Synthesis of Azabicycloalkane Amino Acid Scaffolds as Reverse-Turn Inducer Dipeptide Mimics

Mauro Angiolini,[a] Silvia Araneo,[c] Laura Belvisi,[a] Edoardo Cesarotti,[c] Anna Checchia,[a] Luca Crippa,[a] Leonardo Manzoni,[a] and Carlo Scolastico*[a,b]

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In an effort to design dipeptide structural mimics of protein and peptide reverse-turns, a series of 5,5-, 6,5-, and 7,5-fused 2-oxo-1-azabicycloalkane amino acids has been synthesized. A new and convenient synthetic route utilizing a Horner–Emmons reaction followed by double-bond reduction has been used to prepare the bicyclic lactams in high yields.

Introduction

The synthesis of so-called peptidomimetic molecules has been a very active and productive field of research in drug design.[1] The rationale for the development of peptide analogues is that these molecules will have the same biological effects as natural peptides, but at the same time will be metabolically more stable. Of particular interest has been the replacement of reverse-turn dipeptide motifs with constrained molecules that reproduce their conformational features.[1,2] This goal has been frequently achieved using the oxoazabicyclo[*X*.*Y*.0]alkane skeleton (Figure 1) and/or heteroatom analogues thereof.[3] This has created a demand for efficient synthetic approaches toward such molecules; many methods have been introduced, which have recently been reviewed.[3] One particularly effective and versatile route, developed by Lubell et al., has been employed for the preparation of enantiopure indolizidinone-type 6,5-fused bicyclic lactams (Figure 1, $m = 1$, $n = 1$).[4] Several procedures are also available for the synthesis of 7,5-fused bicyclic lactams (Figure 1, $m = 1$, $n = 2$),[3] the majority of which require relatively long synthetic sequences. On the contrary, there are not many published protocols that allow the synthesis of 5,5-fused bicyclic lactams (Figure 1, $n = 0$).[3]

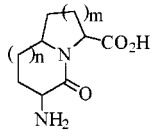

Figure 1. Azabicyclo[*X*.*Y*.0]alkane amino acids

[a] Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano,
via G. Venezian 21, 20133 Milano, Italy
[b] Centro CNR per lo Studio delle Sostanze Organiche Naturali, via G. Venezian 21, 20133 Milano, Italy
[c] Dipartimento di Chimica Inorganica, Organometallica e Analitica, Università degli Studi di Milano,
via G. Venezian 21, 20133 Milano, Italy
Fax: (internat.) + 39-2/236-4369
E-mail: scola@iumchx.chimorg.unimi.it

In the course of our studies on peptide secondary structure mimics, we have synthesized several 6,5- and 7,5-fused 2-oxo-1-azabicyclo[*X*.3.0]alkane amino acids using radical[5a,5b] or ionic reactions.[5c] These structures can be regarded as conformationally restricted substitutes for Ala-Pro and Phe-Pro dipeptide units, and, if their conformations meet certain criteria, they can be used to replace the central ($i + 1$ and $i + 2$) residues of β-turns.[6] All possible diastereomeric 2-oxo-1-azabicyclo[*X*.3.0]alkane amino acids that include a natural [Cα(*S*)] Pro unit and differ in the configuration at the bridgehead atom and at the *N*-bearing C3 are depicted in Figure 2. According to the relative configuration of Pro-Cα and of the bridgehead, they have been classified as *cis*-fused (**1**−**3**, **7**−**9**) or *trans*-fused (**4**−**6**, **10**−**12**) lactams. Their conformational properties have been investigated by computational and spectroscopic means, and the results are reported in the preceding paper in this issue.[6a]

With the aim of obtaining an improved reaction sequence, amenable to large-scale preparation and suitable for the synthesis of many different bicyclic lactams from common intermediates, a new convenient general scheme has now been developed (Scheme 1).

Starting from prolines **13**−**17**, a (*Z*)-selective Horner−Emmons olefination followed by double-bond reduction has been used to build the second ring. The starting aldehydes were stereoselectively synthesized by modifications of known procedures (vide infra). Stereorandom double-bond reduction was performed using H_2/Pd to yield, after cyclization, mixtures of easily separable epimers. Stereoselective hydrogenation was studied for the synthesis of 6,5-fused lactams, and was achieved with 80% *de* using (chiral phosphane)Rh catalysts. Our new strategy offers structural diversity, in terms of ring size and stereochemistry of the azabicycloalkane fragment, as well as access to the less common 5,5-fused bicyclic scaffold.

Following the above procedure, all the *cis*-fused lactams **1**−**3** and **7**−**9**, as well as the 6,5- and 7,5-*trans*-fused lactams **5**, **6**, **11**, and **12** have been synthesized.

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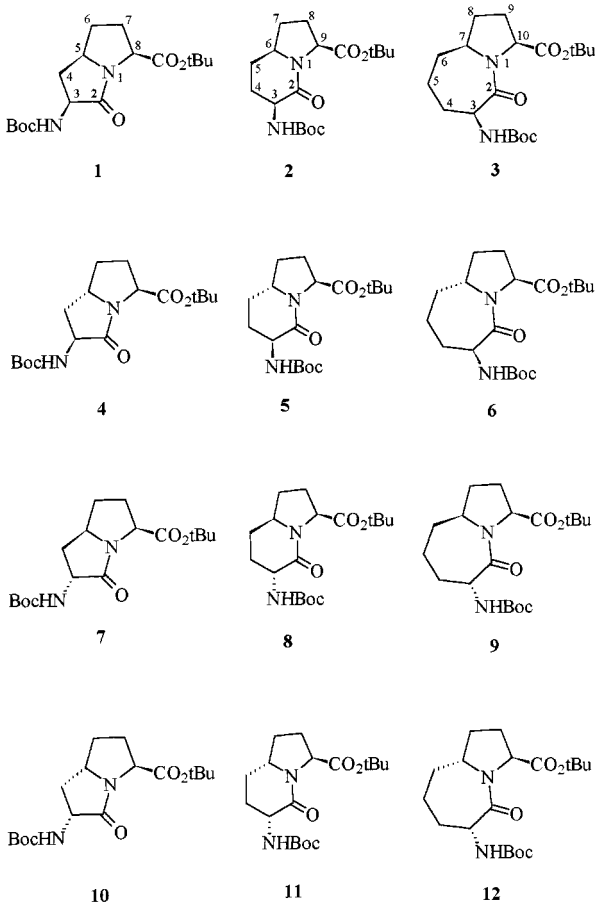
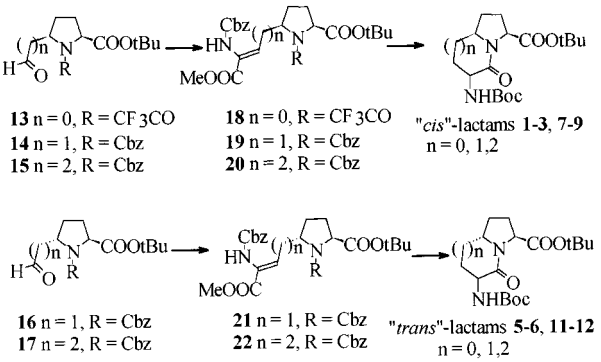


Figure 2. Bicyclic dipeptide mimics **1-12**



Scheme 1

Results and Discussion

The syntheses of lactams **1**−**3**, **5**−**9**, **11**, and **12** were accomplished following the common steps outlined in Scheme 1. Starting from the *cis*- or *trans*-proline aldehydes **13**−**17**, a Horner−Emmons olefination with the potassium enolate of (±)-(*Z*)-α-phosphonoglycine trimethyl ester[7] was used to set up the requisite carbon chain. Following protecting group manipulation (vide infra), reduction of the enamino acrylic acids and treatment with condensing agents gave the lactams of both the "*cis*" and "*trans*" series in good yields.

In all cases where stereoisomeric mixtures of lactams were formed, they could easily be separated by flash chromatography. Their configurations were assigned with the aid of NOE experiments.

The synthetic scheme is best illustrated by the synthesis of the 6,5-fused "*cis*"-lactams **2** and **8** (Scheme 2). The requisite *cis*-aldehyde **14** was obtained from the known *cis*-5-allylproline derivative **23**[8] and treated with the commercially available phosphonate **24**[7] to give **19** in 98% yield with a 7:1 (*Z*)/(*E*) ratio.

Hydrogenation of **19** occurred initially at the enamino Cbz group, and thus resulted in a complex mixture of products. To circumvent this problem, the substrate was treated with Boc_2O to give **25** (98%). Reduction of **25** with H_2/$Pd(OH)_2$ followed by reflux in MeOH gave a 1.4:1 mixture of **8** and **2**, which could easily be separated by flash chromatography. Starting from **14**, the whole sequence requires only two chromatographic separations (purification of **19** and separation of **8** from **2**) and can easily be carried out on a multigram scale.

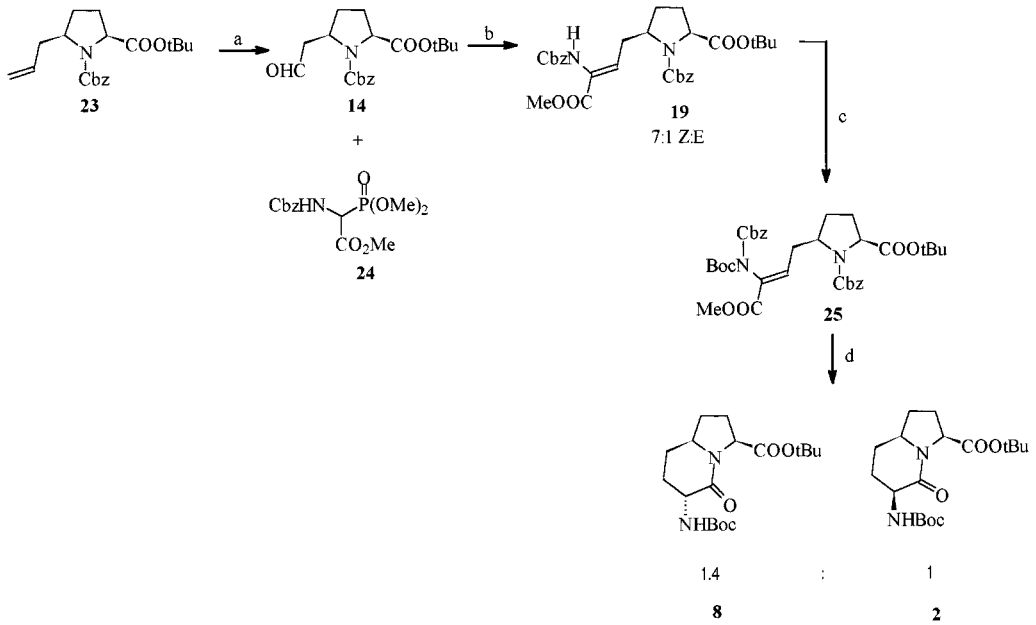
The stereoselective preparation of the two C3 epimers **8** and **2** (Scheme 3) was attempted by means of (chiral phosphane)Rh-catalyzed hydrogenation of the enamino acid **26**.

