Structural diversity using amino acid “Customizable Units”: conversion of hydroxyproline (Hyp) into nitrogen heterocycles

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Abstract
The ability of amino acid “customizable units” to generate structural diversity is illustrated by the conversion of 4-hydroxyproline (Hyp) units into a variety of nitrogen heterocycles. After a first common step, where the unit underwent a one-pot decarboxylation–alkylation reaction to afford 2-alkylpyrrolidines with high stereoselectivity, a divergent step was carried out. Thus, the deprotected 4-hydroxy group was used either to initiate a radical scission that afforded aliphatic β-amino aldehydes, or to carry out an elimination reaction, to give 2-alkyl-2,5-dihydro-1H-pyrroles. In the first case, the amines underwent a tandem reductive amination–cyclization to afford β-amino-δ-lactams, an efficient rigidifying unit in peptides. Different lactam N-substituents, such as alkylamines, peptides, and alkenyl chains suitable for olefin metathesis were introduced this way. In the second case, the pyrrole derivatives were efficiently converted into alkaloid and iminosugar derivatives in good global yields and with excellent stereoselectivity.

Keywords
Customizable units · Structural diversity · N-Acyliminium ion · Radical fragmentation · Hydroxyproline · Nitrogen heterocycles · Amino-δ-lactams · Alkaloids · Iminosugars

Abbreviations
DIB (Diacetoxynido)benzene
DCM Dichloromethane
Hyp Hydroxyproline
MeOH Methanol
EtOAc Ethyl acetate

Introduction
The amino acid “customizable units” have proven very useful to create structural diversity, particularly in the site-selective modification of peptides, where these units are converted into new residues with tailor-made functions. Different customizable units such as glycine, serine, threonine, glutamic acid, proline or hydroxyproline have been described (Boto et al. 2021). We have introduced 4-hydroxyproline as a versatile building block for the production of unusual amino acids (Romero-Estudillo et al. 2015; Cuevas et al. 2021), including N-alkyl derivatives (Saavedra et al. 2019, 2020), and reported its use as a “doubly customizable unit” (Hernández et al. 2021), as shown in Scheme 1. In a first step, the substrates 1 underwent a decarboxylation-alkylation reaction to afford 2-alkyl pyrrolidines 2 with high stereoselectivity. In a second step, the 4-hydroxy group was deprotected and a radical scission-oxidation took place to give β-amino aldehydes. These intermediates were manipulated to yield acyclic compounds 3, which possessed amino groups or longer carbon chains.

Herein we report other applications of this derivatization strategy, to obtain nitrogen heterocycles present in bioactive compounds (Scheme 1), such as β-amino-δ-lactams 4 and alkaloid and iminosugar analogues 5.

Thus, after formation of different 2-alkyl pyrrolidines 2, an oxidative radical scission followed by a tandem reductive amination-cyclization was explored, to obtain β-amino-δ-lactams 4, which are useful rigidifying motifs in peptide chemistry (Weber et al. 2000) and precursors or components of several drugs (Lepovitz et al. 2020; Ungashe et al. 2020; Davies et al. 2012; Chakravarty et al. 2007; Chan-Chun-Kong et al. 2004).
Moreover, the structural diversity would be expanded by elimination of the 4-hydroxy group, to give 2-alkyl-2,5-dihydro-1H-pyrroles, which can be readily converted into iminosugar and alkaloid analogues (Jin et al. 2009; Blunt et al. 2009; Butler et al. 2008; Boto et al. 2009). As reported before, structural diversity could be translated into biological diversity (Cuevas et al. 2021; Pavlinov et al. 2019; Galloway et al. 2014).

Results and discussion

In our previous work, the protection of the 4-hydroxyl moiety in substrate 1 with benzyl, TBS and TBDPS groups was studied (Hernández et al. 2021), as well as its influence in the stereochemical outcome of the decarboxylation–alkylation reaction (conversion 1 → 7, Scheme 2). In this conversion, a stereoelectronic effect described by Woerpel generated mainly the 2,4-cis product 7-cis (Smith and Woerpel 2006; Bonger et al. 2008). Thus, substrate 1 underwent an oxidative radical decarboxylation when treated with (diacetoxyiodo)benzene and iodine and then irradiated with visible light. An intermediate 2-acetoxypyrrolidine was formed, which generated the iminium ion 6 on addition of a Lewis acid. This ionic intermediate presented an envelope conformation, where the approach of the nucleophile was hindered by the axial hydrogens opposite to the OP group. When small nucleophiles were used, the 2,4-cis product 7-cis was obtained exclusively, independently of the size of the protecting group. However, when bulky nucleophiles were chosen, and the PG was also bulky, a mixture of the 7-cis and 7-trans isomers was obtained. In spite of that, the cis-isomer was still the major one (Hernández et al. 2021).

