m, 1 H), 3.38 (dd, J = 13.8, J = 5.1 Hz, 1 H), 3.25–3.13 (m, 1 H), 1.42 (s, 9 H), 1.27 (d, J = 6.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 155.7, 152.7, 149.3, 137.9, 135.2, 129.2, 128.3, 128.2, 127.9, 127.8, 126.4, 125.3, 116.2, 103.0, 81.4, 74.9, 66.5, 61.7, 55.6, 47.4, 36.2, 28.1, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 1710, 1697, 1616, 1506, 1455 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{32}H_{40}O_7N$ 550.2810, found 550.2801.

Benzyl 3-[*tert*-Butoxycarbonyl(2-hydroxy-3-isopropoxy-4-methoxybenzyl)amino]propionate (4b): According to the general procedure, using aldehyde **3c** (0.169 g, 0.8 mmol) and H_2N–βAla–OBn (0.179 g, 1 mmol), the product **4b** (0.416 g, 0.73 mmol, 91%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (br. s, 1 H), 7.40–7.35 (m, 5 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.42 (d, J = 8.4 Hz, 1 H), 5.12 (s, 2 H), 4.52 (br. s, 1 H), 4.38 (s, 2 H), 3.38 (s, 3 H), 3.53 (br. s, 2 H), 2.60 (br. s, 2 H), 1.48 (s, 9 H), 1.31 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 135.7, 128.5, 128.2, 128.2, 127.6, 127.0, 124.6, 117.0, 103.2, 75.0, 66.3, 60.4, 55.8, 46.3, 42.8, 33.6, 28.4, 22.5 ppm. IR (neat): $\tilde{\nu}$ = 1734, 1688, 1652, 1506, 1456 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{26}H_{36}O_7N$ 474.2490, found 474.2429.

Benzyl 4-[*tert*-Butoxycarbonyl(2-hydroxy-3-isopropoxy-4-methoxybenzyl)amino]butyrate (4d): According to the general procedure, using aldehyde **3c** (0.300 g, 1.4 mmol) and H_2N–γAbu–OBn (0.348 g, 1.8 mmol), the product **4d** (0.468 g, 0.96 mmol, 69%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br. s, 1 H), 7.39–7.33 (m, 5 H), 6.81 (d, J = 8.8 Hz, 1 H), 6.40 (d, J = 8.4 Hz, 1 H), 5.13 (s, 2 H), 4.50 (br. s, 1 H), 4.35 (s, 2 H), 3.83 (s, 3 H), 3.25 (br. s, 2 H), 2.36 (t, J = 7.2 Hz, 2 H), 1.89 (quint, J = 7.2 Hz, 2 H), 1.47 (s, 9 H), 1.32 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 156.0, 140.9, 135.9, 133.0, 128.6, 128.6, 128.2, 127.6, 127.0, 124.7, 117.1, 103.1, 75.0, 66.4, 66.3, 65.4, 55.8, 45.7, 31.5, 28.4, 23.3, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 1737, 1690, 1654, 1504, 1455 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{27}H_{37}O_7N$ 487.2570, found 487.2568.

5-Benzyl 1-Methyl 2-[*tert*-Butoxycarbonyl(2-hydroxy-3-isopropoxy-4-methoxybenzyl)amino]pentanedioate (4e): According to the general procedure, using aldehyde **3c** (0.200 g, 0.95 mmol) and H_2N–Glu(OBn)–OMe (0.475 g, 1.3 mmol), the product **4e** (0.277 g, 0.51 mmol, 54%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 5 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.36 (d, J = 8.4 Hz, 1 H), 5.06 (m, 2 H), 4.70 (br. s, 1 H), 4.40 (m, 3 H), 4.08 (m, 1 H), 3.80 (br. s, 3 H), 3.58 (br. s, 3 H), 2.25 (br. m, 4 H), 1.43 (s, 9 H), 1.28 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 171.5, 156.4, 153.6, 151.5, 135.8, 134.0, 128.5, 128.2, 128.2, 127.6, 127.0, 125.3, 123.1, 116.3, 103.1, 102.6, 75.1, 74.9, 66.8, 66.4, 61.0, 60.5, 58.9, 55.7, 53.6, 52.2, 51.7, 46.3, 42.8, 30.8, 30.2, 28.2, 23.5, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 1734, 1688, 1652, 1506, 1456 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{29}H_{39}O_9N$ 545.2625, found 545.2620.

General Procedure for Esterification: To a solution of the phenol in dry MeCN was added the appropriate acid followed by EDCI and DMAP. The reaction mixture was then stirred at room temperature until completion, after which the solvent was evaporated and the residue taken up in EtOAc and washed with a solution of potassium hydrogensulfate (0.5 M, 2×) and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:3–4] to yield the product.