The (chiral phosphane)Rh-catalyzed hydrogenation is a powerful and well-established means of access to both naturally occurring and non-natural amino acids and the catalytic asymmetric hydrogenation of dehydropeptides represents a logical extension of this methodology to the preparation of biologically active chiral oligo- and polypeptides.[9]

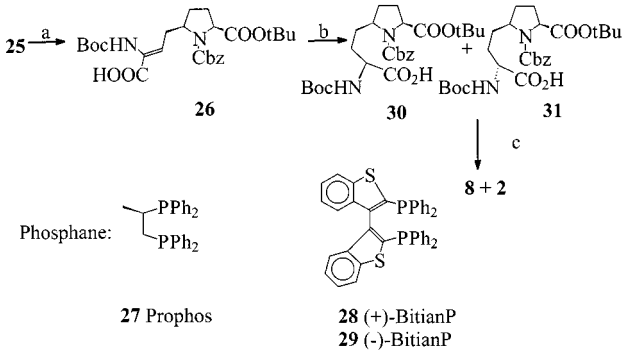
In asymmetric catalytic hydrogenations using (chiral phosphane)Rh catalysts, the highest *de* values are usually obtained starting from (*Z*)-olefins. However, the key requirement for the substrate remains the presence of an acetamido group, or an equivalent thereof, at the double bond.[10] The amide-type carbonyl group is needed in order to allow two-point coordination of the substrate to the metal centre, as has been fully elucidated experimentally.[11] For applications in peptide synthesis, protecting groups such as Boc or Cbz are preferable to the acetamido function, since they allow easy and specific deprotection. However, there have been very few examples of asymmetric catalytic hydrogenation where these protecting groups are found on the enamino nitrogen atom.[12,13] More frequently, Boc or Cbz protecting groups are present in different positions of the dehydropeptides, which are hydrogenated at their *N*-termini.[14,15]

For the catalytic asymmetric hydrogenation of **26**, [Rh(phosphane)(COD)]ClO_4 catalysts were used. The catalysts were prepared by displacing one cyclooctadiene ligand of [$Rh(COD)_2$]ClO_4 with the appropriate phosphane. The ligands investigated were (*R*)-Prophos **27**, (+)-BitianP **28**, and (−)-BitianP **29**. BitianP is a chiral atropisomeric chelating phosphane belonging to a new class of ligands based on a biheteroaromatic framework, which has been shown to give very high *ee* values in asymmetric hydrogenations of olefins and ketones.[16,17]

The results of the present asymmetric hydrogenations are reported in Table 1. The conversion was invariably quantitative and the highest stereodifferentiation was obtained



Scheme 2. a) O_3, Me_2S, 75%; b) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 98%; c) Boc_2O, 4-DMAP, THF, 98%; d) H_2, Pd/C, MeOH; MeOH, reflux, 48 h, 70%



Scheme 3. a) NaOH, MeOH, 85%; b) H_2, Rh-BitianP, MeOH; c) CH_2N_2, MeOH; H_2, Pd/C, MeOH; MeOH, reflux, 48 h, 85%

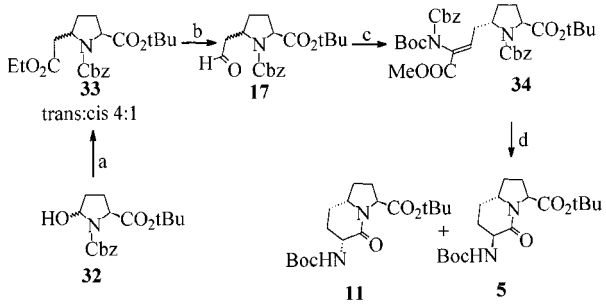
Table 1. Asymmetric hydrogenation of **26**, the reactions were carried out at room temperature for 24 h under 10 atm of H_2

Entry	Catalyst	**30/31**	*de* %
1	Rh-**27**	96:14	72
2	Rh-**28**	13:87	74
2	Rh-**29**	90:10	80

with [Rh/(−)-BitianP] (Entry 3). The results suggest that the configuration at the newly created stereocentre is mainly determined by the catalyst, which overrules the effect of the stereocentre in the substrate (Entries 2 and 3). The results also indicate that the Boc protecting group on the enamino nitrogen atom is a good replacement for the acetamido group and allows chelation of the catalyst by the olefin.

Treatment of crude **30** and **31** with CH_2N_2, followed by hydrogenation and cyclization under the usual conditions (H_2, Pd/C, followed by reflux in MeOH) allowed a stereoselective access to lactams **8** and **2**.

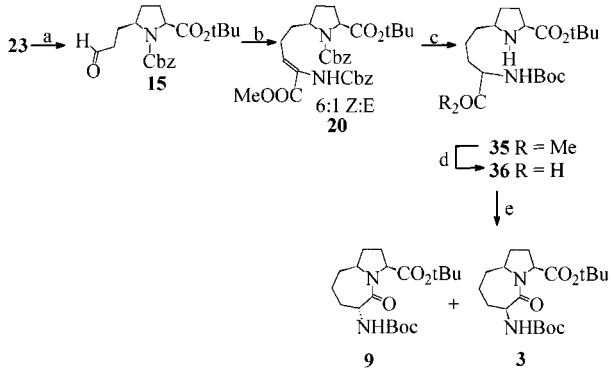
The same synthetic scheme was successfully adopted for the synthesis of the 6,5-fused "*trans*"-lactams **5** and **11**. The starting material for these compounds was the *trans*-substituted proline **17** (Scheme 4). Aldehyde **17** was best obtained from ester **33**, which was prepared in one step from *N*-Cbz-5-hydroxyproline *tert*-butyl ester (**32**)[8] as a 4:1 *trans*/*cis* mixture according to a published procedure.[18] The Horner−Emmons reaction with the potassium enolate of **24** proceeded with 99% yield. Treatment with Boc_2O, separation of the *cis*/*trans* isomers, and subsequent unselective hydrogenation (H_2, Pd/C) of the crude intermediate followed by refluxing in MeOH gave a 1.4:1 mixture of easily separable **5** and **11**.



Scheme 4. a) Triethyl phosphonoacetate, KH, DMF, 75%; b) $LiBH_4$, Et_2O, −10 °C, 94%; Dess−Martin periodinane, CH_2Cl_2, 92%; c) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 99%; Boc_2O, 4-DMAP, THF, 92% (73% *trans* isomer); d) H_2, $Pd(OH)_2$/C, MeOH; MeOH, reflux 70%

All the remaining lactams **1**, **3**, **6**, **7**, **9**, and **12** were synthesized following essentially the same sequence as described above. The main variations in the synthetic scheme arose as a result of the different conditions required for the formation of lactam rings of different sizes.

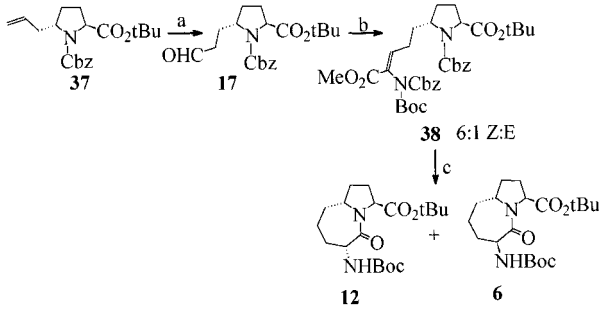
Thus, the 7,5-fused lactams **3** and **9** (Scheme 5) were prepared starting from the *cis*-aldehyde **15**, which was easily obtained from the *cis*-5-allylproline **23**.[8] Horner−Emmons reaction of **15** with **24** gave a 6:1 (*Z*)/(*E*) mixture of 2-aminoacrylates. After *N*-protection, these were reduced with



Scheme 5. a) 9-BBN, H_2O_2, 95%; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 89%; b) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 95%; c) Boc_2O, 4-DMAP, THF, 95%; H_2, Pd/C, MeOH, 83%; d) NaOH, MeOH, 84%; e) EDC, DMAP, HOBt, Et_3N, CH_2Cl_2, 72%, over 2 steps

H_2, Pd/C resulting in a 1:1 diastereomeric mixture. The thermal cyclization of methyl ester **35** could be achieved in refluxing xylene, albeit in low yields. Better results were obtained by ester hydrolysis and subsequent EDC/HOBT-promoted lactam formation to give **3** and **9**, which were easily separated by flash chromatography (51% overall yield from **23**).

The synthesis of the 7,5-fused "*trans*"-lactams **6** and **12** was achieved starting from the "*trans*"-allylproline **37** (Scheme 6).[8] Hydroboration and Swern oxidation (80% over 2 steps) gave the aldehyde **17**, which was treated with **24** to give, after nitrogen protection, **38** as a 6:1 (*Z*)/(*E*) mixture. The usual sequence (NaOH; H_2, Pd/C; lactam ring closure) allowed the isolation of **6** and **12** in 40% overall yield. However, the catalytic hydrogenation step in this case proved to be capricious, as it was often accompanied by variable quantities of by-products resulting from Michael addition of the proline nitrogen atom to the 2-aminoacrylate. Thus, L-Selectride reduction of **38** was also attempted, which yielded the diastereoisomeric methyl esters in an 85:15 ratio, with the (*R*) isomer predominating. After NaOH hydrolysis, hydrogenolytic removal of the Cbz protecting groups followed by thermally induced lactam ring formation yielded **6** and **12** in 40% overall yield in a 15:85 ratio.

