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Divergent synthetic routes to biologically relevant types of compounds: chiral polyfunctional γ-lactams and amino acids

Jordi Aguilera, Albertina Moglioni [†], Àlex Mor, Jimena Ospina, Ona Illa, Rosa M. Ortuño [*]

Departament de Química, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Barcelona, Spain

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ABSTRACT

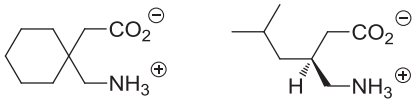
Divergent and versatile synthetic routes leading to the title compounds are described. They start from a common chiral precursor derived from (−)-(*S*)-verbenone and afford polyfunctional γ-lactams and γ- and ε-amino acids. The cyclobutane moiety in these molecules acts as a chiral and polyfunctional platform providing stereogenic centres with unambiguous absolute configuration that control the chirality of the newly produced asymmetric carbons. Furthermore, it affords functional groups and carbon chains suitable not only to create the basic skeleton of the desired products but additional functional groups. These features confer on these derivatives a great versatility for further uses in the development of new drugs and as synthetic building blocks.

1. Introduction

γ-Lactams (pyrrolidon-2-ones) are attractive targets for organic chemists, not only for their biological and pharmacological properties[1] but for their use in organic synthesis as precursors to amino acids,[2] among other products.

These compounds are remarkable in their wide presence in nature, their biological activities, and their structural characteristics. As such they have become interesting molecules in different research fields. Thus, γ-lactams are found in a wide range of biologically active compounds. They are present in many natural products with very complex structures but they are also important as part of simple molecules.

γ-Amino acids play crucial roles in the neurotransmission processes in mammalians. γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and due to its multiple regulation functions,[3] medicinal chemists are interested in the development of GABA agonists and antagonists as well as other agents for the treatment of CNS related disorders. Among them, gabapentin (Chart 1) was originally developed against epilepsy but is currently used to relieve neuropathic pain.[4]



gabapentin (*S*)-pregabalin

Chart 1. Examples of γ-amino acids as GABAergic drugs.

Another more recently commercialized agent is pregabalin, a potent anticonvulsant drug used to treat also neuropathic pain,[5] whose biological activity resides primarily on the (*S*)-enantiomer.[6] Another case is baclofen commercialized in its racemic form and primarily used to treat spasticity[7] although it is in the early research stages for other uses such as the treatment of alcoholism.

Moreover, baclofen has been involved in studies for the development of GABAergic prodrugs with improved properties because the zwitterionic form of amino acids avoids the possibility of most of the amino acid-based drugs to cross the blood-brain barrier and arrive to the specific recognition site. Furthermore, γ-lactams and γ-amino acids are closely related to pyrrolidine metabolism in vivo. For instance, Wall and Baker developed a retro-metabolic approach with 3-(4-chlorophenyl)pyrrolidine as a prodrug for baclofen. They observed the formation of the metabolites resulting from the oxidation of the sterically less-hindered 5-position to afford baclofen and its γ-lactam analogue (Scheme 1).[7]

Accounting for all these features, the efforts to develop synthetic methodologies for the preparation of γ-amino acids and γ-lactams

* Corresponding author. Tel.: +34 935811602; fax: +34 935812477; e-mail address: rosa.ortuno@uab.es (R.M. Ortuño).
† Present address: Química Medicinal, Departamento de Farmacología, Universidad de Buenos Aires, Junín 956, 1113 Buenos Aires, Argentina.

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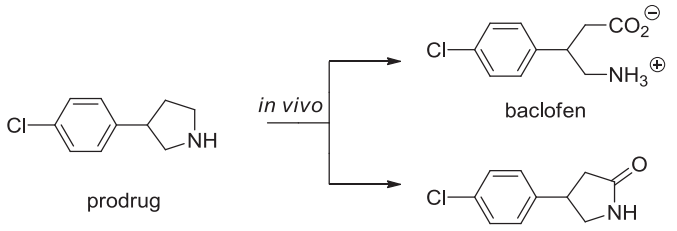


Scheme 1. Biotransformation of 3-(4-chlorophenyl)pyrrolidine.

are understandable. They display molecular structures synthetically related to the open-chain and cyclic forms of equivalent functional products and/or they are formally interconnected by means of simple manipulation of functional groups. We can usually find in the literature specific synthetic routes for each family starting from suitable precursors but not general routes giving access to a variety of products according to divergent ways from common precursors and intermediates.

Many synthetic strategies have been developed to access the pyrrolidin-2-one backbone and its derivatives. Among them, the microwave assisted Ugi reaction,[8] the synthesis based on the Zr-catalyzed reaction of EtMgCl with imines and subsequent treatment with methyl chloroformate,[9] the stereoselective palladium-catalyzed intramolecular allylation,[10] the cyclization of amide dianions with epibromohydrin,[11] and the highly diastereoselective Sc(OTf)$_3$-catalyzed imino Mukaiyama-aldol reaction are remarkable.[12] Fulop et al. have recently developed elegant and efficient methodologies to prepare optically active γ-lactams and pharmacologically important γ-amino acids through enzymatic approaches.[2,13]

(−)-Verbenone has been used in our laboratory as a suitable chiral precursor to afford a variety of chiral highly-functional cyclobutane derivatives such as amino alcohols and diamines with analgesic properties,[14] and α-,[15] β-,[16] and γ-amino acids.[17] Some of these compounds have been incorporated into C_3-symmetric peptide dendrimers[18] or in hybrid γ-peptides, which show properties as cell-penetrating agents,[19] as well as other peptides.[20]

In this work, we describe synthetic routes starting from a chiral nitro ester derivative as a common precursor, prepared in turn from (−)-verbenone, and leading to different kinds of chiral compounds such as γ-lactams, γ- and ε-amino acids (Scheme 2). Alternative pathways giving access to some of these products are presented and discussed showing the versatility and the efficiency of the synthetic strategies described herein. The cyclobutane moiety in these molecules acts as a chiral and polyfunctional platform providing stereogenic centres with unambiguous absolute configuration that control the chirality of the newly produced asymmetric carbons. Furthermore, it affords functional groups and carbon chains suitable not only to create the basic skeleton of the desired products but additional functional groups. These features confer to these derivatives a great versatility for further uses in the development of new drugs and as synthetic building blocks.