Benzyl 2-[{2-[3-(Benzyloxycarbonylamino)propionyloxy]-3-isopropoxy-4-methoxybenzyl}(*tert*-butoxycarbonyl)amino]-3-phenylpropionate (5a): According to the general procedure, using phenol **4a** (0.100 g, 0.18 mmol) and Cbz–β-Ala–OH (0.080 g, 0.36 mmol), the product **5a** (0.096 g, 0.13 mmol, 71%) was obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.04 (m, 15 H), 6.80 (d, J = 8.5 Hz, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 5.65 (br. s, 1 H), 5.13–5.05 (m, 5 H), 4.36 (m, 2 H), 3.88 (br. s, 1 H), 3.79 (s, 3 H), 3.55 (br. s, 3 H), 3.34 (m, 1 H), 3.06 (m, 1 H), 2.71 (br. m, 2 H), 1.44 (s, 9 H), 1.16 (br. d, J = 6.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.8, 156.3, 154.6, 153.0, 143.6, 138.2, 136.4, 135.3, 129.2, 129.1, 128.3, 128.1, 127.9, 126.4, 124.5, 122.2, 109.4, 80.9, 75.2, 66.7, 66.4, 60.9, 55.7, 46.9, 36.5, 36.3, 34.2, 28.2, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 1723, 1698, 1498, 1454 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{43}H_{51}O_{10}N_2$ 755.3545, found 755.3527.

6-({[2-(Benzyloxycarbonyl)ethyl](*tert*-butoxycarbonyl)amino}-methyl)-2-isopropoxy-3-methoxyphenyl 2-(Benzyloxycarbonylamino)-3-phenylpropionate (5b): Cbz–Phe–F (0.127 g, 0.42 mmol) and DIPEA (0.073 mL, 0.42 mmol) were added to a solution of the phenol **4b** (0.100 g, 0.21 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc (15 mL) and washed with water (2 × 15 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:4] to yield the product **5b** (0.133 g, 0.18 mmol, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 15 H), 7.03 (bd, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 5.17–4.99 (m, 5 H), 4.51 (br. s, 1 H), 4.28–4.17 (br. m, 2 H), 3.86 (s, 3 H), 3.46–3.14 (br. m, 4 H), 2.59–2.50 (br. m, 2 H), 1.48 (s, 9 H), 1.23 (br. d, J = 14.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 169.5, 155.8, 155.4, 152.1, 141.8, 137.0, 135.7, 129.5, 129.3, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.0, 126.9, 124.0, 120.1, 110.2, 80.1, 75.2, 66.9, 66.3, 60.4, 55.8, 54.8, 45.2, 43.1, 37.8, 33.5, 28.4, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 1769, 1727, 1693, 1498, 1454 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{43}H_{50}O_{10}N_2$ 754.3465, found 754.3450.

Benzyl 4-[{2-[2-(Benzyloxycarbonylamino)-3-phenylpropionyloxy]-3-isopropoxy-4-methoxybenzyl}(*tert*-butoxycarbonyl)amino]butyrate (5d): Cbz–Phe–F (0.579 g, 1.92 mmol) and DIPEA (0.334 mL,

1.92 mmol) were added to a solution of the phenol **4d** (0.468 g, 0.96 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc (45 mL) and washed with water (2 × 45 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:4] to yield the product **5d** (0.447 g, 0.58 mmol, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 15 H), 6.97 (br. d, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 5.13–5.09 (m, 4 H), 4.99 (q, J = 7.6 Hz, 1 H), 4.52 (br. s, 1 H), 4.25–4.13 (br. m, 2 H), 3.86 (s, 3 H), 3.45–3.14 (br. m, 4 H), 2.30 (m, 2 H), 1.88–1.63 (m, 2 H), 1.49 (br. s, 9 H), 1.36–1.22 (br. m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 169.5, 155.8, 135.9, 129.5, 128.7, 128.5, 128.4, 128.4, 128.1, 128.0, 127.1, 126.9, 124.0, 120.1, 110.2, 79.8, 75.2, 66.9, 66.2, 60.3, 56.0, 54.9, 45.2, 44.2, 37.9, 31.4, 28.4, 23.2, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 1769, 1729, 1694, 1498, 1455 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{44}H_{52}O_{10}N_2$ 768.3622, found 768.3624.