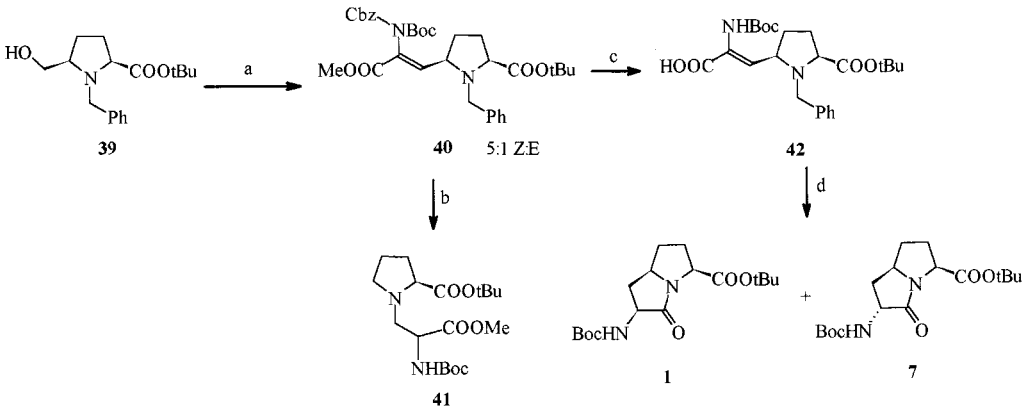


Scheme 6. a) 9-BBN, H_2O_2, 98%; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 82%; b) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 90%; Boc_2O, 4-DMAP, THF, 98%; c) NaOH, MeOH; H_2, Pd/C, 40% over 2 steps

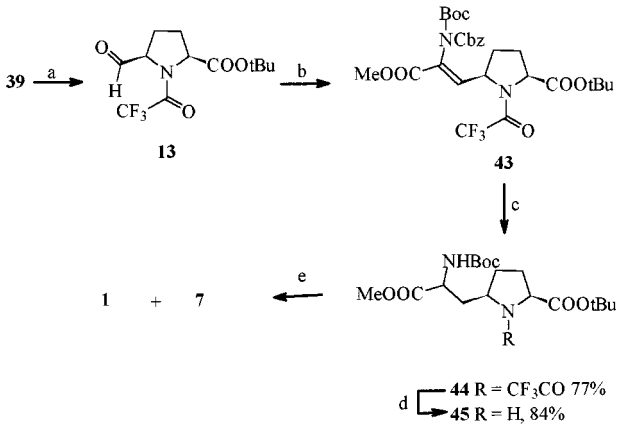
Finally, the starting material for the synthesis of the 5,5-fused "*cis*"-lactams **1** and **7** (Scheme 7) was the alcohol **39**.[5b] Oxidation and Horner−Emmons reaction with **24** followed by *N*-Boc protection gave **40** as a 5:1 (*Z*)/(*E*) mixture in 57% yield. Hydrogenation of **40** [H_2/$Pd(OH)_2$] resulted in a complex mixture of products, from which the 1,2-diamino ester **41** could be isolated in 40% yield. Some **42** was also formed, which may be attributed to initial *N*-debenzylation of **41** followed by intramolecular Michael addition to the enamino ester double bond and hydrogenolysis of the resulting aziridine. The problem could be partly circumvented by carrying out the hydrogenation starting from the acid **42**. Treatment of **42** with H_2, Pd/C followed by reflux in MeOH gave an easily separable 1:1 mixture of **1** and **7** in 40% yield.

An alternative synthesis of these lactams was also devised starting from the trifluoroacetamido aldehyde **13** (Scheme 8). Aldehyde **13** was synthesized from **39** through a series of five high-yielding steps. Horner−Emmons reaction and nitrogen protection gave **43** (46% over 7 steps), which could be directly reduced to give a 1:1 diastereomeric mixture of the fully protected ester **44** (77%). Removal of the trifluoroacetamido protecting group ($NaBH_4$ in MeOH, 84%) followed by treatment in refluxing xylene gave the lactams **1** and **7** in 78% yield.

In conclusion, we have devised a practical route for the synthesis of the 5,5-, 6,5-, and 7,5-fused bicyclic lactams **1**−**3**, **5**−**9**, **11**, and **12** using a Horner−Emmons olefination



Scheme 7. a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 81%; (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 98%; Boc_2O, 4-DMAP, THF, 98%; b) H_2, Pd/C, MeOH; c) NaOH, MeOH; d) H_2, Pd/C, MeOH; xylene, reflux, 40% over 2 steps



Scheme 8. a) TBDMSCl, Et_3N, 94%; H_2, $Pd(OH)_2/C$, MeOH, 94%; trifluoroacetic anhydride, pyridine, 89%; Bu_4NF, THF, 98%; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 93%; b) (±)-(*Z*)-α-phosphonoglycine trimethyl ester, *t*BuOK, CH_2Cl_2, −78 °C, 68%; Boc_2O, 4-DMAP, THF, 95%; c) H_2, $Pd(OH)_2/C$, MeOH, 77%; d) $NaBH_4$, MeOH, 84%; e) xylene, reflux

as the key step. After hydrogenation, the lactams were usually obtained as easily separable stereoisomeric mixtures at the *N*-bearing carbon atom, but stereoselective syntheses (80% *de*) could also be achieved by means of (chiral phosphane)Rh-catalyzed hydrogenation.

These amino acid motifs may be used as scaffolds on which pharmacologically relevant groups can be appended. Alternatively, the motifs may be utilized as conformationally constrained entities that mimic segments of natural peptide substrates. Initial applications of these compounds as reverse-turn inducers have been reported.[6b,6c]

Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or C_6D_6 solution as indicated, at 200 (or 300) and 50.3 MHz, respectively. The chemical shift values are given in ppm and the coupling constants in Hz. − Optical rotation data were obtained with a Perkin−Elmer model 241 polarimeter. − Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out using Merck silica gel 60, 200−400 mesh. − Solvents were dried according to standard procedures, and reactions requiring anhydrous conditions were performed under nitrogen. Solutions containing the final products were dried with Na_2SO_4, filtered, and concentrated under reduced pressure using a Büchi rotary evaporator. − Elemental analyses were performed by the staff of the microanalytical laboratory of our department. − Compounds **23**,[8] **39**,[5b] **37**,[8] and **32**[8] have been described previously.

General Procedure A: Preparation of Acrylic Esters 18−22 by Horner−Emmons Reaction (Scheme 1): To a stirred solution of *t*BuOK (7.36 mmol) in dry CH_2Cl_2 (40 mL) under nitrogen, a solution of (*Z*)-α-phosphonoglycine trimethyl ester **24**[7] (7.36 mmol) in dry CH_2Cl_2 (5.0 mL) was added at −78 °C. The resulting mixture was stirred for 30 min at this temperature and then a solution of the appropriate aldehyde (6.13 mmol) in dry CH_2Cl_2 (25 mL) was added. After 5 h, the solution was allowed to warm to room temperature and neutralized with phosphate buffer. The aqueous phase was extracted with CH_2Cl_2, the combined extracts were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate) to afford the acrylic ester as a (*Z*)/(*E*) diastereoisomeric mixture.

General Procedure B: Preparation of the *N*-Boc-Protected Acrylic Esters: A solution of the acrylic ester (11.0 mmol), $(Boc)_2O$ (22.0 mmol), and a catalytic amount of DMAP in dry THF (40 mL) was stirred for 30 min under nitrogen. The solution was then quenched with water (40 mL) and extracted with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate) to yield the Boc-protected acrylic ester.

General Procedure C: Preparation of the Alcohols through Hydroboration: To a solution of allylproline (2.34 mmol) in dry THF (4.2 mL) was added a 0.5 M solution of 9-BBN in THF (2.52 mL, 1.26 mmol). The reaction mixture was stirred for 12 h, then cooled to 0 °C, whereupon water (0.6 mL), a 3 N solution of NaOH (0.5 mL), and 30% H_2O_2 (0.44 mL) were added. The resulting mixture was stirred for 1 h at room temperature and then refluxed for a further 2 h. After cooling, the aqueous phase was extracted with AcOEt and the combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate) to yield the alcohol as a yellow oil.

General Procedure D: Preparation of the Aldehydes by Swern Oxidation: To a stirred solution of oxalyl chloride (16.9 mmol) in CH_2Cl_2 (35 mL), DMSO (23.1 mmol), a solution of the appropriate alcohol (5.66 mmol) in CH_2Cl_2 (21 mL), and TEA (28.2 mmol) were added at −60 °C. The reaction mixture was allowed to warm to room temperature and after 1 h it was washed with water (50 mL) and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane/ethyl acetate) to yield the aldehyde.

Synthesis of the 6,5-Fused "*cis*"-Lactams 2 and 8 (Scheme 2)

Aldehyde 14: A stirred solution of **23**[8] (6.0 g, 17.4 mmol) in CH_2Cl_2 (84 mL) was cooled to −60 °C, whereupon O_3 was bubbled through it (flow rate = 30 L/h). After 1.5 h, the solution was allowed to warm to room temperature, and then N_2 was bubbled through it in order to eliminate the excess O_3. The solution was then cooled to 0 °C by means of an ice bath and Me_2S (101.8 mmol, 38 mL) was added. After stirring for 5 d at room temperature, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane/ethyl acetate, 8:2) to yield 4.53 g of **14** (75%) as a yellow oil. − $[\alpha]_D^{22} = -22.0$ (c = 1.27, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.4−1.5 [2 s, 9 H, $C(CH_3)_3$], 1.6−2.4 (m, 4 H, CH_2CH_2), 2.4−3.2 (2 m, 2 H, CH_2CHO), 4.3−4.5 (m, 2 H, CH_2CHN, $NCHCOOtBu$), 5.15 (s, 2 H, CH_2Ph), 7.30 (m, 5 H, arom.), 9.8 (2 s, 1 H, CHO). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 200.8, 171.7, 154.0, 136.2, 128.3, 128.0, 127.8, 127.6, 81.4, 67.0, 66.9, 60.8, 60.3, 54.0, 53.2, 49.0, 48.3, 31.0, 30.2, 29.5, 28.9, 28.0, 27.7. − FAB$^+$MS: calcd. for $C_{19}H_{25}NO_5$ 347.4; found 348.