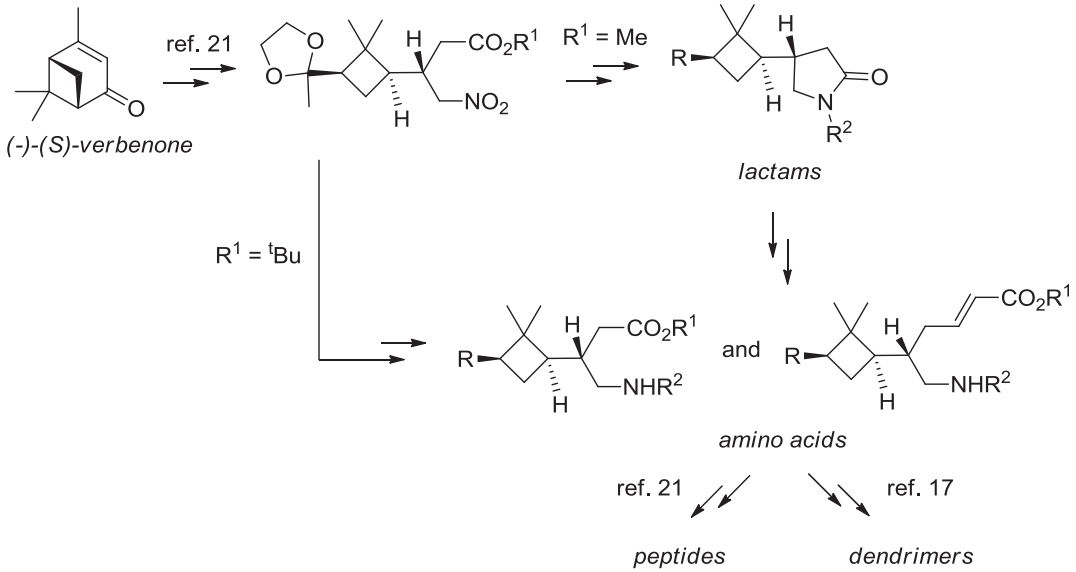
2. Results and discussion

2.1. Synthesis of γ-lactams

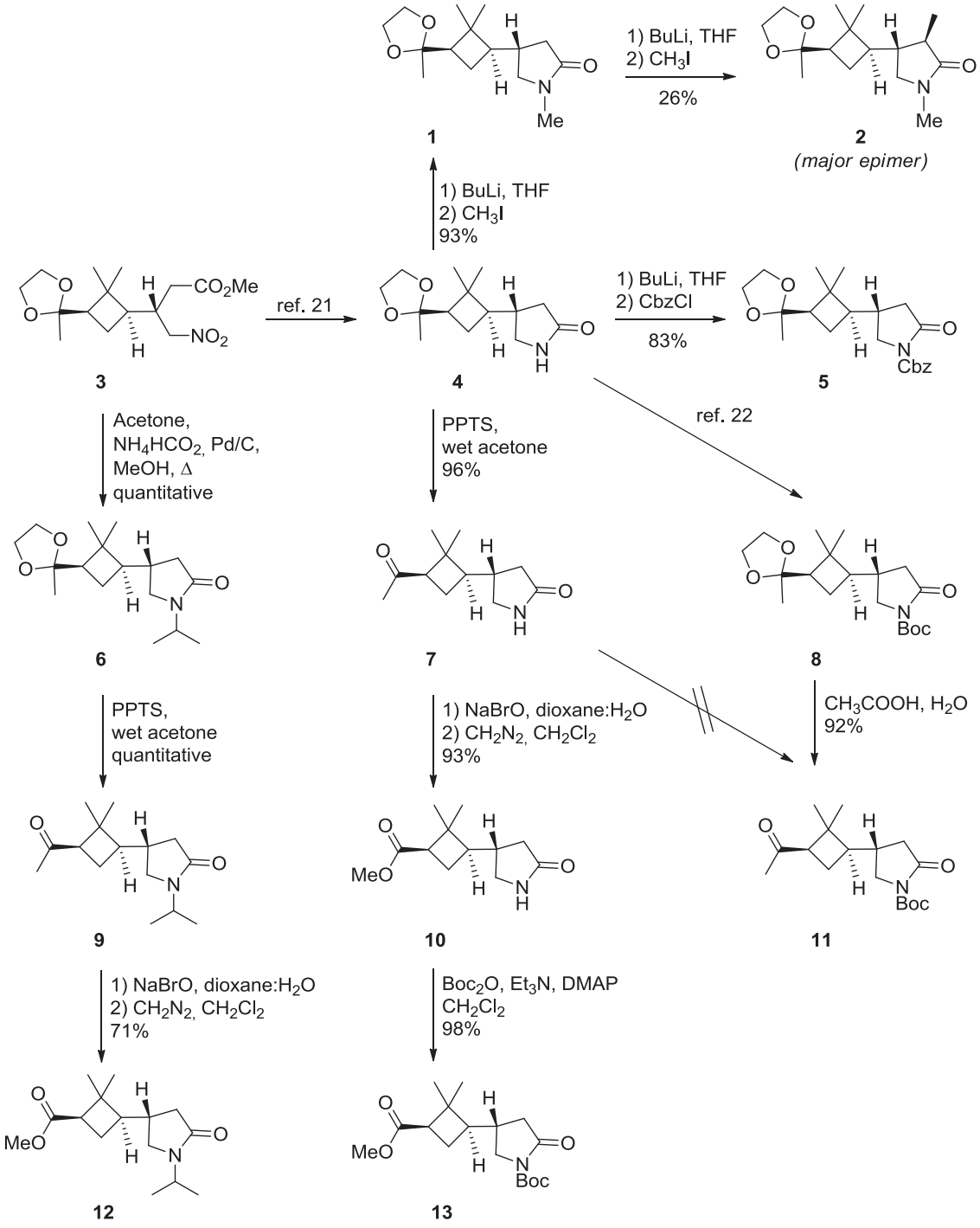
γ-Lactams were synthesized from nitro ester **3** (Scheme 3). As we had previously reported, the lactam ring formation took place through reduction of the nitro group followed by subsequent intramolecular cyclization, displacing methoxide to afford **4** as a single stereoisomer, whose absolute configuration was unambiguously assigned by X-ray structural analysis.[21,22] In the present work, functionalization on the nitrogen atom of the lactam ring and/or on the cyclobutane side-chain was achieved by means of selective transformations starting from lactam **4**, as shown in Scheme 3.

For instance, *N*-alkyl substituted lactams were synthesized through two different strategies. According to the first one, acid-base reaction of **4** with BuLi followed by treatment with methyl iodide afforded the new compound **1** in 93% yield. Additional alkylation at the carbonyl α-position of **1** was studied using BuLi or lithium diisopropylamide (LDA) to form the enolate followed by addition of an excess of methyl iodide. Influence that the solvent, number of equivalents of methyl iodide, time to form the enolate prior to the addition of the alkylating agent, and overall reaction time exert on the yield and the diastereomeric ratio (*dr*) was investigated. Selected results are collected in Table 1. Yields were moderated in all experiments. Conversion was higher when using BuLi probably due to the easier enolate formation pointing out severe steric restrictions due to the proximity of the *gem*-dimethyl substitution. The use of HMPA as a highly solvating polar co-solvent did not improve conversion when using LDA as a base (entry 5). Regarding diastereoselectivity, this was better with LDA than with BuLi (compare entries 1–3 with entry 4 in Table 1).