We adapted this strategy to obtain the new products 8–10. In this paper, we report a novel simplified procedure where the decarboxylation-alkylation and the hydroxyl group deprotection were carried out without isolation of the intermediates. In the example shown in Scheme 2, the TBDMS-protected substrate 1 (PG = TBDMS) underwent the scission-alkylation reaction, using the silyl enol ether $\text{Nu}_1^1$ or the silyl ketenes $\text{Nu}_2^1$ and $\text{Nu}_3^1$. The resulting pyrrolidines

Scheme 1 Conversion of 4-hydroxyproline (Hyp) customizable unit into structurally diverse nitrogen heterocycles

Scheme 2 Simplified procedure for the scission-alkylation and 4-hydroxy group deprotection
were not purified, but treated with TBAF in THF to afford the alcohols $8, 9$ and $10$-cis/10-trans. To our satisfaction, the reaction with $\text{Nu}^1$ gave only the 2,4-cis isomer $8$. Interestingly, the smaller ketene $\text{Nu}^2$ gave exclusively the 2,4-cis isomer $9$, but the larger dimethyl ketene $\text{Nu}^3$ afforded a 1:1 ratio of the cis:trans products $10$ (67% global yield).

The conversion of the $\beta$-amino esters $9$, $10$-cis and $10$-trans into a variety of $\beta$-amino-$\delta$-lactams took place in two steps. Thus, substrate $9$ underwent an oxidative radical scission to give the aldehyde $11$ in good yield (Scheme 3). Then a tandem reductive amination-cyclization reaction afforded the lactam $12$ as a single enantiomer. Since aldehyde $9$ underwent oxidation or other side-reactions over time, we developed a simplified procedure, where the crude scission product was immediately treated under reductive amination conditions. Thus, an increased global yield for lactam $12$ (59%) was achieved.

The new amide can also be used to extend the peptide chain. In the conversion $9 \rightarrow 13$ (79%) an allylamine was used as reagent. The resulting olefinic chain can be used in olefin metathesis, to greatly increase the variety of the library. Finally, when the reacting amine belongs to a peptide, a ligation reaction takes place, as illustrated in conversion $9 \rightarrow 14$. Only one stereoisomer was obtained in the process, indicating that racemization of the lactam stereogenic center (through a retro-Michael reaction prior to scission and readdition of the $N$-carbamate) had not taken place. This results match those reported previously for a related reaction affording $\alpha$-amino-$\gamma$-lactams with retention of their configuration (Romero-Estudillo and Boto 2013). This ligation reaction coupled to the formation of a rigid lactam can be quite useful in the design of bioactive peptide libraries.

The process was repeated with substrates $10$-cis and $10$-trans (Scheme 4), providing the $\alpha,\alpha$-dimethyl $\beta$-amino-$\delta$-lactams $15$–$17$ in satisfactory yields (52–60%). In the case of lactams $15$ and $17$, the benzyl group can be easily cleaved to afford the deprotected amide, which can be used as a rigidifying moiety in peptide chemistry (Weber et al. 2000). In the conversion $10$-cis $\rightarrow$ $16$ (Scheme 4), a monoprotected diamine was used as reagent, to generate a linker with a terminal $N$-carbamate. The Boc group can be easily removed in acid media, and the resulting amine can be coupled to amino acid or peptide chains, or to other functionalities.

The preparation of $\alpha,\alpha$-disubstituted $\beta$-amino-$\delta$-lactams such as $15$–$17$ is not trivial, due to the steric hindrance posed by the quaternary center to the approach of the amine nucleophile to the carbonyl group. This procedure affords an easy way to obtain these hindered lactams as pure enantiomers. In these cases, the retro-Michael-readdition reaction is not

![Scheme 3](image1.png)

**Scheme 3** Simplified procedure to obtain $\beta$-amino-$\delta$-lactams

![Scheme 4](image2.png)

**Scheme 4** Formation of $\alpha,\alpha$-disubstituted $\beta$-amino-$\delta$-lactams
possible, but to rule out other side reactions causing epimerization (such as radical H-abstraction from C-α to give an imine, followed by its isomerization to an encarbamate and reprotonation), the reductive amination was carried out with a chiral amine (1S- or 1R-methylbenzylamine). Interestingly, the secondary amine was not able to cyclize to a lactam, and thus esters 18 or 19 were obtained. The stereochemistry of the amine had little influence in the reaction outcome, and the yields were similar for both products. In both cases, a single diastereomer was obtained, which confirms that the stereochemical integrity of the product was preserved. The ability to control whether an acyclic or cyclic product is obtained, depending on the amine reagent, could be quite interesting for synthetic purposes.