Acrylic Ester 19: According to General Procedure A, **14** was subjected to the Horner−Emmons reaction. The crude product was purified by flash chromatography (hexane/ethyl acetate, 65:35) to afford **19** (98%) in a 7:1 (*Z*)/(*E*) ratio as separable colourless oils. − (*Z*) isomer: $[\alpha]_D^{22} = +38.8$ (c = 1.26, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ =

1.3−1.5 [2 s, 9 H, $C(CH_3)_3$], 1.5−2.3 (m, 4 H, CH_2CH_2), 2.4−2.7 (2 m, 2 H, =CH−CH_2), 3.7 (2 s, 3 H, $COOCH_3$), 4.2 (2 m, 2 H, CH_2CHN, NCHCOOtBu), 5.10 (m, 4 H, CH_2Ph), 6.15 (m, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 172.4, 164.9, 154.5, 136.2, 132.5, 128.3, 128.2, 127.8, 127.7, 127.6, 81.8, 67.2, 66.9, 60.8, 60.3, 57.9, 57.2, 52.1, 33.8, 33.2, 30.7, 29.8, 29.5, 29.0, 28.0, 27.7, 27.6. − FAB$^+$MS: calcd. for $C_{30}H_{36}N_2O_8$ 552.6; found 553. − (*E*) isomer: $[\alpha]_D^{22}$ = −4.1 (*c* = 1.17, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.25−1.50 [3 s, 9 H, $C(CH_3)_3$], 1.5−2.3 (m, 4 H, CH_2CH_2), 2.8−3.3 (2 m, 2 H, =CH−CH_2), 3.8 (2 s, 3 H, $COOCH_3$), 4.1 (m, 1 H, CH_2CHN), 4.25 (m, 1 H, NCHCOOtBu), 5.15 (2 s, 4 H, CH_2Ph), 6.30 (m, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.8, 164.4, 154.1, 153.6, 136.4, 135.9, 128.7, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 126.5, 125.9, 81.2, 80.9, 66.7, 61.0, 60.6, 60.2, 58.8, 58.1, 52.2, 32.7, 32.0, 31.8, 29.9, 29.5, 29.2, 28.8, 27.8, 27.7, 22.5, 14.0.

Acrylic Ester 25: According to General Procedure B, **19** was *N*-Boc-protected. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield **25** (98%) as a yellow oil. − (*Z*) isomer: $[\alpha]_D^{22}$ = +16.9 (*c* = 1.86, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.3−1.5 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.2 (m, 4 H, CH_2CH_2), 2.3−2.8 (2 m, 2 H, =CH−CH_2), 3.7 (s, 3 H, $COOCH_3$), 4.1−4.2 (2 m, 2 H, =CH−CH_2CHN, NCHCOOtBu), 5.15 (m, 4 H, CH_2Ph), 6.95 (dd, *J* = 8.5, *J* = 6.4 Hz, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.4, 163.8, 154.6, 154.3, 152.1, 150.4, 139.0, 138.8, 136.2, 135.1, 129.7, 128.3, 128.2, 128.1, 127.8, 127.6, 83.3, 81.2, 77.1, 68.2, 66.8, 60.9, 60.4, 57.5, 56.7, 52.1, 32.8, 32.1, 29.9, 29.1, 28.8, 27.7. − (*E*) isomer: $[\alpha]_D^{22}$ = +7.34 (*c* = 1.33, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.3−1.5 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.2 (m, 4 H, CH_2CH_2), 3.0−3.3 (m, 2 H, =CH−CH_2), 3.75 (2 s, 3 H, $COOCH_3$), 4.1−4.2 (2 m, 2 H, =CH−CH_2CHN, NCHCOOtBu), 5.1−5.2 (m, 4 H, CH_2Ph), 6.3 (m, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.6, 163.8, 154.5, 154.3, 152.1, 150.4, 142.8, 142.5, 136.3, 135.2, 128.7, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 83.2, 81.1, 68.2, 66.8, 61.1, 60.6, 58.1, 57.4, 51.7, 32.7, 32.0, 29.5, 29.4, 28.9, 28.7, 27.7.

6,5-Fused Bicyclic Lactams 2, 8: A solution of **25** (0.320 g, 0.49 mmol) in MeOH (5 mL) containing a catalytic amount of 10% Pd/C was stirred for about 12 h under H_2. The catalyst was then removed by filtration through Celite and the collected solid was washed with MeOH. The combined filtrate and washings were then concentrated under reduced pressure, the residue was redissolved in MeOH, and this solution was refluxed for 48 h. The solvent was then removed and the two diastereoisomers thus obtained were separated by flash chromatography (hexane/ethyl acetate, 7:3) to yield 0.122 g of **8** and **2** (70%) in a 1.4:1 diastereoisomeric ratio as a white foam. − **2:** $[\alpha]_D^{22}$ = −10.7 (*c* = 1.29, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43−1.45 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.5 (m, 8 H, CH_2CH_2, BocN−CHCH_2CH_2), 3.69 (m, 1 H, CH−N), 4.1 (m, 1 H, CH−NBoc), 4.38 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1 H, NCHCOOtBu), 5.59 (d, *J* = 5.4 Hz, 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.7, 165.8, 155.8, 147.1, 81.4, 79.3, 59.0, 56.2, 49.9, 32.0, 29.5, 29.1, 28.2, 27.8, 27.0, 26.5. − FAB$^+$MS: calcd. for $C_{18}H_{30}N_2O_5$ 354.46; found 354. − **8:** $[\alpha]_D^{22}$ = −45.07 (*c* = 1.69, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44−1.46 [2 s, 18 H, $C(CH_3)_3$], 1.55−2.2 (m, 7 H, CH_2CH_2, BocN−CHCHHCH_2), 2.5 (m, 1 H, BocN−CHCHH), 3.75 (m, *J* = 11.2 Hz, *J* = 4.2 Hz, 1 H, CH−N), 3.90 (m, 1 H, CH−NBoc), 4.32 (d, *J* = 9.2 Hz, 1 H, NCHCOOtBu), 5.59 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.6, 167.9, 155.7, 81.2, 79.4, 77.5, 60.4, 59.0, 52.2, 31.4, 28.5, 28.3, 28.2, 27.8, 27.6. − FAB$^+$MS: calcd. for $C_{18}H_{30}N_2O_5$ 354.46; found 354.

Stereoselective Synthesis of 2 and 8 by Rh-Catalyzed Hydrogenation of 26 (Scheme 3)

Acid 26: To a solution of **25** (0.640 g, 0.980 mmol) in MeOH (4.9 mL) was added 1 N NaOH (4.9 mL, 4.9 mmol). After stirring for 18 h at room temperature, the solvents were evaporated under reduced pressure. The solid residue was redissolved in water (5 mL), 2 N aq. HCl was added until pH = 3 was reached, and then the aqueous solution was extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to yield 0.420 g of **26** (85%) as a white solid. − (*Z*) isomer: $[\alpha]_D^{22}$ = −57.0 (*c* = 1.99, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.30−1.50 [2 s, 18 H, $C(CH_3)_3$], 1.7−2.7 (m, 6 H, CH_2CH_2, =CH−CH_2), 4.2−4.3 (m, 2 H, =CH−CH_2CHN, NCHCOOtBu), 5.1 (m, 2 H, CH_2Ph), 6.6 (m, 1 H, =CH), 7.30 (m, 6 H, arom., NHBoc). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.5, 168.3, 154.8, 154.5, 140.6, 136.4, 136.1, 133.9, 133.5, 128.3, 128.2, 128.1, 127.8, 127.4, 126.9, 81.3, 80.9, 67.1, 66.9, 65.0, 66.9, 65.0, 57.5, 56.8, 33.4, 32.4, 29.5, 28.5, 28.5, 28.0, 27.8, 27.7, 27.4. − (*E*) isomer: $[\alpha]_D^{22}$ = −41.63 (*c* = 1.87, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.35−1.50 [3 s, 18 H, $C(CH_3)_3$], 1.7−2.4 (m, 4 H, CH_2CH_2), 2.7−3.2 (m, 2 H, =CH−CH_2), 4.2−4.3 (m, 2 H, =CH−CH_2CHN, NCHCOOtBu), 5.1 (m, 2 H, CH_2Ph), 6.7−6.9 (m, 2 H, =CH, NHBoc), 7.30 (m, 5 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.7, 167.2, 154.9, 154.5, 154.3, 136.5, 136.2, 128.3, 128.2, 127.7, 127.5, 126.9, 126.3, 126.1, 81.2, 80.4, 66.9, 65.0, 60.7, 60.4, 58.3, 57.7, 32.9, 32.0, 29.5, 28.4, 28.1, 27.8, 27.7, 27.4, 27.1, 14.0.

Acids 30 and 31: To [Rh-(−)-BitianP] catalyst, prepared as described in the literature,[16,17] **26** (0.16 mmol) and MeOH (30 mL) were added and the resulting solution was stirred for 30 min. A 200-mL stainless steel autoclave, equipped with a magnetic stirrer and a thermostatted bath, was pressurized with hydrogen and vented three times. The solution was then transferred to the autoclave by means of a syringe, the autoclave was pressurized to 10 KPa with hydrogen, and stirring was maintained for 24 h at 30 °C. The hydrogen pressure was then released and the solvent was evaporated. The crude product was used for the next reaction without further purification.

6,5-Fused Bicyclic Lactam 2: To a solution of crude **30** and **31** (0.15 mmol), as obtained from [Rh-(−)-BitianP]-catalyzed hydrogenation of **26** in MeOH (1.5 mL) as described above, a solution of CH_2N_2 in Et_2O was added until TLC analysis showed that the reaction had reached completion. The solution was then concentrated to dryness, the residue was redissolved in MeOH (2 mL), and a catalytic amount of Pd/C was added. The resulting mixture was stirred under H_2 for 12 h. The catalyst was then removed by filtration through a Celite pad and washed with MeOH. The combined filtrate and washings were concentrated under reduced pressure and the crude product, obtained as a white foam, was refluxed in MeOH for 48 h. The solvent was subsequently evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 7:3) to afford **2** (85%) as a white solid.

6,5-Fused Bicyclic Lactam 8: This bicyclic lactam was prepared according to the same synthetic sequence as followed for the lactam **2**, using the [Rh-(+)-BitianP] catalyst for the asymmetric hydrogenation.