Only major stereoisomer **2** could be isolated by column chromatography, whereas the minor stereoisomer was always obtained



Scheme 2. General scheme of structural possibilities and their synthetic interconnections.



Scheme 3. Synthesis of γ-lactams.

contaminated with its epimer. The *dr* was determined from the integration of the signals of the lately introduced methyl group as doublets centred at 1.20 ppm (major isomer) and 1.19 ppm (minor), respectively, in the high resolution ^{1}H NMR spectrum of the reaction mixture. The absolute stereochemistry of the newly formed stereogenic centre could not be unambiguously determined but was assigned as shown in Scheme 3 assuming that methylation takes place on the less-hindered enolate-face, which is close to the hydrogen atom at the β-carbonyl position (Fig. 1). This hypothesis was supported by theoretical calculations and agrees with NMR experiments (see Supplementary data).

Alternatively, *N*-alkyl substituted lactams could also be prepared starting from nitro ester **3** by means of one-pot reductive amination of a carbonyl compound. For example, the new isopropyl derivative **6** was quantitatively obtained under treatment of **3** with ammonium formate in the presence of Pd/C and 4 equiv of acetone. The process probably involves reduction of the nitro group to primary amine followed by reaction with acetone to afford an imine. This is a variant of Leuckart reaction, which involves the use of ammonium formate.[23] The imine produced was reduced in situ to give a secondary amine that reacted intramolecularly with the methyl ester to provide *N*-isopropyl lactam **6**.

Table 1
C-alkylation of γ-lactam **1**

Entry	Base[a]	MeI (equivalents)	Solvent	Partial time[b]	Total time[c]	Conversion	Yield[d]	*dr*[e]
1	BuLi	10	THF	0.25	15.5	79	35	73:27
2	BuLi	25	THF	1	16	80	41	68:32
3	BuLi	10	THF	1.5	18	78	59	68:32
4	LDA	10	THF	2	18	53	62	87:13
5	LDA	10	THF–10% HMPA	2.5	20	52	—	—

[a] 1.1 equiv in all cases.
[b] Time to form the enolate in hours.
[c] Total reaction time in hours.
[d] Calculated on converted starting material.
[e] Diastereomeric ratio determined by NMR.

2.2. Synthesis of amino acids and derivatives

Previously, we had reported on the preparation of γ-amino acids, such as **14** and **15**, from lactam **8** (Scheme 4).[22] Now, we decided to prepare ε-amino acids through a partial reduction of lactam **8** with 1 equiv of superhydride and in situ reaction of the resultant hemiaminal with (methoxycarbonylmethylene)triphenylphosphorane to afford amino dehydroester **16** as a 10:1 mixture of *E*:*Z* isomers, in 88% yield over the two steps. The diastereomeric mixture **16** (the major isomer is shown in Scheme 4) was easily hydrogenated in the presence of catalytic Pd/C to provide orthogonally protected ε-amino acid **17** in 97% yield. This compound is a cyclobutyl analogue of ε-amino caproic acid that is a fibrinolytic

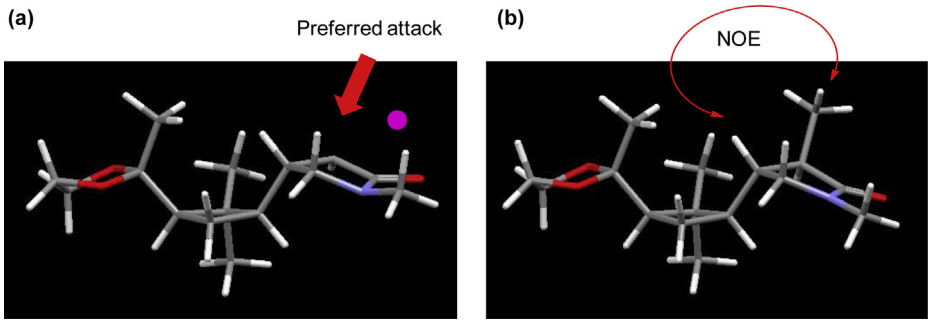


Fig. 1. Conformational bias for the lithium enolate from **1** and for the major epimer of **2** optimized at the M06-2X/6-31G(d) level of theory. (a) Preferred attack to the less sterically hindered face of the enolate. Lithium cation is represented as a pink ball. (b) NOE interactions between the methyl protons and the proton at the β-carbonyl position of **2** observed in NOESY spectrum (see Supplementary data).

From this compound, ester **12** was prepared in 71% overall yield through quantitative hydrolysis of the ketal in the cyclobutane side-chain using pyridinium *p*-toluenesulfonate (PPTS) in wet acetone, subsequent Lieben degradation of the resultant methyl ketone **9** by using sodium hypobromite, and methylation of the intermediate carboxylic acid with a dichloromethane solution of diazomethane. Mild conditions were required in these synthetic steps to prevent epimerization on the cyclobutane ring. In general, epimerization to afford *trans*-diastereoisomers in this series can be easily detected by ^{1}H NMR by the appearance of a second set of singlets corresponding to the two *gem*-methyl groups at much less differentiated chemical shifts and placed between the signals corresponding to the two highly diastereotopic methyl groups in the *cis*-diastereoisomer.

N-Free lactams were prepared by means of similar transformations starting from **4**. Thus, deprotection of the methyl ketone (PPTS in wet acetone) led to acetyl derivative **7** in 96% yield. The methyl ketone was submitted to Lieben degradation followed by methylation with diazomethane to yield methyl ester **10** in 93% yield over the two steps.

Bearing in mind the possible use of these lactams as synthetic intermediates in further transformations, the corresponding *N*-protected lactam was prepared by reaction with di-(*tert*-butyl) dicarbonate in the presence of DMAP and triethylamine to afford the *N*-Boc-derivative **13** with excellent yield (98%). Similarly, *tert*-butoxycarbamate **8** was prepared,[22] and the chemoselective cleavage of the ketal was achieved by using 90% aqueous acetic acid to afford methyl ketone **11** in excellent yield (92%). This synthetic pathway to prepare **11** is more suitable than N-protection on compound **7** because of the sensitivity of the methyl ketone to epimerization at the α-carbonyl position promoted in basic medium. Moreover, orthogonally protected *N*-Cbz derivative **5** was synthesized by treatment of **4** with BuLi, followed by reaction with benzyl chloroformate (83% yield).