The application of the hydroxyproline unit to the synthesis of alkaloids would require a variation of the previous strategy. Instead of using the 4-hydroxyl group for an oxidative radical scission, it would serve as a leaving group. In the example shown in Scheme 5, the preparation of the methyl carbamate of (+)-norsedamine from substrate 8 is illustrated. Norsedamine is a five-membered analogue of sedamine, a belladone alkaloid which is clinically used to reduce stomach and intestinal cramping (Tirel et al. 1989; Bates et al. 2002). The generation of alkaloid analogues facilitates the study of structure–activity relationships.

The synthesis used a tosylation in the first step. The tosylate 20 was converted into an intermediate selenide which underwent in situ elimination to afford the dihydropyrrole 21. The latter was reduced to the pure (+)−22 enantiomer in excellent yield.

With the scission-alkylation protocol, both enantiomers of an alkaloid can be obtained using either 4R- or 4S-hydroxyproline as substrate. The 4R- isomer is a natural, low-cost aminoacid, and the 4S isomer can be readily prepared therefrom in two efficient steps (Hernández et al. 2021). In Scheme 6, the conversion of Hyp units 23–25 into the 2R- or 2S-allylpyrrolidines 26 and 27 is shown.

In this case, two different protecting groups were used to compare results. With substrate 23, the scission-alkylation went smoothly (91%) as well as the deprotection step (92%), to give compound 26 in 84% global yield. In the case of the epimeric substrate 24, the scission-alkylation proceeded in lower but still good yield (78%), and the deprotection took place in 89% yield. For silyl-protected substrate 25, the scission took place in 71% yield, but the deprotection afforded product 27 in 95% yield. As a result, both global yields were similar.

Compound 27 was then used to prepare the methyl carbamate of (−)-norconiine, which is a ring-contracted analogue of (−)-coniine, the most active alkaloid in the hemlock poison (Passarella et al. 2005; Amat et al. 2003; Blarer et al. 1983). Thus, using the standard protocols commented before, the double bond in substrate 27 was reduced, and the hydroxyl group was tosylated. The tosylate was quickly converted into an intermediate selenide, which was oxidized with hydrogen peroxide to a selenoxide. In-situ elimination afforded the dihydropyrrole 28 in good yield. Hydrogenation of the olefin proceeded quantitatively to give (−)-norconiine methyl carbamate (29). The synthesis of the other norconiine
Structural diversity using amino acid “Customizable Units”: conversion of hydroxyproline...

enantiomer (ent-29) was carried out using the same methodology, with identical NMR and matching absolute values for the optical activities (see Experimental Section).

The dihydropyrroles are valuable intermediates in the synthesis of other compounds, such as iminosugars and related hydroxylated compounds (Drug Bank, 2021). Many iminosugars are promising glycosidase inhibitors, and some have displayed promising antidiabetic, cytotoxic and antimicrobial activities (Sousa and Alves 2021; Tyrrell et al. 2017; Risseeuw et al. 2013; Horne et al. 2011; Nash et al. 2011; Doddi and Vankar 2007). Therefore, the study of these substances has elicited much interest.

In the example shown in Scheme 7, ent-28 was transformed into three iminosugar derivatives. Thus, it underwent dihydroxylation to give compound 30, and epoxidation to afford compound 31. The epoxide was cleaved by treatment with thiophene in the presence of triethylamine, affording the thio derivative 32. In a similar way, other nucleophiles could be introduced to generate a variety of iminosugar analogs.

Conclusions

The Hyp “customizable unit” can be a valuable intermediate for the formation of nitrogen heterocycles with a variety of lateral chains or functionalities. In a first step, a decarboxylation-alkylation takes place to provide 2-alkyl-4-hydroxyproline derivatives in good yield; remarkably, the 2,4-cis diastereomer is the major or sole isomer. In a second, divergent step, a variety of nitrogen heterocycles are built, either by scission of the C₄-C₅ bond followed by reductive amination, or by elimination of the 4-hydroxy group.