Synthesis of the 6,5-Fused "*trans*"-Lactams 5 and 11 (Scheme 4)

Ester 33: To a stirred suspension of KH (0.777 g, 19.4 mmol) in anhydrous DMF (80 mL), triethyl phosphonoacetate (19.4 mmol, 3.9 mL) was added. The mixture was stirred at room temperature for 1 h and then a solution of hemiaminal **32**[8] (5.2 g, 16.2 mmol) in DMF (80 mL) was added. The reaction mixture was stirred for about 12 h at room temperature, then quenched with saturated aqueous NH_4Cl solution, and extracted with AcOEt. The combined organic extracts were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by flash chromatography to yield 4.8 g of **33** (75%) in a 4:1 *trans*/*cis* diastereoisomeric ratio. − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.2−1.35 (m, 3 H, C*H*$_3$CH$_2$O), 1.35, 1.40, 1.45, 1.50 [4 s, 9 H, C(CH$_3$)$_3$], 1.60−2.60 (m, 5 H, CH$_2$CH$_2$, C*H*CO$_2$Et), 2.70−3.1 (2 dd, J_1 = 4 Hz, J_2 = 15 Hz, 1 H, C*H*CO$_2$Et, *trans* isomer), 3.2−3.5 (2 dd, J_1 = 4 Hz, J_2 = 15 Hz, 1 H, C*H*CO$_2$Et, *cis* isomer), 4.13 (dq, $J_1 = J_2$ = 7 Hz, 2 H, CH$_3$C*H*$_2$O) 4.27 (m, 1 H, C*H*CO$_2$*t*Bu), 4.45 (m, 1 H, CH$_2$C*H*N), 5.15−5.35 (m, 2 H, C*H*$_2$Ph), 7.3−7.4 (m, 5 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.4, 171.3, 171.1, 171.0, 154.4, 154.1, 153.8, 136.5, 136.3, 128.3, 128.2, 127.7, 127.6, 81.2, 66.9, 66.8, 60.8, 60.5, 60.3, 60.2, 55.5, 55.2, 54.5, 39.1, 38.0, 30.4, 29.7, 28.9, 28.7, 28.2, 28.0, 27.8, 27.7, 27.1, 14.1. − FAB$^+$MS: calcd. for $C_{21}H_{29}NO_6$ 391.2; found 392.

Aldehyde 17: To a stirred solution of **33** (1.205 g, 3.08 mmol) in dry diethyl ether (31 mL), 2 M $LiBH_4$ in THF (1.5 mL, 3.08 mmol) was added at −10 °C. After 24 h, a saturated solution of $NaHCO_3$ (40 mL) was added and the resulting mixture was extracted with AcOEt. The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (hexane/ethyl acetate, 1:1) to yield 1.01 g of the alcohol (94%) as a yellow oil. − *trans* isomer: $[\alpha]_D^{22}$ = −32.3 (*c* = 1.02, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, C(CH$_3$)$_3$], 1.5−2.4 (m, 6 H, CH$_2$CH$_2$, C*H*$_2$CH$_2$O), 3.5−3.7 (m, 2 H, C*H*$_2$OH), 3.82 (br. s, 1 H, OH), 4.22 (dd, *J* = 7.5 Hz, *J* ≈ 0 Hz, 1 H, C*H*CO$_2$*t*Bu), 4.38 (m, 1 H, CH$_2$C*H*N), 5.15 (m, 2 H, C*H*$_2$Ph), 7.32 (s, 5 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.4, 156.1, 136.0, 128.4, 128.3, 127.9, 127.8, 127.7, 81.2, 81.1, 67.2, 67.0, 60.4, 59.9, 59.0, 55.2, 55.1, 38.6, 37.7, 28.9, 28.7, 27.8, 27.7. − *cis* isomer: $[\alpha]_D^{22}$ = −54.0 (*c* = 1.51, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 [s, 9 H, C(CH$_3$)$_3$], 1.4−1.24 (m, 6 H, CH$_2$CH$_2$, C*H*$_2$CH$_2$O), 3.6−3.9 (m, 2 H, C*H*$_2$OH), 4.08 (dd, *J* = 9.5 Hz, *J* = 4 Hz, 1 H, OH), 4.25 (dd, $J_1 = J_2$ = 8.5 Hz, 1 H, C*H*CO$_2$*t*Bu), 4.40 (m, 1 H, CH$_2$C*H*N), 5.15 (m, 2 H, C*H*$_2$Ph), 7.35 (s, 5 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.7, 28.9, 30.4, 37.4, 55.4, 58.8, 60.5, 67.4, 81.3, 127.7, 127.9, 128.3, 136.1, 155.9, 171.8. − A solution of the alcohol (0.304 g, 0.87 mmol) in dry CH_2Cl_2 (2.5 mL) was added to a suspension of Dess−Martin periodinane (0.408 g, 1.13 mmol) in dry CH_2Cl_2 (2.5 mL) at room temperature. After 1 h, Et_2O and 1 N NaOH were added until a clear solution was obtained. The aqueous phase was then extracted twice with Et_2O, and the combined organic layers were washed with H_2O, dried with Na_2SO_4, and concentrated to dryness. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to afford 0.277 g of a 4:1 stereoisomeric mixture of aldehydes **17** and **14** (92%). − *trans* isomer **17**: $[\alpha]_D^{22}$ = −48.6 (*c* = 1.01, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.35−1.45 [2 s, 9 H, C(CH$_3$)$_3$], 1.6−2.6 (m, 4 H, CH$_2$CH$_2$), 2.8−3.1 (2 m, 2 H, C*H*$_2$CHO), 4.3 (m, 1 H, CHO−CH$_2$C*H*N), 4.6 (m, 1 H, NCHCOOR), 5.15 (m, 2 H, C*H*$_2$Ph), 7.30 (m, 5 H, arom.), 9.1, 9.3 (2 m, 1 H, CHO). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 200.3, 171.4, 154.1, 136.2, 128.4, 128.2, 128.0, 127.8, 127.7, 81.3, 67.1, 66.9, 60.5, 60.1, 53.4, 52.5, 49.0, 48.4, 29.5, 28.6, 28.3, 27.8, 27.7, 27.3.

***N*-Boc-Protected Acrylic Ester 34:** The 4:1 mixture of aldehydes **14** and **17** obtained as described above was subjected to the Horner−Emmons reaction according to General Procedure A. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to afford the enamide in 99% yield as a *trans*/*cis*, (*Z*)/(*E*) mixture. − *trans*-(*Z*) isomer: $[\alpha]_D^{22}$ = −61.8 (*c* = 1.01, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.35−1.50 [2 s, 9 H, C(CH$_3$)$_3$], 1.6−2.3 (m, 4 H, CH$_2$CH$_2$), 2.3−2.8 (2 m, 2 H, =CH−C*H*$_2$), 3.75 (s, 3 H, COOCH$_3$), 4.15−4.25 (2 m, 2 H, CH$_2$C*H*N and NC*H*COO*t*Bu), 5.15 (m, 4 H, C*H*$_2$Ph), 6.55 (t, *J* = 8.5 Hz, 1 H, =CH), 7.35 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.4, 164.8, 164.6, 154.4, 153.9, 153.7, 136.4, 136.2, 135.9, 135.7, 133.0, 132.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 126.7, 81.2, 67.3, 67.2, 67.0, 66.8, 60.6, 60.2, 57.6, 56.7, 52.3, 33.5, 32.5, 28.5, 27.7, 27.4. − FAB$^+$MS: calcd. for $C_{30}H_{36}N_2O_8$ 552.6; found 552. − *trans*-(*E*) isomer: $[\alpha]_D^{22}$ = −50.2 (*c* = 1.48, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.35−1.45 [2 s, 9 H, C(CH$_3$)$_3$], 1.6−2.4 (m, 4 H, CH$_2$CH$_2$), 2.7−3.1 (2 m, 2 H, =CH−C*H*$_2$), 3.8 (2 s, 3 H, COOCH$_3$), 4.1−4.3 (2 m, 2 H, CH$_2$C*H*N, NC*H*COO*t*Bu), 5.10 (m, 4 H, C*H*$_2$Ph), 6.50 (m, 1 H, =CH), 7.25 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.7, 171.5, 164.2, 164.0, 154.7, 154.3, 153.5, 136.6, 136.4, 135.8, 128.4, 128.3, 128.2, 128.1, 127.7, 126.2, 125.9, 125.8, 81.0, 87.1, 66.8, 66.6, 60.8, 60.4, 58.2, 57.3, 52.2, 32.8, 31.9, 28.5, 28.1, 27.8, 27.7, 27.4, 27.1. − The mixture of acrylic esters (0.394 g, 0.71 mmol) was directly subjected to *N*-Boc protection according to General Procedure B. Flash chromatography of the crude product (hexane/ethyl acetate, 75:25) afforded 0.287 g (73%) of the pure *trans* isomer **34**. − *trans*-(*Z*) isomer: $[\alpha]_D^{22}$ = −50.9 (*c* = 1.56, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.3−1.5 [4 s, 18 H, C(CH$_3$)$_3$], 1.7−2.6 (m, 6 H, CH$_2$CH$_2$ and =CH−C*H*$_2$), 3.7 (s, 3 H, COOCH$_3$), 4.1−4.3 (m, 2 H, CH$_2$C*H*N and NC*H*COO*t*Bu), 5.15 (m, 4 H, C*H*$_2$Ph), 6.8 (m, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.4, 163.9, 154.6, 154.5, 150.0, 146.2, 138.5, 138.0, 136.2, 129.9, 128.3, 128.2, 128.1, 127.8, 83.4, 81.2, 68.3, 67.0, 66.8, 60.6, 60.2, 56.9, 56.2, 52.2, 32.9, 32.0, 28.3, 27.8, 27.7, 27.3. − FAB$^+$MS: calcd. for $C_{35}H_{44}N_2O_{10}$ 652.7; found 652. − *trans*-(*E*) isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3−1.4 [2 s, 18 H, C(CH$_3$)$_3$], 1.5−2.3 (m, 4 H, CH$_2$CH$_2$), 3.0 (2 m, 2 H, =CH−C*H*$_2$), 3.65 (2 s, 3 H, COOCH$_3$), 4.2 (m, 2 H, CH$_2$C*H*N and NC*H*COO*t*Bu), 5.15 (m, 4 H, C*H*$_2$Ph), 6.1 (2 t, *J* = 8.5 Hz, 1 H, =CH), 7.30 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.5, 163.7, 154.6, 154.3, 152.2, 150.4, 142.7, 142.2, 136.3, 135.1, 128.9, 128.3, 128.2, 128.0, 127.8, 127.7, 83.4, 83.3, 81.1, 77.1, 68.3, 66.9, 66.7, 60.7, 60.3, 57.6, 56.8, 51.7, 32.9, 32.0, 28.4, 28.0, 27.7, 27.3, 27.0.