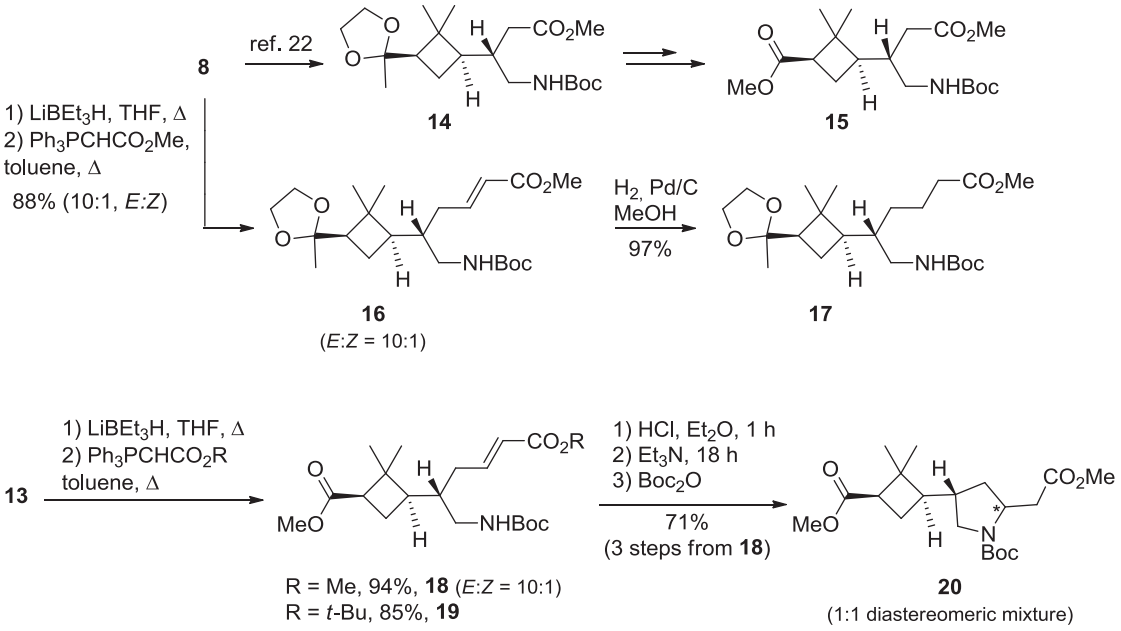
inhibitor,[24] which is used for the treatment of excessive postoperative bleeding and in the management of haemophilic patients.[25]

Other ε-amino α,β-dehydroacids with related structures were obtained following a similar strategy from *N*-Boc protected lactam **13**. Reaction with 1 equiv of superhydride in refluxing THF followed by reaction with the desired phosphorane (methyl or *tert*-butyl ester containing) led to compound **18** as a 10:1 mixture of *E*:*Z* isomers in 94% yield and to compound **19** as only *E* isomer in 85% yield, respectively. These products, which present in the same molecule a Michel-type acceptor and a nucleophilic group, could be used as key intermediates for the synthesis of pyrrolidine-2-acetic acid. Compounds with this backbone are related to numerous biological activities such as potential inhibitors of the GABA transport proteins GAT-1 and GAT-3,[26] and have also been used as organocatalysts in asymmetric aldol reactions,[27] and conjugate additions.[28]

Starting from **18**, the compound resulting from conjugate addition could be obtained. The synthetic sequence involved deprotection of the amino group through acidolysis of the Boc-carbamate with HCl in Et_2O, followed by stirring in the presence of triethylamine to create the pyrrolidine ring. Finally, N-protection with Boc anhydride led to the formation of **20** as a 1:1 mixture of diastereoisomers, in 71% yield over the three steps. The isomers could not be isolated by the usual means. The lack of diastereoselection in the conjugate addition can be probably due to the conformational flexibility at this part of the molecule and to the fact that the stereochemical information from the nearest chiral centres is too far from the reacting sites.

3. Conclusions

Divergent synthetic routes leading to γ-lactams (Scheme 3), ε-amino acids and some derivatives (Scheme 4) are reported in this



Scheme 4. Synthesis of γ- and ε-amino acids and pyrrolidine-2-acetic acid derivatives from lactams.

work. The common chiral precursor used is a cyclobutyl nitro ester obtained, in turn, from cheap and commercially available (−)-(*S*)-verbenone. Functional group manipulation and chemical bond creation have been accomplished with high yields by using sometimes chemoselective procedures. In conclusion, in this article we provide versatile and convenient synthetic entries to a variety of products, most of them belonging to chemical families that are relevant in the treatment of diseases mainly related to mammalian CNS, such as neuropathic pain and epilepsy, or presenting other remarkable biological activities. Moreover, possible applications of these compounds as chiral scaffolds for asymmetric synthesis confer on these molecules further interest and usefulness.

4. Experimental

4.1. General procedures

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents when needed. Wet acetone means using acetone with no prior distillation. All reactions were performed avoiding moisture by standard procedures and under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 360 and 90 MHz, 400 and 100 MHz or 500 and 125 MHz. Melting points were determined on a hot stage and are uncorrected. Optical rotations were measured at 22±2 °C. High resolution mass spectra were recorded with a direct inlet system (ESI). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory.

4.2. (4*S*,1′*R*,3′*R*)-4-[2′,2′-Dimethyl-3′-(2″-methyl-[1″,3″]-dioxolan-2″-yl)cyclobutyl] *N*-methyl-pyrrolidin-2-one (1)

To a stirred solution of **4**[21] (860 mg, 3.4 mmol) in THF (25 mL) was added 1.6 M BuLi in hexane (2.33 mL, 3.7 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min. Methyl iodide (1.48 mL, 23.8 mmol) was then added and the resulting reaction mixture was stirred for 16 h. Solvents and the reactants in excess were evaporated under reduced pressure and the crude was poured into EtOAc (40 mL) and washed with aqueous $NaHCO_3$ (3×20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in* vacuum. The obtained residue was purified by flash chromatography on silica gel (EtOAc–hexane 1:1 to EtOAc) to give compound **1** (842 mg, 93% yield). White solid. Mp 70–71 °C (acetone). $[\alpha]_D^{25}$ −1.4 (*c* 1.2 in CH_2Cl_2). IR (ATR): 2947, 2874, 1684, 1500, 1460, 1401, 1368 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.77–4.02 (m, 4H), 3.38 (dd, *J*=9.9, *J*′=8.1 Hz, 1H), 2.94 (dd, *J*=9.9, *J*′=5.7 Hz, 1H), 2.81 (s, 3H), 2.46 (dd, *J*=16.4, *J*′=8.9 Hz, 1H), 2.25–2.37 (m, 1H), 2.11 (dd, *J*=10.8, *J*′=7.4 Hz, 1H), 2.11 (dd, *J*=10.8, *J*′=7.4 Hz, 1H), 2.00 (dd, *J*=16.4, *J*′=6.5 Hz, 1H), 1.89 (dt, *J*=9.9, *J*′=7.4 Hz, 1H), 1.68–1.76 (m, 1H), 1.52–1.54 (m, 1H), 1.22 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.4, 109.7, 65.4, 63.6, 53.3, 49.1, 47.8, 40.8, 36.5, 32.6, 31.9, 29.5, 23.6, 22.9, 17.2; Elemental analysis calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24; found: C, 67.65; H, 9.60; N, 5.03.