5-Benzyl 1-Methyl 2-[{2-[2-(Benzyloxycarbonylamino)-3-phenylpropionyloxy]-3-isopropoxy-4-methoxybenzyl}(*tert*-butoxycarbonyl)amino]pentanedioate (5e): Cbz–Phe–F (0.307 g, 1.02 mmol) and DIPEA (0.178 mL, 1.02 mmol) were added to a solution of the phenol **4e** (0.277 g, 0.51 mmol) in dry CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc (15 mL) and washed with water (2 × 15 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (boiling range 40–65 °C), 1:4] to yield the product **5e** (0.421 g, 0.51 mmol, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 15 H), 7.06 (br. d, J = 8.0 Hz, 1 H), 6.75 (d, J = 8.4 Hz, 1 H), 5.08–4.95 (m, 5 H), 4.46 (br. s, 1 H), 4.37–4.29 (br. m, 2 H), 4.06 (q, J = 6.8 Hz, 1 H), 3.81 (br. s, 3 H), 3.56 (br. s, 3 H), 3.44 (m, 1 H), 3.15 (m, 1 H), 2.31 (m, 3 H), 2.02 (m, 1 H), 1.66 (m, 1 H), 1.41 (s, 9 H), 1.18 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 171.5, 169.5, 155.7, 155.0, 153.3, 143.4, 138.7, 136.3, 135.8, 129.4, 128.4, 128.3, 128.3, 128.1, 127.7, 127.1, 126.8, 124.6, 122.6, 109.8, 80.9, 75.1, 66.6, 66.1, 60.3, 58.6, 58.3, 55.9, 54.8, 51.8, 46.4, 37.7, 31.8, 28.2, 25.4, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 2977, 1731, 1500, 1454 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{46}H_{54}O_{12}N_2$ 826.3677, found 826.3677.

General Procedure for Tethered Lactamisation and Consecutive Ring Contraction: The starting material was dissolved in EtOAc/*i*PrOH (4:1). Pd/C (20%) was then added, and the mixture was brought under hydrogen and stirred for 16 h. The reaction mixture was then filtered through Celite and concentrated in vacuo. The remaining residue was dissolved in CH_2Cl_2/DMF (4:1; c = 10^{-3} M) followed by addition of EDCI (4 equiv.) and HOBt (4 equiv.). The mixture was then stirred at room temperature for 4–6 h, after which the reaction mixture was diluted with diethyl ether, extracted (3×) and washed with saturated sodium hydrogencarbonate solution, a potassium hydrogensulfate solution (0.5 M) and brine. The organic phase was then dried with Na_2SO_4 and concentrated in vacuo to give the crude medium-sized lactam, which was used in the consecutive ring contraction without purification. The medium-sized lactam was dissolved in a mixture of TFA/CH_2Cl_2 (1:1) and stirred at room temperature for 16 h. The solvent was evaporated, after which the remaining TFA salt was dissolved in EtOAc (c = 10^{-2} M) and an excess of solid sodium hydrogencarbonate was added. After 4–5 h, the reaction mixture was washed with a solution of potassium hydrogensulfate (0.5 M, 2×) and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The remaining residue can be purified by flash column chromatography [silica gel; ethyl acetate/petroleum ether (40:65), 1:1 → ethyl acetate/10% *i*PrOH] to yield the product.

3-Benzyl-4-(2-hydroxy-3-isopropoxy-4-methoxybenzyl)-1,4-diazepan-2-one (7a): According to the general procedure, using **5a** (0.089 g, 0.12 mmol), the product **7a** (0.033 g, 0.080 mmol, 68%) was obtained as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (br. s, 1 H), 7.38–7.20 (m, 10 H), 6.66 (d, J = 8.6 Hz, 1 H), 6.36 (d, J = 8.6 Hz, 1 H), 4.85 (AB, J = 14.5 Hz, 1 H), 4.59 (X part of ABX, J_{AX} + J_{BX} = 14.3 Hz, 1 H), 4.53 (sept, J = 6.2 Hz, 1 H), 3.82 (m, 1 H), 3.80 (s, 3 H), 3.49–3.33 (m, 2 H), 3.37 and 3.24 (AB part of ABX, J_{AB} = 13.6, J_{BX} = 9.8, J_{AX} = 4.5 Hz, 2 H), 3.20 (AB, J = 14.4 Hz, 1 H), 2.79 (m, 1 H), 1.23 (d, J = 6.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 172.3, 152.7,149.0, 136.6, 133.3, 129.5, 129.3, 129.2, 129.0, 128.8, 128.6, 127.4, 125.3, 115.2, 103.4, 75.1, 55.8, 55.7, 48.7, 40.4, 40.0, 36.1, 22.5 ppm. IR (neat): $\tilde{\nu}$ = 2923, 2852, 1654, 1503, 1458 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{23}H_{29}O_5N_2$ 413.2078, found 413.2095.