6,5-Fused Bicyclic Lactams 5 and 11: A solution of **34** (0.489 g, 0.75 mmol) in MeOH (7.5 mL) containing 20% $Pd(OH)_2$/C (catalytic amount) was stirred for about 12 h under H_2. The catalyst was then filtered off and the filtrate was refluxed for 24 h. The solvent

was then removed and the two diastereoisomeric products were separated by flash chromatography (hexane/ethyl acetate, 6:4) to yield 0.186 g of **5** and **11** (70%) in a 1.4:1 diastereoisomeric ratio. − **5:** $[\alpha]_D^{22} = -36.5$ ($c = 0.97$, $CHCl_3$). − ^1H NMR (200 mhz, $CDCl_3$): δ = 1.45−1.50 [2 s, 18 H, $C(CH_3)_3$], 1.55−2.60 (m, 8 H, CH_2CH_2 and BocN−CHCH_2CH_2), 3.68 (tt, J = 14.9 Hz and 4.2 Hz, 1 H, CH−N), 4.05 (m, 1 H, CH−NBoc), 4.35 (t, J = 8.5 Hz, 1 H, NC*H*COO*t*Bu), 5.28 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 59.0, 58.4, 51.3, 32.7, 28.6, 28.2, 27.8, 27.7, 27.6, 27.3. − FAB$^+$MS: calcd. for $C_{18}H_{30}N_2O_5$ 354.46; found 354. − **11:** $[\alpha]_D^{22} = -107.9$ ($c = 1.7$, $CHCl_3$). − ^1H NMR (200 mhz, $CDCl_3$): δ = 1.45−1.50 [2 s, 18 H, $C(CH_3)_3$], 1.75−2.50 (m, 8 H, CH_2CH_2 and BocN−CHCH_2CH_2), 3.70 (m, 1 H, CH−N), 4.15 (m, 1 H, CH−NBoc), 4.50 (t, J = 7.0 Hz, 1 H, NC*H*COO*t*Bu), 5.55 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.6, 168.5, 155.5, 81.4, 79.3, 59.0, 56.2, 49.9, 32.3, 28.1, 27.8, 26.5, 25.9. − FAB$^+$MS: calcd. for $C_{18}H_{30}N_2O_5$ 354.46; found 354.

Synthesis of 7,5-Fused "*cis*"-Lactams 3 and 9 (Scheme 5)

Aldehyde 15: Hydroboration of **23**[8] according to General Procedure C gave the primary alcohol, which was obtained as a yellow oil (95%) following purification by flash chromatography (hexane/ethyl acetate, 7:3). − ^1H NMR (200 MHz, $CDCl_3$) δ = 1.4 [s, 9 H, $C(CH_3)_3$], 1.6−2.4 (m, 8 H, CH_2CH_2), 3.5−3.8 (2 m, 2 H, CH_2OH), 4.1 (m, 1 H, CH_2C*H*N), 4.25 (m, 1 H, NC*H*COO*t*Bu), 5.15 (s, 2 H, CH_2Ph), 7.30 (m, 5 H, arom.). − The alcohol was oxidized according to General Procedure D and the crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield **15** (89%) as an oil. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.4−1.5 [2 s, 9 H, $C(CH_3)_3$], 1.6−2.8 (m, 4 H, CH_2CH_2), 4.05 (m, 1 H, CH_2C*H*N), 4.25 (m, 1 H, NC*H*COO*t*Bu), 5.15 (s, 2 H, CH_2Ph), 7.30 (m, 5 H, arom.), 9.6−9.8 (2 s, 1 H, CHO).

Acrylic Ester 20: According to General Procedure A, **15** was subjected to the Horner−Emmons reaction. The resulting residue was purified by flash chromatography to yield the acrylic ester (95%) as a yellow oil. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.36, 1.41 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.5 (m, 8 H, CH_2CH_2), 3.8 (s, 6 H, COOMe), 4.01 (m, 2 H, CH_2C*H*N), 4.4 (m, 2 H, NC*H*COO*t*Bu), 5.1 (s, 4 H, CH_2Ph), 6.58 (m, 2 H, HC=), 6.9 (br. s, 2 H, NH), 7.30 (m, 5 H, arom.).

Acrylic Ester 35: Compound **20** was *N*-Boc-protected according to General Procedure B. The crude product was purified by flash chromatography to yield the *N*-Boc-protected compound (95%) as a white solid. A solution of this compound (0.96 mmol) in MeOH (1 mL) containing a catalytic amount of Pd/C was stirred under hydrogen for 12 h. The catalyst was then removed by filtration through a Celite pad. The filtrate was concentrated to dryness under reduced pressure to yield 0.320 g of **35** (83%) as a white solid (mixture of two diastereoisomers). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47, 1.48 [2 s, 18 H, $C(CH_3)_3$], 1.40−2.1 (m, 10 H, CH_2CH_2, BocN−CHC*H*HCH_2), 3.00 (m, 1 H, CH−N), 3.6 (m, 1 H, NC*H*COO*t*Bu), 4.3 (m, 1 H, CH−NBoc), 5.05 (br. d, 1 H, NH).

Amino Acid 36: To a solution of **35** (0.288 g, 0.720 mmol) in MeOH was added 1 N NaOH. After 1.5 h, the solution was acidified to pH = 3 with 1 N HCl, and then the solvents were evaporated. The crude residue was used for the next reaction without further purification.

7,5-Fused Bicyclic Lactams 3 and 9: To a solution of the crude **36** (0.720 mmol) in CH_2Cl_2 (80 mL), Et_3N (0.720 mmol, 0.220 mL), HOBt (0.166 g, 1.22 mmol), and a catalytic amount of DMAP were added sequentially. After 15 min, EDC (0.180 g, 0.937 mmol) was added and the mixture was stirred for 24 h. Thereafter, H_2O (40 mL) was added, the aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford 0.191 g of **3** and **9** in a 1:1 diastereoisomeric ratio (72% yield over the 2 steps). − **3:** $[\alpha]_D^{22} = -34.6$ ($c = 1$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41, 1.42 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.5 (m, 10 H, CH_2CH_2), 3.80 (m, 1 H, CH−N), 4.2 (m, 1 H, CH−NBoc), 4.51 (dd, J = 4.8 Hz, 1 H, NC*H*COO*t*Bu), 5.54 (br. d, 1 H, NH). −^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 61.2, 59.0, 54.2, 34.2, 32.8, 31.7, 28.3, 27.6, 27.7, 27.9. − FAB$^+$MS: calcd. for $C_{19}H_{32}N_2O_5$ 368.6; found 391 [M + Na$^+$]. − **9:** $[\alpha]_D^{22} = -53.2$ ($c = 1$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42, 1.43 [2 s, 18 H, $C(CH_3)_3$], 1.50−2.2 (m, 10 H, CH_2CH_2), 3.8 (m, 1 H, CH−N), 4.25 (dd, J = 4.6 Hz, J = 9.6 Hz, 1 H, CH−NBoc), 4.42 (dd, J = 2.3 Hz, J = 7.2 Hz, 1 H, NC*H*COO*t*Bu), 5.30 (br. s, 1 H, NH). −^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 62.1, 58.5, 34.2, 32.9, 32.8, 28.3, 27.9, 27.5, 27.3, 22.6. − FAB$^+$MS: calcd. for $C_{19}H_{32}N_2O_5$ 368.6; found 391 [M + Na$^+$].

Synthesis of 7,5-Fused "*trans*"-Lactams 6 and 12 (Scheme 6)

Aldehyde 17: According to General Procedure C, **37**[8] was subjected to hydroboration. The crude product was purified by flash chromatography to afford the alcohol in 98% yield. − ^1H NMR (200 MHz, $CDCl_3$) δ = 1.32 [s, 9 H, $C(CH_3)_3$], 1.4−2.4 (m, 8 H, CH_2CH_2), 3.5−3.7 (m, 2 H, CH_2OH), 4.1 (m, 1 H, CH_2C*H*N), 4.24 (m, 1 H, NC*H*COO*t*Bu), 5.05 (s, 2 H, CH_2Ph), 7.25 (m, 5 H, arom.). − The alcohol was then oxidized according to General Procedure D. The crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to afford **17** in 82% yield. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.32, 1.45 [2 s, 9 H, $C(CH_3)_3$], 1.5−2.7 (m, 8 H, CH_2CH_2), 4.1 (m, 1 H, CH_2C*H*N), 4.25 (m, 1 H, NC*H*COO*t*Bu), 5.15 (s, 2 H, CH_2Ph), 7.20−7.40 (m, 5 H, arom.), 9.6−9.8 (2 m, 1 H, CHO).

Acrylic Ester 38: According to General procedure A, **17** was subjected to the Horner−Emmons reaction. The crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to afford the acrylic ester in 90% yield [diastereomeric ratio (*Z*)/(*E*) = 7:1]. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.32, 1.42 [s, 9 H, $C(CH_3)_3$], 1.5−2.7 (m, 8 H, CH_2CH_2), 3.71 (s, 1 H, $COOCH_3$), 4.1 (m, 1 H, CH_2C*H*N), 4.22 (m, 1 H, NC*H*COO*t*Bu), 5.0−5.20 (m, 4 H, CH_2Ph), 6.6 (m, 1 H, =CH), 7.20−7.45 (m, 10 H, arom.). − According to General Procedure B, the acrylic ester was *N*-Boc-protected. The crude product was purified by flash chromatography to yield **38** (98%). − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.32, 1.42 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.2 (m, 8 H, CH_2CH_2), 3.71 (s, 1 H, $COOCH_3$), 3.9 (m, 1 H, CH_2C*H*N), 4.22 (m, 1 H, NC*H*COO*t*Bu), 5.0−5.20 (m, 4 H, CH_2Ph), 6.9 (m, 1 H, =CH), 7.20−7.45 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 141.6, 128.4, 128.2, 128.1, 127.8, 127.7, 68.2, 66.8, 60.5, 58.1, 52.1, 31.3, 29.5, 27.1, 27.3, 24.6.

***trans*-7,5-Fused Bicyclic Lactams 6 and 12:** To a solution of **38** (0.093 g, 0.141 mmol) in MeOH (2 mL) was added 1 N NaOH (0.705 mmol, 0.705 mL) and the resulting mixture was stirred for 1.5 h. The solution was then acidified to pH = 3 with 1 N aq. HCl and the solvents were evaporated. The crude residue was used in the next reaction without further purification. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.25, 1.48 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.4 (m, 8 H, CH_2CH_2), 4.1

(m, 1 H, CH_2CHN), 4.3 (m, 1 H, NC*H*COO*t*Bu), 5.12 (s, 2 H, CH_2Ph), 6.65 (m, 1 H, =CH), 7.1−7.4 (m, 5 H, arom.), 9.00 (br. s, 1 H, COOH). − A solution of the aforementioned crude product in xylene was refluxed for 48 h. The solvent was then evaporated and the residue was purified by flash chromatography to yield **6** and **12** in 40% yield. − **6:** ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.43, 1.45 [2 s, 18 H, $C(CH_3)_3$], 1.51−2.40 (m, 10 H, CH_2CH_2), 3.75 (m, 1 H, CH−N), 4.22 (m, 1 H, CH−NBoc), 4.48 (t, *J* = 17 Hz, 1 H, NC*H*COO*t*Bu), 5.7 (br., 1 H, N*H*). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 61.7, 59.3, 53.2, 34.0, 28.4, 28.2, 27.9, 26.4, 22.9. − FAB$^+$MS: calcd. for $C_{19}H_{32}N_2O_5$ 368.6; found 391 [M + Na^+]. − **12:** ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.47, 1.48 [2 s, 18 H, $C(CH_3)_3$], 1.55−2.50 (m, 8 H, CH_2CH_2), 4.0 (m, 1 H, CH−N), 4.30 (m, 1 H, CH−NBoc), 4.50 (dd, *J* = 5.4 Hz, *J* = 17 Hz, 1 H, NC*H*COO*t*Bu), 6.0 (br. d, 1 H, NH). − FAB$^+$MS: calcd. for $C_{19}H_{32}N_2O_5$ 368.6; found 369 [M + 1].