4.3. (3*R*,4*R*)-4-((1′*R*,3′*R*)-2,2-Dimethyl-3′-(2″-methyl-1″,3″-dioxolan-2″-yl)cyclobutyl)-1,3-dimethyl-pyrrolidin-2-one (2)

Compound **1** (0.52 g, 1.94 mmol) in anhydrous THF (15 mL) was cooled down to −80 °C. 1.6 M BuLi in hexane (1.34 mL, 2.13 mmol) was added and the reaction was stirred for 1.5 h at that temperature. Next, methyl iodide (1.80 mL, 29.1 mmol) was added and the reaction was stirred for 18 h. The solvent was evaporated under vacuum and CH_2Cl_2 (100 mL) was added to the residue. The resulting solid was filtered and the filtrate was evaporated under vacuum. The obtained residue was purified by flash chromatography on silica gel (EtOAc–hexane 3:2) to give pure compound **2** (0.14 g, 26%) as the major diastereomer and in a separate fraction a mixture of **2** and its epimer on C3 (0.18 g, 33%). Description for pure **2**: Colourless oil. $[\alpha]_D^{25}$ +2.1 (*c* 1.33 in CH_2Cl_2); IR (ATR): 2936, 2873, 1686, 1499, 1456, 1402, 1369, 1260, 1173, 1076, 1042, 949, 865, 718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.78–4.04 (m, 4H), 3.35 (dd, *J*=9.7, *J*′=7.6 Hz, 1H), 2.88 (dd, *J*=9.7, *J*′=5.1 Hz, 1H), 2.82 (s, 3H), 2.08 (dd, *J*=11.2, *J*′=7.6 Hz, 1H), 2.00–2.09 (m, 1H), 1.91–2.01 (m, 1H), 1.87 (dt, *J*=10.0, *J*′=7.6 Hz, 1H), 1.78 (ddd, *J*=10.4, *J*′=10.1, *J*″=7.6 Hz, 1H), 1.53 (dd, *J*=20.5, *J*′=*J*″=10.0 Hz, 1H), 1.24 (s, 3H), 1.20 (d, *J*=7.2 Hz, 3H), 1.17 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.1, 109.8, 65.4, 63.7, 51.1, 48.9, 46.7, 42.4, 41.3, 40.5, 31.9, 29.7,

23.7, 22.7, 17.8, 15.9. Elemental analysis calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98; found: C, 68.25; H, 9.75; N, 4.81.

4.4. (*S*)-Benzyl 4-((1′*R*,3′*R*)-2′,2′-dimethyl-3′-(2″-methyl-1,″3″-dioxolan-2″-yl)cyclobutyl)-2-oxopyrrolidine-1-carboxylate (5)

To a stirred solution of **4**[21] (113 mg, 0.45 mmol) in anhydrous THF (7 mL) cooled to 0 °C was added 1.6 M BuLi in hexane (0.34 mL, 0.54 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 30 min. Benzyl chloroformate (0.13 mL, 0.90 mmol) was then added and the resulting reaction mixture was stirred at room temperature overnight. Solvents and the reactants in excess were evaporated under reduced pressure and the crude was poured into EtOAc (50 mL) and washed with aqueous NaCl (2×5 mL). The organic phase was dried over $MgSO_4$ and concentrated *in* vacuum. The obtained residue was purified by flash chromatography on silica gel (EtOAc–hexane 2:8) to give compound **5** (145 mg, 83% yield). White solid. Mp 100–101 °C (CH_2Cl_2/pentane). $[\alpha]_D^{25}$ +6.9 (*c* 1.45 in CH_2Cl_2). IR (ATR): 2960, 2933, 2871, 1744, 1713, 1383, 1369, 1296, 1178 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.32–7.48 (m, 5H), 5.17 (s, 2H), 3.76–4.03 (m, 5H), 3.32 (dd, *J*=10.7, *J*′=6.9 Hz, 1H), 2.59 (dd, *J*=16.6, *J*′=7.4 Hz, 1H), 2.24–2.36 (m, 1H), 2.05–2.19 (m, 1H), 1.91 (dd, *J*=9.4, *J*′=7.9 Hz, 1H), 1.71 (dt, *J*=10.3, *J*′=6.9 Hz, 1H), 1.55 (d, *J*=20.4, *J*′=10.4 Hz, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 174.0, 152.0, 135.8, 129.1, 128.9, 128.7, 110.1, 68.5, 65.9, 64.2, 50.6, 49.7, 46.9, 41.4, 39.1, 32.8, 32.4, 24.1, 23.4, 17.8. Elemental analysis calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61; found: C, 68.44; H, 7.60; N, 3.58.

4.5. (4*S*,1′*R*,3′*R*)-4-[2′,2′-Dimethyl-3′-(2″-methyl-[1″,3″]-dioxolan-2″-yl)cyclobutyl]-*N*-isopropylpyrrolidin-2-one (6)

A mixture containing nitro ester **3**[21] (330 mg, 1.1 mmol), acetone (200 μL), ammonium formate (240 mg, 7.7 mmol) and 10% Pd/C (160 mg) in anhydrous MeOH (100 mL) was heated to reflux for 1 h under nitrogen atmosphere. The reaction mixture was filtered through Celite and the solvent was evaporated. The crude was purified by chromatography on silica gel (Et_2O) to afford **6** (310 mg, quantitative yield). White solid. Mp 78–79 °C (pentane); $[\alpha]_D^{25}$ −13 (*c* 1.05 in CH_2Cl_2); IR (ATR): 2954, 2875, 1681, 1459 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 4.34 (hept, *J*=6.8 Hz, 1H), 3.83–4.09 (m, 4H), 3.33 (dd, *J*=9.5, *J*′=7.3 Hz, 1H), 2.85 (dd, *J*=9.5, *J*′=6.5 Hz, 1H), 2.43 (dd, *J*=16.2, *J*′=8.2 Hz, 1H), 2.24–2.28 (m, 1H), 1.73–2.16 (m, 3H), 1.45–1.65 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H), 1.11 (d, *J*=6.8 Hz, 6H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.9, 110.2, 65.8, 64.1, 49.6, 47.3 45.9, 42.6, 41.3, 37.9, 33.5, 32.4, 24.1, 23.5, 20.2, 20.1, 17.7. HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{29}NO_3Na$ $(M+Na)^+$ 318.2040, found 318.2038.