In the first case, valuable β-amino-δ-lactams are generated, with different N-substituents such as alkylamines, peptides, and alkenyl chains suitable for olefin metathesis. The lactams are useful rigidifying motifs in peptide chemistry and precursors of drugs.

In the second case, dihydropyrroles are formed, that were further functionalized by dihydroxylation, reduction, or epoxidation followed by nucleophile addition, among many possible modifications. In this way, a variety of alkaloid and iminosugar analogues could be generated. This structural diversity from a parent customizable unit could translate into biological diversity, and thus these transformations would be valuable for structure–activity relationship studies.

Experimental

Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. Melting points were determined by a hot-stage apparatus and were uncorrected. Optical rotations were measured at the sodium line and ambient temperature (26 °C) in CHCl₃ solutions. NMR spectra were determined at 500 or 400 MHz for ¹H and 125.7 or 100.6 MHz for ¹³C, at 25 °C or 70 °C, as stated for each case. Sometimes, due to slower rotamer interconversion at 26 °C, two (or more) sets of signals are visible at room temperature, while only one set of signals (rotamer average) is seen at 70 °C due to faster rotamer interconversion. For some compounds, the ¹H NMR spectra show some signals as broad bands (br b) due to equilibria between rotamers.

¹H NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, q = quartet, m = multiplet, br = broad, br b = broad band, br s = broad singlet; coupling constant(s) in hertz). Mass spectra were recorded using electrospray ionization techniques (ESI) or electronic impact (EI); the latter was determined at 70 eV using an ion trap mass analyzer. Merck silica gel 60 PF254 and 60 (0.063–0.2 mm) were used for preparative thin-layer chromatography (TLC) and column chromatography, respectively. The reagent for TLC analysis was KMnO₄ in NaOH/K₂CO₃ aqueous (aq) solution, and the TLC was heated until development of color.

Simplified procedure for the scission–alkylation and protecting group removal: to a solution of the acid substrate (0.2 mmol) in dry dichloromethane (4 mL) were added iodine (25.4 mg, 0.1 mmol) and (diacetoxyiodo)benzene (DIB, 128.9 mg, 0.4 mmol). The resulting solution was stirred for 3 h at 26 °C, under irradiation with visible light (80 W tungsten-filament lamp). Then the reaction mixture was cooled to 0 °C and BF₃•OEt₂ (50 µL, 57.0 mg, 0.4 mmol) and the nucleophile (0.6–1.0 mmol) were added. The solution was stirred for 1 h; then was poured into a...
1:1 mixture of 10% aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂. The organic layer was dried over sodium sulfate, filtered, and evaporated under vacuum. The crude product was dissolved in THF (3 mL) and treated with TBAF (0.4 mmol, 105.0 mg) for 2 h. Then the reaction mixture was poured into water and extracted with ethyl acetate. After solvent removal, the residue was purified by rotatory chromatography (hexanes/EtOAc) to give the 2-alkyl-4-hydroxypyrrolidine derivatives 8, 9 or 10-cis/10-trans.

Synthesis of (2R,4R)-4-Hydroxy-2-(2-oxo-2-phenylethyl)-N-(methoxycarbonyl)pyrrolidine (8): Substrate 4R-((tert-butylimidethylsilyl)oxy)-1-(methoxycarbonyl)-L-proline 1a was obtained as reported before (Hernández et al. 2021). Product 8 was obtained from the acid 1a (61.0 mg, 0.2 mmol) according to the simplified procedure, using 1-phenyl-1-trimethylsiloxyethylene (205 μL, 192.3 mg, 1.0 mmol) as the nucleophile in the decarboxylation-alkylation step. After usual work-up and solvent removal, the residue was purified by rotatory chromatography (hexanes/EtOAc, 30:70) yielding the phenyl ketone derivative 8 (35.0 mg, 66%). Product 8 has already been described (Hernández et al. 2021).