L-Selectride Reduction of 38: To a solution of **38** (0.8385 g, 1.258 mmol) in THF, a 1 M solution of L-Selectride in THF (3.2 mL, 3.145 mmol) was added at −78 °C. After 30 min, a saturated solution of NH_4Cl was added and the resulting mixture was extracted with AcOEt. The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield 0.7224 g of the reduced compound (86%). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.30, 1.40 [2 s, 9 H, $C(CH_3)_3$], 1.75−2.20 (m, 10 H, CH_2CH_2), 3.65 (s, 1 H, $COOCH_3$), 4 (m, 1 H, CH_2CHN), 4.20 (m, 1 H, NC*H*COO*t*Bu), 4.90 (m, 1 H, C*H*COOMe), 5.10−5.30 (m, 4 H, CH_2Ph), 7.20−7.45 (m, 10 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 68.7, 66.6, 60.1, 58.5, 52.1, 33.0, 29.9, 29.6, 28.6, 27.8, 27.7, 26.9. − FAB$^+$MS: calcd. for $C_{35}H_{48}N_2O_8$ 668.7; found 691 [M + Na^+].

Synthesis of the 5,5-Fused "*cis*"-Lactams 1a and 7a (Scheme 7)

Acrylic Ester 40: According to General Procedure D, compound **39**[5b] was oxidized. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield the aldehyde (81%) as an oil. − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.48 [s, 9 H, $C(CH_3)_3$], 1.8−2.2 (m, 4 H, CH_2CH_2), 3.21 (m, 1 H, CH_2CHN), 3.45 (m, 1 H, NC*H*COO*t*Bu), 3.70 (d, *J* = 12 Hz, 1 H, HC*H*Ph), 4.10 (d, *J* = 12 Hz, 1 H, HC*H*Ph), 7.30 (m, 5 H, arom.), 9.12 (d, 1 H, CHO). − According to General Procedure A, the aforementioned aldehyde was subjected to the Horner−Emmons reaction. The crude product was purified by flash chromatography (hexane/ethyl acetate, 65:35) to afford the acrylic ester (98%) in a 9:1 (*Z*)/(*E*) ratio as separable colourless oils. − (*Z*) isomer − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 [s, 9 H, $C(CH_3)_3$], 1.7−2.2 (m, 4 H, CH_2CH_2), 3.3 (m, 1 H, NC*H*COO*t*Bu), 3.5 (s, 1 H, CH_2CHN), 3.66 (d, *J* = 13.2 Hz, HC*H*Ph), 3.73 (s, 1 H, $COOCH_3$), 3.79 (d, 1 H, HC*H*Ph), 5.11 (d, *J* = 12.5 Hz, 1 H, OHC*H*Ph), 5.15 (d, *J* = 12.5 Hz, 1 H, OHC*H*Ph), 6.07 (d, *J* = 7.4 Hz, 1 H, =CH), 7.10−7.6 (m, 10 H, arom.), 8.15 (br. s, 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.7, 165.1, 154.1, 137.4, 136.1, 129.5, 128.5, 128.3, 128.0, 127.8, 127.7, 127.1, 80.5, 66.9, 65.3, 62.3, 57.5, 52.0, 30.1, 28.9, 27.7. − According to General Procedure B, the acrylic ester synthesized as described above was *N*-Boc-protected. The crude product was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield **40** (98%). − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.3−1.5 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.2 (m, 4 H, CH_2CH_2), 3.1 (m, 1 H, NC*H*COO*t*Bu), 3.5 (m, 1 H, CH_2CHN), 3.7 (s, 1 H, $COOCH_3$), 3.7 (d, *J* = 12 Hz, 1 H, HC*H*Ph), 3.9 (d, *J* = 12 Hz, 1 H, HC*H*Ph), 5.20 (d, *J* = 12 Hz, 1 H, HC*H*Ph), 7.0 (d, *J* = 8.6 Hz, 1 H, =CH), 7.1−7.4 (m, 10 H, arom.).

Amino Acid 42: To a solution of **40** (0.424 g, 0.713 mmol) in MeOH (4 mL) was added 1 N NaOH (4 mmol, 4 mL) and the resulting mixture was stirred for 1.5 h. It was then acidified to pH = 3 with 1 N HCl and the solvents were evaporated. The crude product was used in the next reaction without further purification. − ^{1}H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 1.35, 1.5 [2 s, 18 H, $C(CH_3)_3$], 1.7−2.3 (m, 4 H, CH_2CH_2), 3.3 (m, 1 H, NC*H*COO*t*Bu), 3.65 (m, 1 H, CH_2CHN), 3.7 (d, *J* = 12.8 Hz, 1 H, HC*H*Ph), 3.9 (d, *J* = 12.8 Hz, 1 H, HC*H*Ph), 6.5 (d, *J* = 7.6 Hz, 1 H, =CH), 7.1−7.4 (m, 10 H, arom.), 9.00 (br. s, 1 H, COOH).

5,5-Fused Bicyclic Lactams 1 and 7: A solution of **42** (0.713 mmol) in MeOH (7 mL), containing a catalytic amount of 20% $Pd(OH)_2$/C, was stirred under hydrogen for 12 h. The catalyst was then removed by filtration through a Celite pad and the filtrate was concentrated to dryness under reduced pressure. The residue was redissolved in MeOH and this solution was refluxed for 48 h. Thereafter, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to afford 0.097 g of a 1:1 diastereomeric mixture of **1** and **7** as a white solid in 40% yield (over 2 steps). − **1:** $[\alpha]_D^{22}$ = −4.8 (*c* = 1.20, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50, 1.51 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.4 (m, 5 H, CH_2CH_2, BocN−CHC*H*H), 2.95 (m, 1 H, BocN−CHCH*H*), 3.85 (m, 1 H, CH−N), 4.15 (d, *J* = 8.8 Hz, 1 H, NC*H*COO*t*Bu), 4.60 (m, 1 H, CH−NBoc), 5.25 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.7, 169.7, 155.6, 81.8, 79.5, 58.8, 56.5, 56.0, 55.8, 39.5, 33.4, 29.5, 28.2, 27.8. − FAB$^+$MS: calcd. for $C_{17}H_{28}N_2O_5$ 340.41; found 341. − **7:** $[\alpha]_D^{22}$ = −4.8 (*c* = 1.20, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.5 (m, 6 H, CH_2CH_2, BocN−CHC*H*$_2$), 4.05 (d, *J* = 8.8 Hz, 1 H, NC*H*COO*t*Bu), 4.12 (m, 1 H, CH−N), 4.25 (m, 1 H, CH−NBoc), 5.05 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 170.9, 169.8, 155.2, 82.2, 81.8, 79.9, 77.1, 61.2, 58.8, 57.6, 56.0, 55.8, 34.4, 33.8, 33.4, 29.9, 29.5, 29.2, 28.5, 28.1, 27.7. − FAB$^+$MS: calcd. for $C_{17}H_{28}N_2O_5$ 340.41; found 341.

Alternative Synthesis of the 5,5-Fused "*cis*"-Lactams 1 and 7 (Scheme 8)

Aldehyde 13: To a stirred solution of **39**[5b] (1.5 g, 5.14 mmol) in dry CH_2Cl_2 (39 mL) under nitrogen, TBDMSCl (0.931 g, 6.17 mmol), TEA (6.17 mmol, 0.94 mL), and DMAP (0.063 g, 0.51 mmol) were added sequentially. After 12 h, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 9:1) to yield 1.910 g of the silyl ether (94%) as a colourless oil. − $[\alpha]_D^{22}$ = −3.6 (*c* = 2.52, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = −0.5 (s, 6 H, CH_3Si), 0.85 [s, 9 H, $(CH_3)_3C$−Si], 1.4 [s, 9 H, $C(CH_3)_3$], 1.5−2.1 (m, 4 H, CH_2CH_2), 2.9 (m, 1 H, SiO−CH_2CHN), 3.3−3.4 (m, 3 H, NC*H*COO*t*Bu, SiO−CH_2), 3.9 (s, 2 H, CH_2Ph), 7.3 (m, 5 H, arom.). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.6, 139.3, 129.1, 127.9, 126.7, 19.9, 67.5, 66.8, 65.8, 58.8, 28.4, 28.0, 27.8, 25.8, 18.1, −3.6. − A solution of the silyl-protected alcohol (1.850 g, 4.55 mmol) in MeOH (45 mL), containing 20% $Pd(OH)_2$ (0.250 g, 0.45 mmol), was stirred under hydrogen for 4 h. The catalyst was then removed by filtration through a Celite pad and washed with MeOH. The combined filtrate and washings were concentrated un-