4.6. (4*S*,1′*R*,3′*R*) 4-[3′-Acetyl-(2′,2′-dimethylcyclobutyl)]pyrrolidin-2-one (7)

A mixture of **4**[21] (640 mg, 2.5 mmol) and pyridinium *p*-toluensufonate (PPTS) (338 mg, 2.75 mmol) in wet acetone (60 mL; 20:1 acetone–water mixture) was heated under reflux for 5 h. The reaction mixture was cooled and solvent was removed at reduced pressure. The residue was poured into EtOAc (30 mL) and the resultant solution was washed with a saturated aqueous solution of $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated under vacuum to dryness obtaining a white powder, which was recrystallized in CH_2Cl_2 to afford pure **7** (500 mg, 96% yield). White solid. Mp 160–163 °C (CH_2Cl_2). $[\alpha]_D^{25}$ −4.7 (*c* 0.85 in MeOH). IR (ATR): 3195, 3090, 2951, 2915, 2865, 1687, 1369 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.48 (broad s, 1H), 3.42 (dd, *J*=8.7, *J*′=8.3 Hz, 1H), 2.94 (dd, *J*=8.7, *J*′=8.3 Hz, 1H), 2.82 (dd, *J*=9.2, *J*′=7.3 Hz, 1H), 2.31–2.43 (m, 1H), 2.04 (s, 3H), 1.89–1.97 (m, 4H), 1.83–1.97 (m, 1H), 1.33 (s, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 206.9, 177.6, 52.9, 45.8, 45.5, 42.6, 35.00, 35.2, 30.8, 29.9, 20.9, 17.1. MS *m*/*z* calcd for $C_{12}H_{19}NO_2$ 209.1, found 209.1. Elemental analysis calcd for $C_{12}H_{19}NO_2$: C, 68.87%; H, 9.15%; N, 6.69%; Found: C, 68.65%; H, 9.19%; N, 6.31%.

4.7. (4*S*,1′*R*,3′*R*)-3′-Acetyl-[2′,2′-dimethylcyclobutyl]-*N*-isopropylpyrrolidin-2-one (9)

A mixture of **6** (750 mg, 2.54 mmol) and PPTS (270 mg, 2.2 mmol, 0.85 equiv) in wet acetone (60 mL) was heated under reflux for 2 h. The reaction mixture was cooled down and solvent was removed at reduced pressure. The residue was poured into EtOAc (30 mL) and the resultant solution was washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated under vacuum to dryness to afford **9** as a white powder, which was crystallized in CH_2Cl_2 to afford pure ketone (613 mg, quantitative yield). White solid. Mp 115–117 °C (pentane); $[\alpha]_D^{25}$ −29 (*c* 0.75 in CH_2Cl_2); IR (ATR): 2968, 1682, 1653, 1421, 1176 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz) δ 4.36 (hept, *J*=6.8 Hz, 1H), 3.36 (dd, *J*=10.5, *J*′=7.2 Hz, 1H), 2.85–2.87 (m, 2H), 2.44 (dd, *J*=15, *J*′=9.7 Hz, 1H), 2.24–2.27 (m, 1H), 2.07 (s, 3H), 1.73–2.11 (m, 3H), 1.35 (s, 3H), 1.12 (d, *J*=6.8 Hz, 3H), 1.12 (d, *J*=6.8 Hz, 3H), 0.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 207.34 173.1, 53.3, 46.2, 45.2, 43.0, 42.3, 37.2, 32.9, 31.2, 30.3, 21.3, 19.8, 19.7, 17.5. HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{25}NNaO_2$ $(M+Na)^+$ 274.1778, found 274.1772.

4.8. (1*R*,3*R*,3′*S*)-(2,2-Dimethyl-3-(5′-oxopyrrolidin-3′-yl))cyclobutanecarboxylate (10)

An ice-cooled solution of sodium hypobromite [prepared from bromine (2.8 mL, 69 mmol) and sodium hydroxide (17.9 g, 196 mmol)] in 75 mL of water was added to a solution of **7** (2.1 g, 9.8 mmol) in a 3:1 mixture of dioxane-water, previously cooled at −5 °C. The mixture was diluted with more dioxane (35 mL) and stirred at −5 °C for 5 h. Then, the reaction mixture was washed with CH_2Cl_2 (4x50 mL), treated with sodium bisulfite and, finally, 5% HCl was added to reach pH 2–3. The acid solution was extracted with CH_2Cl_2 (4×50 mL) and the organic extracts were dried over $MgSO_4$. Solvent was removed to afford the corresponding acid (1.9 g, 93% yield), which was used in the next step without further purification. This acid (500 mg, 2.4 mmol) was methylated with an excess of diazomethane (3 equiv) as a CH_2Cl_2 solution to provide methyl ester **10** (530 mg, quantitative). White solid. Mp 115–118 °C (CH_2Cl_2). $[\alpha]_D^{25}$ −12.5 (*c* 2.0 in MeOH); IR (ATR): 3090, 2950, 2910, 2875, 1700, 1325 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 5.60 (broad s, 1H), 3.68 (s, 3H), 3.49 (dd, *J*=9.06, *J*′=7.7 Hz, 1H), 3.00 (dd, *J*=9.5, *J*′=5.9 Hz, 1H), 2.71–2.76 (m, 1H), 2.47–2.50 (m, 1H), 2.37–2.40 (m, 1H), 2.04–1.93 (m, 1H), 1.27 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 178.5, 173.5, 51.7, 46.9, 46.5, 45.7, 42.8, 36.5, 35.8, 30.1, 23.3, 18.3. Elemental analysis calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22; found: C, 63.82; H, 8.79; N: 5.93.

4.9. *tert*-Butyl (4*S*,1′*R*,3′*R*)-3′-acetyl-[2′,2′-dimethylcyclobutyl]-2-oxopyrrolidine-1-carboxylate (11)

A mixture of **8** (1 g, 2.83 mmol) in acetic acid (108 mL) and H_2O (12 mL) was stirred at room temperature for 20 h. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford pure **11** (805 mg, 92% yield). Colourless oil. $[\alpha]_D^{25}$ −19 (*c* 0.9 in CH_2Cl_2). IR (ATR): 2951, 1781, 1746, 1702, 1459, 1366, 1312 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz) δ 3.67 (dd, *J*=10.8, *J*′=7.7 Hz, 1H), 3.12 (dd, *J*=10.8, *J*′=6.6 Hz, 1H), 2.72–2.74 (m, 1H), 2.43 (dd, *J*=16.8, *J*′=7.9 Hz, 1H), 2.35–2.38 (m, 1H), 2.02–2.05 (m, 1H), 2.02 (s, 3H), 1.73–1.88 (m, 3H), 1.38 (s, 9H), 1.21(s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 207.0, 173.3, 149.9, 82.7, 53.1, 49.7, 45.5, 42.8, 38.3, 31.7, 30.9, 30.2,

27.9, 21.1, 17.3. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{27}NNaO_4$ $(M+Na)^+$ 332.1832, found 332.1834.