Synthesis of (2R,4R)-4-(Hydroxy)-2-(2-methoxy-2-oxoethyl)-1-(methoxycarbonyl)pyrrolidine (9): Obtained from the aldehyde 11 (33.0 mg, 60%) as a viscous oil. [α]D²⁰ = + 15 (c 0.48, CHCl₃). IR (CHCl₃) νmax: 3604, 3437, 1721, 1635, 1515, 1455, 1391 cm⁻¹. ¹H NMR (500 MHz, 70 °C, CDCl₃). Rotameric equilibrium; two sets of signals at 26 °C, one set at 70 °C as broad bands: δ 9.71 (s, 1H), 5.43–5.36 (m, 2H), 4.73/4.56 (br b/br b, 1H), 3.13 (s, 3H), 3.69 (s, 3H), 3.65 (dd, J = 11.7, 6.0, Hz, 1H), 2.99 (dd, J = 14.0 Hz, 1H). 13C NMR (125.7 MHz, 26 °C, CDCl₃). Two sets of signals at 26 °C, one set at 70 °C: δ 199.4 (CH), 155.4 (C), 70.5 (CH), 55.3 (CH₂), 54.0 (CH), 52.3 (CH₂), 51.3 (CH₂), 39.5 (CH₂), 39.3 (CH₂). HRMS (ESI-TOF) [M + Na⁺] calcd for C₁₁H₁₇NO₇Na 330.1165, found 330.1166. Anal. Calcd for C₁₁H₁₇NO₇: C, 49.76; H, 6.96. Found: C, 49.73; H, 6.91.

(R)-1-Benzyl-4-(N-acetoxymethyl)-aminopiperidine-2-one (12): A solution of the aldehyde 11 (27.5 mg, 0.1 mmol) in dry methanol (2.5 mL) was treated with benzylamine (15.3 μL, 15.0 mg, 0.14 mmol) and triethylamine (15 μL, 0.1 mmol). After 1 h at 26 °C, sodium borohydride (6 mg, 0.2 mmol) was added, and the reaction mixture was warmed to 45 °C for 20 h. Then the mixture was allowed to reach room temperature, poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under vacuum, and the residue was purified by rotatory chromatography (hexanes/EtOAc, 50:50) yielding lactam 12 (19.3 mg, 74%) as a viscous oil. [α]D²⁰ = + 8 (c 0.77, CHCl₃). IR (CHCl₃) νmax: 3440, 1721, 1635, 1515, 1496, 1266, 1071 cm⁻¹. ¹H NMR (500 MHz, 26 °C, CDCl₃): δ 7.30 (dd, J = 7.5, 7.0 Hz, 2H), 7.25 (dd, J = 7.5, 7.0 Hz, 1H), 7.20 (d, J = 7.0 Hz, 2H), 5.02 (br s, 1H), 4.59 (d, J = 15.0 Hz, 1H), 4.54 (d, J = 15.0 Hz, 1H), 4.01–3.92 (m,
1H), 3.63 (s, 3H), 3.24–3.30 (m, 2H), 2.80 (ddd, J = 17.3, 5.5, 1.5 Hz, 1H), 2.33 (dd, J = 17.5, 9.0 Hz, 1H), 2.08–2.02 (m, 1H), 1.78–1.69 (m, 1H). 13C NMR (125.7 MHz, 26 °C, CDCl3): δ 167.7 (C), 156.2 (C), 136.7 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.5 (CH), 52.1 (CH3), 49.8 (CH2), 45.5 (CH), 44.0 (CH3), 38.6 (CH2), 29.0 (CH3). HRMS (ESI-TOF) calcd for C14H12N2O3Na [M + Na]+ 285.1215, found 285.1216. Anal. Calc’d for C14H12N2O3: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.26; H, 7.67; N, 13.30.