der reduced pressure to yield 1.34 g of the *N*-deprotected compound (94%) as a colourless oil. − $[\alpha]_D^{22} = -5.8$ ($c = 1.99$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.4 (s, 6 H, CH_3Si), 0.92 [s, 9 H, $(CH_3)_3C-Si$], 1.49 [s, 9 H, $C(CH_3)_3$], 1.5−2.1 (m, 4 H, CH_2CH_2), 2.35 (br., 1 H, NH), 3.2 (m, 1 H, $SiO-CH_2CHN$), 3.65 (m, 3 H, $NCHCOOtBu$, $SiO-CH_2$). − To a stirred solution of the aforementioned compound (1.2 g, 3.79 mmol) in CH_2Cl_2 (38 mL) were added pyridine (11.39 mmol, 0.92 mL) and $(CF_3CO)_2O$ (8.35 mmol, 1.16 mL). After 1.5 h, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 9:1) to yield 1.4 g of the trifluoroacetamide-protected pyrrolidine (89%) as a colourless oil. − $[\alpha]_D^{22} = -8.6$ ($c = 2.11$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.4 (s, 6 H, CH_3Si), 0.9 [s, 9 H, $(CH_3)_3C-Si$], 1.47 [s, 9 H, $C(CH_3)_3$], 1.7−2.4 (m, 4 H, CH_2CH_2), 3.5 (m, 1 H, $SiO-CHH$), 3.75 (dd, $J = 10.6$ Hz, $J = 4.2$ Hz, 1 H, $SiO-CHH$), 4.2 (m, 1 H, $SiO-CH_2CHN$), 4.35 (t, $J = 8.5$ Hz, 1 H, $NCHCOOtBu$). − *O*-Desilylation was achieved by treating a stirred solution of the *N*-protected pyrrolidine (1.2 g, 2.91 mmol) in THF (29 mL) at −40 °C with a 1 M solution of TBAF in THF (3.20 mmol, 3.2 mL). The mixture was allowed to warm at room temp. over a period of 2.5 h, and then brine (30 mL) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate, 6:4) to yield 0.850 g of the *O*-deprotected compound (98%) as a colourless oil. − $[\alpha]_D^{22} = -6.4$ ($c = 1.45$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.5 [s, 9 H, $C(CH_3)_3$], 2.0−2.4 (m, 4 H, CH_2CH_2), 3.4−3.7 (m, 2 H, $HO-CH_2$), 4.2−4.6 (m, 3 H, $NCHCOOtBu$, $HO-CH_2CHN$). − According to General Procedure D, the aforementioned alcohol was oxidized. The crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to yield the aldehyde **13** (93%) as a white solid. − $[\alpha]_D^{22} = +22.5$ ($c = 1.53$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.5 [s, 9 H, $C(CH_3)_3$], 1.8−2.5 (m, 4 H, CH_2CH_2), 4.5−4.7 (m, 2 H, $CHO-CHN$, $NCHCOOtBu$), 9.7 (s, 1 H, CHO).

Acrylic Ester 43: According to General Procedure A, compound **13** was subjected to the Horner−Emmons reaction. The crude product was purified by flash chromatography to afford the enamide (68%) as a colourless oil [diastereoisomeric ratio (*Z*)/(*E*) = 1:1]. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism and refer to the mixture of two diastereoisomers): δ = 1.5 [s, 9 H, $C(CH_3)_3$], 1.6−2.45 (m, 4 H, CH_2CH_2), 3.75 (s, 3 H, $COOCH_3$), 4.6 (m, 1 H, $NCHCOOtBu$), 4.8 (dd, $J = 18$ Hz, $J = 10$ Hz, 1 H, $=CH-CHN$), 5.12 (s, 2 H, CH_2Ph), 6.3, 6.8 [2 d, $J = 10$ Hz, 1 H, =CH of (*Z*) isomer, (*E*) isomer], 7.35 (m, 5 H, arom.). − According to General Procedure B, the acrylic ester was *N*-Boc-protected. The crude product was purified by flash chromatography to afford **43** in 95% yield as a colourless oil. − ^1H NMR (200 MHz, C_6D_6) (signals are split due to amidic isomerism and refer to the mixture of two diastereoisomers): δ = 1.3, 1.5 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.35 (m, 4 H, CH_2CH_2), 3.7 (s, 3 H, $COOCH_3$), 4.6−4.8 (m, 2 H, $NCHCOOtBu$, $=CH-CHN$), 5.25 (m, 2 H, CH_2Ph), 7.0 (m, 1 H, =CH), 7.35 (m, 5 H, arom.). − ^{13}C NMR (50.3 MHz, C_6D_6) (signals are split due to amidic isomerism and refer to the mixture of two diastereoisomers): δ = 169.1, 163.9, 141.2, 136.1, 129.9, 128.4, 128.2, 127.4, 119.4, 113.7, 83.6, 82.5, 82.0, 68.8, 68.5, 68.2, 62.5, 60.9, 60.8, 58.5, 57.6, 56.8, 53.2, 51.9, 51.7, 51.6, 33.7, 31.8, 30.2, 27.7, 27.5, 26.9.

Amino Ester 44: A (*Z*)/(*E*) mixture of **43** (0.609 g, 1.01 mmol) and 20% $Pd(OH)_2/C$ (0.054 g) in MeOH (10 mL) was stirred under hydrogen for 18 h. The catalyst was then removed by filtration through a Celite pad and washed with MeOH. The combined filtrate and washings were concentrated to dryness under reduced pressure and the residue was purified by flash chromatography (toluene/Et_2O, 85:15) to yield 0.365 g of **44** (77%) as a yellow oil. − ^1H NMR (200 MHz, $CDCl_3$) (signals are split due to amidic isomerism and refer to the mixture of two diastereoisomers): δ = 1.45 [s, 18 H, $C(CH_3)_3$], 1.6−2.7 (m, 6 H, CH_2CH_2, $BocN-CHCH_2$), 3.75 (2 s, 3 H, $COOCH_3$), 4.25−4.4 (2 m, 2 H, BocN−CH, $BocN-CHCH_2CH$), 4.55 (m, 1 H, $NCHCOOtBu$), 5.30 (d, $J = 8.5$ Hz, 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism and refer to the mixture of two diastereoisomers): δ = 172.4, 170.0, 155.8, 128.9, 128.0, 82.7, 82.0, 79.7, 61.4, 60.6, 58.0, 56.5, 52.2, 51.5, 37.7, 36.4, 35.5, 30.2, 29.7, 29.0, 28.4, 28.1, 27.6, 25.5. − FAB^+MS: calcd. for $C_{20}H_{31}F_3N_2O_7$ 468.47; found 468.

Amino Acid 45: A solution of **44** (0.184 g, 0.393 mmol) and $NaBH_4$ (0.0298 g, 0.781 mmol) in MeOH (8 mL) was stirred for 1 h at room temperature. It was then concentrated and the residue was taken up in water (10 mL). The aqueous solution thus obtained was extracted with ethyl acetate, the combined organic phases were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The two diastereoisomers formed in the previous reactions were separated at this stage by flash chromatography (ethyl acetate/hexane, 6:4) to afford 0.123 g of **45** (3*R*) and **45** (3*S*) (84%) in a 2.6:1 diastereoisomeric ratio as a colourless oil. − **45** (3*R*): ^1H NMR (200 MHz, C_6D_6) (signals are split due to amidic isomerism): δ = 1.30, 1.45 [2 s, 18 H, $C(CH_3)_3$], 1.5−1.9 (m, 6 H, CH_2CH_2, $BocN-CHCH_2$), 2.85 (m, 1 H, $BocN-CHCH_2CH$), 3.2−3.4 (m, 4 H, $COOCH_3$, $NCHCOOtBu$), 4.65 (m, 1 H, BocN−CH), 6.6 (br., 1 H, NHBoc). − ^{13}C NMR (50.3 MHz, C_6D_6) (signals are split due to amidic isomerism): δ = 174.1, 173.2, 155.8, 81.4, 81.3, 79.5, 60.6, 60.4, 56.5, 56.3, 52.5, 52.0, 37.7, 31.9, 30.0, 29.8, 28.2, 28.0, 27.9. − FAB^+MS: calcd. for $C_{18}H_{32}N_2O_6$ 372.46; found 373. − **45** (3*S*): ^1H NMR (200 MHz, C_6D_6) (signals are split due to amidic isomerism): δ = 1.30, 1.50 [2 s, 18 H, $C(CH_3)_3$], 1.50−1.80 (m, 6 H, CH_2CH_2, $BocN-CHCH_2$), 2.8 (m, 1 H, $BocN-CHCH_2CH$), 3.3 (s, 3 H, $COOCH_3$), 3.4 (dd, $J = 9.1$ Hz, $J = 5.9$ Hz, 1 H, $NCHCOOtBu$), 4.45 (m, 1 H, BocN−CH), 5.3 (br., 1 H, NHBoc). − ^{13}C NMR (50.3 MHz, C_6D_6) (signals are split due to amidic isomerism): δ = 171.7, 171.5, 164.2, 164.0, 154.7, 154.3, 153.5, 136.6, 136.4, 135.8, 128.4, 128.3, 128.2, 128.1, 127.7, 126.2, 125.9, 125.8, 81.0, 87.1, 66.8, 66.6, 60.8, 60.4, 58.2, 57.5, 52.3, 52.2, 32.8, 31.9, 28.5, 28.1, 27.8, 27.7, 27.4, 27.1. − FAB^+MS: calcd. for $C_{18}H_{32}N_2O_6$ 372.46; found 373.

5,5-Fused Bicyclic Lactam 1: A stirred solution of **45** (3*S*) (0.028 g, 0.075 mmol) in *p*-xylene (1.5 mL) was heated to 130 °C for 24 h. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate, 7:3) to yield 19 mg of **1** (74%) as a white foam. − $[\alpha]_D^{22} = -4.8$ ($c = 1.20$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50, 1.51 [2 s, 18 H, $C(CH_3)_3$], 1.6−2.4 (m, 5 H, CH_2CH_2, $BocN-CHCHH$), 2.95 (m, 1 H, $BocN-CHCHH$), 3.85 (m, 1 H, CH−N), 4.15 (d, $J = 8.8$ Hz, 1 H, $NCHCOOtBu$), 4.60 (m, 1 H, CH−NBoc), 5.25 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 171.7, 169.7, 155.6, 81.8, 79.5, 58.8, 56.5, 56.0, 55.8, 39.5, 33.4, 29.5, 28.2, 27.8. − FAB^+MS: calcd. for $C_{17}H_{28}N_2O_5$ 340.41; found 341.

5,5-Fused Bicyclic Lactam 7: Compound **7** was obtained from compound **45** (3*R*) according to the same procedure as described for the synthesis of **1**. It was obtained in 65% yield as a white foam. − $[\alpha]_D^{22} = -4.8$ ($c = 1.20$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 [2 s, 18 H, $C(CH_3)_3$], 1.5−2.5 (m, 6 H, CH_2CH_2,

BocN−CHCH_2), 4.05 (d, J = 8.8 Hz, 1 H, NCHCOOtBu), 4.12 (m, 1 H, CH−N), 4.25 (m, 1 H, CH−NBoc), 5.05 (br., 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$) (signals are split due to amidic isomerism): δ = 170.9, 169.8, 155.2, 82.2, 81.8, 79.9, 77.1, 61.2, 58.8, 57.6, 56.0, 55.8, 34.4, 33.8, 33.4, 29.9, 29.5, 29.2, 28.5, 28.1, 27.7. − FAB$^+$MS: calcd. for $C_{17}H_{28}N_2O_5$ 340.41; found 341.

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