3-Benzyl-1-(2-hydroxy-3-isopropoxy-4-methoxybenzyl)-1,4-diazepane-2,5-dione (7b): According to the general procedure, using **6b** (0.075 g, 0.1 mmol), the product **7b** (0.028 g, 0.068 mmol, 68%) was obtained as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 6.95 (d, J = 8.6 Hz, 1 H), 6.75 (s, 1 H), 6.43 (d, J = 8.6 Hz, 1 H), 5.59 (s, 1 H), 4.68 (AB, J = 14.3 Hz, 1 H), 4.56 (m, 2 H), 4.54 (AB, J = 12.0 Hz, 1 H) 3.87 (m, 1 H), 3.82 (s, 3 H), 3.49 (m, 1 H), 3.41 and 2.89 (AB part of ABX, J_{AB} = 14.7, J_{BX} = 9.6, J_{AX} = 4.7 Hz, 2 H), 2.50 (m, 2 H), 1.27 (d, J = 12 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 170.2, 152.8, 149.0, 136.1, 133.6, 129.2, 129.1, 127.3, 125.3, 115.4, 103.8, 75.2, 55.8, 53.9, 45.8, 42.2, 36.9, 35.1, 22.5 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2853, 1649, 1504, 1454 cm^{-1}. HRMS (FAB$^+$): calcd. for $C_{23}H_{29}O_5N_2$ 413.2078, found 413.2069.

3-Benzyl-1-(2-hydroxy-3-isopropoxy-4-methoxybenzyl)-1,4-diazocane-2,5-dione (7d): According to the general procedure, using **5d** (0.400 g, 0.52 mmol), the product **7d** (0.059 g, 0.35 mmol, 67%) was obtained as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H), 6.75 (d, J = 8.4 Hz, 1 H), 6.38 (d, J = 8.4 Hz, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 4.67 (AB, J = 14.4 Hz, 1 H), 4.52 (m, 2 H), 4.31 (AB, J = 14.4 Hz, 1 H), 3.83 (s, 3 H), 3.52 (m, 2 H), 3.33 and 3.03 (AB part of ABX, J_{AB} = 14.0, J_{BX}= 7.2, J_{AX} = 7.2 Hz, 2 H), 2.53 (m, 2 H), 1.88 (m, 2 H), 1.30 (dd, J = 12.6, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 172.6, 153.1, 149.4, 137.0, 134.0, 129.2, 128.7, 126.9, 124.8, 115.4, 103.4, 75.1, 55.8, 54.1, 49.0, 46.7, 36.7, 35.9, 25.6, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2974, 2853, 1651, 1504, 1454 cm^{-1}. HRMS (FAB$^+$): fcalcd. or $C_{24}H_{30}O_5N_2$ 426.2155, found 426.2158.

Methyl 2-Benzyl-4-(2-hydroxy-3-isopropoxy-4-methoxybenzyl)-3,8-dioxo-1,4-diazocane-5-carboxylate (7e): According to the general procedure, using **5e** (0.400 g, 0.48 mmol), the product **7e** (0.07 g, 0.014 mmol, 30%) was obtained as a white solid. Recrystallisation from hexane/CH_2Cl_2 gave the product as white needles. M.p. 180–181.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 5 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.69 (d, J = 8.8 Hz, 1 H), 6.19 (d, J = 9.2 Hz, 1 H), 4.98 (q, J = 8.8 Hz, 1 H), 4.28 (quint, J = 6.4 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.54 (AB, J = 10.8 Hz, 1 H), 3.47 (AB, J = 10.8 Hz, 1 H), 3.36 and 3.09 (AB part of ABX, J_{AB} = 14.2, J_{BX} = 8.0, J_{AX} = 7.6 Hz, 2 H), 3.31 (dd, J = 10.0, J = 3.6 Hz, 1 H), 2.42 (m, 1 H), 2.08 (m, 3 H), 1.69 (br. s, 1 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.01 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 173.5, 167.5, 153.4, 143.8, 139.9, 136.5, 129.3, 129.0, 128.6, 126.9, 124.6, 124.2, 109.5, 75.4, 62.3, 56.0, 54.2, 51.9, 48.6, 36.3, 35.5, 26.6, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 2973, 2838, 1749,

1731, 1664, 1534, 1498 cm^{-1}. HRMS (FAB^+): calcd. for $C_{26}H_{32}O_7N_2$ 484.2210, found 484.2199.

3-Benzyl-1,4-diazepane-2,5-dione (2a): Bis(lactams) **7a** and **7b** were dissolved in TFA (ca. 2–4 mL), and anisole (10 equiv.) was added. The reaction mixture was stirred at 60 °C for 16 h, after which it was concentrated in vacuo. The pure product was isolated by precipitation with diethyl ether and pentane, to provide **2a**.[8d,10]

Supporting Information (see footnote on the first page of this article): Analytical, LC-MS and NMR spectroscopic data of all new compounds.

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