4.10. Methyl (1*R*,3*R*,3′*S*)-3′-(1′-isopropyl-5-oxopyrrolidin-3-yl))-2,2-dimethylcyclobutane-carboxylate (12)

An ice-cooled solution of sodium hypobromite [prepared from bromine (0.55 mL, 7 mmol) and sodium hydroxide (1.6 g, 14 mmol)] in water (40 mL) was added to a solution of ketone **9** (500 mg, 1.99 mmol) in a 3:1 mixture of dioxane–water (28 mL), previously cooled at −5 °C. The mixture was diluted with more dioxane (15 mL) and stirred at −5 °C for 5 h. Then, the reaction mixture was washed with CH_2Cl_2 (3×20 mL), treated with sodium bisulfite and, finally, 5% HCl aqueous solution was added to reach pH 2–3. The acid solution was extracted with CH_2Cl_2 (3×20 mL) and the organic extracts were dried over $MgSO_4$. Solvent was removed to afford the corresponding carboxylic acid. This acid was directly methylated with an excess of diazomethane (3 equiv) as a CH_2Cl_2 solution. The residue was purified by flash chromatography in silica gel (EtOAc) to provide **12** (380 mg, 71% yield over the two steps). Colourless oil. $[\alpha]_D^{25}$ −6.0 (*c* 1.4 in CH_2Cl_2); IR (ATR): 2955, 1732, 1690, 1436, 1199 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 4.25 (hept, J=6.7 Hz, 1H), 3.56 (s, 3H), 3.26 (dd, J=9.6, J'=7.5 Hz, 1H), 2.71 (dd, J=9.6, J'=5.7 Hz, 1H), 2.58 (dd, J=10.0, J'=7.2 Hz, 1H), 2.18–2.29 (m, 1H), 2.32–2.38 (m, 1H), 1.73–2.12 (m, 6H), 1.12 (s, 3H), 1.01 (d, J=6.7 Hz, 3H), 1.0 (d, J=6.7 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.4, 173.3, 51.5, 46.9, 45.6, 45.5, 42.7, 42.6, 37.4, 33.5, 31.2, 23.2, 20.1, 20.0, 18.1. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{25}NNaO_3$ $(M+Na)^+$ 290.1727, found 290.1729.

4.11. *tert*-Butyl (4*S*,1′*R*,3′*R*)-3′-[(methoxycarbonyl)-2′,2′-dimethylcyclobutyl]-2-oxopyrrolidine-1-carboxylate (13)

Compound **10** (200 mg, 0.9 mmol) was dissolved in CH_2Cl_2 (10 mL). Triethylamine (0.12 mL, 0.9 mmol), Boc_2O (0.36 mL, 0.9 mmol) and DMAP (99 mg, 0.4 mmol) were added. The mixture was stirred at room temperature overnight. The reaction was quenched with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×15 mL) with the aid of a separatory funnel. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude residue was purified by flash column chromatography (EtOAc-hexane 1:1) to afford carbamate **13** (277 mg, 98% yield). Colourless oil. $[\alpha]_D^{25}$ −8.8 (*c* 0.98 in CH_2Cl_2). IR (ATR): 2954, 1786, 1733, 1715, 1457, 1367, 1316 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 3.82 (dd, J=12.3, J'=7.25 Hz, 1H), 3.69 (s, 3H), 3.27 (dd, J=12.3, J'=8.5 Hz, 1H), 2.70–2.74 (m, 1H), 2.58 (dd, J=15, J'=5.0 Hz, 1H), 2.30–2.34 (m, 1H), 2.13–2.20 (m, 2H), 1.94–1.98 (m, 2H), 1.55 (s, 9H), 1.25 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.6, 173.4, 150.6, 83.4, 51.7, 50.3, 46.5, 45.8, 42.4, 38.8, 32.5, 31.2, 28.4, 23.2, 18.2. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{27}NNaO_5$ $(M+Na)^+$ 348.1781, found 348.1775.

4.12. Methyl (5*S*,1′*R*,3′*R*)-6-(*tert*-butoxycarbonylamino)-5-[2′,2′-dimethyl-3′-(2″-methyl-[1″,3″]-dioxolan-2″-yl)cyclobutyl]hex-2-enoate (16)

A 2 M solution of $LiBEt_3H$ in THF (0.12 mL, 0.25 mmol) was added to a solution of **8**[21] (90 g, 0.25 mmol) in anhydrous THF (10 mL). The mixture was heated to reflux under nitrogen atmosphere for 1 h. Excess hydride was eliminated by slow addition of methanol (5 mL) and solvents were evaporated to dryness. The residue containing the hemiaminal was poured into anhydrous toluene (15 mL) and added drop-wise to a solution of (methoxycarbonylmethylene)-triphenylphosphorane (127 mg, 0.38 mmol) under nitrogen atmosphere and heated to reflux for 18 h. Toluene was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (Et_2O–hexane) to provide pure olefin **16** as a mixture of *E*/*Z*-isomers (10:1), (91 mg, 88% for the two steps). Yellow oil. IR (ATR): 3369, 2950, 1701, 1690, 1523 cm^{-1}. *Description for major isomer*: ^1H NMR ($CDCl_3$, 360 MHz) δ 6.96 (ddd, J=15.5, J'=8.3, J''=6.9 Hz, 1H), 5.86 (d, J=15.5 Hz, 1H), 4.42 (broad s, 1H), 3.74–3.95 (m, 4H), 3.70 (s, 3H), 3.14–3.15 (m, 1H), 2.92–2.94 (m, 1H), 1.99–2.33 (m, 3H), 1.66–1.92 (m, 3H), 1.61–1.62 (m, 1H), 1.48 (s, 9H), 1.24 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.1, 162.4, 155.8, 122.6, 109.7, 79.1, 65.4, 63.7, 51.7, 49.2, 46.5, 44.5, 41.3, 39.3, 32.2, 28.7, 27.2, 23.9, 16.9. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{37}NNaO_6$ $(M+Na)^+$ 434.2513, found 434.2524.

4.13. Methyl (5*S*,1′*R*,3′*R*)-6-*tert*-butoxycarbonylamino-5-[2′,2′-dimethyl-3′-(2″-methyl-[1″,3″]-dioxolan-2″-yl)cyclobutyl]hexanoate (17)

A mixture of *E*/*Z*-olefins **16** (130 mg, 0.31 mmol) in methanol (10 mL) was hydrogenated under 2 atm of pressure in the presence of 10% Pd/C (20 mg) for 1 h. The reaction mixture was filtered through Celite and solvent was removed under vacuum to provide ε-amino acid, which was purified by column chromatography using silica gel (Et_2O) to afford pure **17** (127 mg, 97% yield). Colourless oil. $[\alpha]_D^{25}$ +9.4 (*c* 1.6 in CH_2Cl_2). IR (ATR): 3369, 2950, 1712, 1690, 1518 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 4.56 (broad s, 1H), 3.71–4.03 (m, 4H), 3.72 (s, 3H), 3.20–3.24 (m, 1H), 2.98–3.03 (m, 1H), 2.35 (t, J=7.2 Hz, 2H), 1.51–2.10 (m, 7H), 1.50 (s, 9H), 1.28 (s, 3H), 1.22 (s, 3H), 1.20–1.22 (m, 2H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 174.0, 156.1, 109.9, 79.0, 65.5, 63.2, 51.5, 49.5, 44.5, 41.3, 40.4, 39.2, 34.3, 32.2, 29.6, 23.8, 21.4, 16.9. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{39}NNaO_6$ $(M+Na)^+$ 436.2670, found 436.2675.

4.14. Methyl (1*R*,3*R*,2′*S*)-3-[6-methoxy-1-(*tert*-buthoxycarbonylamino)-hex-4-(*E*)-en-2-yl]-2,2-dimethyl-cyclobutanocarboxylate (18)

A 2 M solution of $LiBEt_3H$ in THF (0.24 mL, 0.49 mmol) was added to a solution of **13** (160 mg, 0.49 mmol) in anhydrous THF (15 mL). The mixture was heated to reflux and stirred under nitrogen atmosphere for 1 h. Excess hydride was eliminated by slow addition of methanol (5 mL) and solvents were evaporated to dryness. The residue containing the hemiaminal was poured into anhydrous toluene (30 mL) and added drop-wise to a solution of (methoxycarbonylmethylene)-triphenylphosphorane (426 mg, 0.54 mmol) under nitrogen atmosphere and heated to reflux for 18 h. Toluene was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (Et_2O) to provide pure olefin **18** as a mixture of *E*/*Z*-isomers (10:1), (176 mg, 94% over the two steps). Yellow oil. IR (ATR): 3388, 2952, 1724, 1698, 1172 cm^{-1}. *Description for major isomer*: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.83 (ddd, J=15.4, J'=8.2, J''=6.9 Hz, 1H), 5.86 (dd, J=15.4, J'=1.5 Hz, 1H), 4.48 (broad s, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.99–3.10 (m, 1H), 2.94–2.97 (m, 1H), 2.64 (dd, J=9.9, J'=8.0 Hz, 1H), 2.16–2.19 (m, 2H), 1.96–2.03 (m, 2H), 1.73–1.79 (m, 2H), 1.43 (s, 9H), 1.25 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.4, 167.0, 156.3, 146.7, 123.5, 79.61, 51.8, 51.5, 46.1, 44.8, 43.4, 41.8, 40.1, 33.7, 31.3, 28.82, 24.1, 17.7. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{33}NNaO_6$ $(M+Na)^+$ 406.2200, found 406.2199.

4.15. Methyl (1*R*,3*R*,2′*S*)-3-[6-*tert*-butoxy-1-(*tert*-butoxycarbonylamino)-6-oxohex-4-(*E*)-en-2-yl]-2,2-dime-thylcyclobutanecarboxylate (19)

A 2 M solution of $LiBEt_3H$ in THF (0.55 mL, 1.1 mmol) was added to a solution of **13** (250 mg, 1.1 mmol) in anhydrous THF (20 mL). The mixture was heated to reflux and stirred under nitrogen atmosphere for 1 h. Excess hydride was eliminated by slow addition of methanol (5 mL) and solvents were evaporated to dryness. The residue containing the hemiaminal was poured into anhydrous

toluene (30 mL) and added drop-wise to a solution of (*tert*-butoxycarbonylmethylene)-triphenylphosphorane (954 mg, 1.21 mmol) under nitrogen atmosphere and heated to reflux for 18 h. Toluene was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (Et_2O–hexane 1:1) to provide pure olefin **19** (*E*-isomer, 397 mg, 85% over the two steps). Colourless oil. $[\alpha]_D^{25}$ +13.3 (*c* 0.5 in CH_2Cl_2). IR (ATR): 3383, 2957, 1712, 1698, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.83 (ddd, J=15.4, J'=8.0, J''=6.9 Hz, 1H), 5.79 (d, J=15.4 Hz, 1H), 4.22 (broad s, 1H), 3.67 (s, 3H), 3.12–3.15 (m, 1H), 2.96–2.98 (m, 1H), 2.67 (dd, J=10.0, J'=8.0 Hz, 1H), 2.06–2.07 (m, 2H), 2.01–2.02 (m, 2H), 1.70–1.82 (m, 2H), 1.49 (s, 9H), 1.46 (s, 9H), 1.27 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.3, 165.8, 156.1, 145.0, 125.1, 80.4, 79.4, 51.3, 45.8, 44.3, 43.1, 41.5, 39.6, 33.6, 31.0, 28.5, 28.2, 23.9, 17.4. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{39}NNaO_6$ $(M+Na)^+$ 448.2670, found 448.2656.

4.16. *tert*-Butyl (4*S*,1′R,3′R)-2-(2″methoxy-2″-oxoethyl)-4-[3′-methoxycarbonyl-(2′,2′-dimethylclobutyl)]-pyrrolidine-1-carboxylate (20)

2 N hydrochloric acid (0.13 mL, 0.26 mmol) was added to a solution of **18** (100 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the solution was stirred for 1 h at room temperature. Volatiles were then removed under reduced pressure and the residue was redissolved in anhydrous THF (5 mL). Excess Et_3N (0.2 mL, 1.45 mmol) was added to it and the mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum, poured into CH_2Cl_2 (20 mL) and DMAP (7 mg, 0.05 mmol), Et_3N (0.65 mL, 0.39 mmol) and Boc_2O (0.22 mL, 0.39 mmol) were added. The resulting mixture was stirred at room temperature for 18 h. The mixture was then washed with $NaHCO_3$ (3×10 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel (EtOAc) to give cyclised product **20** (70 mg, 71%, ratio of epimers 1:1). Colourless oil. IR (ATR): 2955, 1738, 1695, 1393, 1174 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.96–4.14 (m, 2H), 3.68 and 3.71 (2 s, 6H), 0.98 (s, 3H), 3.68–3.69 (m, 1H), 2.69–2.74 (m, 2H), 2.49 (dd, J=14, J'=7 Hz, 1H), 1.91–2.10 (m, 3H), 1.75 (ddd, J=10, J'=8, J''=3 Hz, 1H), 1.48 (s, 9H), 1.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 173.5, 154.3, 79.9, 64.4, 54.6, 51.5, 51.1, 44.8, 42.9, 41.8, 40.1, 30.6, 29.3, 28.5, 23.5 and 17.6. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{33}NNaO_6$ $(M+Na)^+$ 406.2200, found 448.2206.

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Supplementary data

Standard ^1H and ^{13}C NMR spectra of new compounds **1**, **2**, **5**, **6**, **7**, **9**, **10**, **11**, **12**, **13**, **16**, **18**, **19** and **20** and NOESY spectrum of **2** are provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.07.011.

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