2-[4-(4R-(N-Methoxycarbonyl)amino-2-oxo-1-piperidinyl)butyl]-2-(N-(tert-butoxycarbonyl)-L-glutamyl-L-isoleucine methyl ester (14): Obtained from the 4-hydroxy pyrrrolidine 9 (43.5 mg, 0.2 mmol) according to the general Scission and Reductive Amination procedure, using N-(tert-butoxycarbonyl)-L-lysyl-L-isoleucine methyl ester (104.5 mg, 0.3 mmol) as the amine. After work-up and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 85:15) yielding the lactam 15 (40.4 mg, 60%) as a syrup. [α]D 20 = +5 (c 0.67, CHCl3). IR (CHCl3) νmax: 3444, 1732, 1614, 1532, 1457, 1266, 1196 cm–1. 1H NMR (400 MHz, 70 °C, CD3CN): δ 7.33 (t, J = 7.0 Hz, 2H), 7.26 (dd, J = 7.5, 7.0 Hz, 1H), 7.20 (d, J = 7.0 Hz, 2H), 4.72 (br d, J = 8.5 Hz, 1H), 4.57 (d, J = 14.5 Hz, 1H), 4.53 (d, J = 14.5 Hz, 1H), 3.89 (t, J = 8.3 Hz, 1H), 3.67 (s, 3H), 3.29–3.32 (m, 1H), 3.21–3.16 (m, 1H), 2.01–1.97 (m, 1H), 1.88–1.80 (m, 1H), 1.73 (s, 3H), 1.21 (s, 3H). 13C NMR (100 MHz, 70 °C, CD3CN): δ 174.8 (C), 156.6 (C), 137.1 (C), 128.6 (2 × CH), 127.9 (2 × CH), 127.4 (CH), 53.8 (CH), 52.2 (CH2), 50.4 (CH2), 44.0 (CH2), 43.0 (C), 25.3 (CH3 + CH2), 21.2 (CH2). HRMS (ESI) [M + Na]+ calcd for C16H20N2O4Na 273.1358, found 273.1352. 

1-[3-[(tert-butoxycarbonyl)amino-3,3-dimethyl-4-(N-methoxycarbonyl)aminopiperidin-2-one (16): Obtained from the 4-hydroxy pyrrrolidine 10-cis (49.0 mg, 0.2 mmol) according to the general Scission and Reductive Amination procedure, using 1-tert-butoxycarbonyl-1,3-propanediamine (49 µL, 49.0 mg, 0.3 mmol) as the amine. After work-up and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 40:60) yielding the lactam 16 (40.4 mg, 60%) as a syrup. [α]D 20 = +9 (c 0.98, CHCl3). IR (CHCl3) νmax: 3444, 1732, 1614, 1532, 1457, 1266, 1196 cm–1. 1H NMR (100 MHz, 70 °C, CD3CN): δ 5.0–5.50 (m, 2H), 3.81 (t, J = 9.6, 3.5 Hz, 1H), 3.62 (s, 3H), 3.40–3.23 (m, 4H), 3.00 (q, J = 6.4 Hz, 2H), 2.02–1.84 (m, 2H), 1.68–1.61 (m, 2H), 1.43 (s, 9H), 1.14 (s, 3H), 1.10 (s, 3H). 13C NMR (100.6 MHz, 70 °C, CD3CN): δ 176.0 (C), 158.1 (C), 157.3 (C), 79.3 (C), 55.5 (CH), 52.7 (CH2), 45.7 (CH2), 45.6 (CH2), 44.3 (C), 39.0 (CH2), 29.1 (3 × CH3), 23.9 (CH2), 23.6 (CH2), 22.9 (CH2), 22.7 (CH2). 3H NMR (100 MHz, 70 °C, CD3CN): δ 173.3 (C), 168.8 (C), 157.6 (C), 157.1 (C), 80.5 (C), 58.0 (CH), 56.1 (CH), 52.7 (CH2), 52.6 (CH2), 47.3 (CH), 47.1 (CH2), 45.7 (CH2), 39.7 (CH2), 38.7 (CH2), 32.5 (CH2), 30.2 (CH2), 29.0 (3 × CH3), 27.6 (CH2), 26.4 (CH2), 23.9 (CH2), 16.3 (CH2), 12.0 (CH3). HRMS (ESI) [M + Na]+ calcd for C23H25N3O4Na 515.3057, found 515.3061.
28.4 (CH3), 26.51 (CH3), 3.67 (s, 3H), 3.29–3.24 (m, 1H). 1H NMR (400 MHz, 26 °C, CD3CN): δ 7.32–7.28 (m, 4H), 7.24–7.19 (m, 1H), 5.38 (d, J = 8.0, 7.5 Hz, 2H), 7.45 (dd, J = 7.5, 7.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 5.11–5.07 (m, 1H), 1.88–1.80 (m, 1H), 1.33 (s, 3H), 1.21 (s, 3H). 13C NMR (125.7 MHz, 26 °C, CDCl3): δ 177.8 (C), 158.4 (C), 147.5 (C), 129.3 (2 × CH2), 127.7 (2 × CH2), 59.0 (CH), 56.3 (CH), 52.6 (CH3), 52.5 (CH3), 47.7 (C), 45.6 (CH2), 32.2 (CH2), 24.8 (CH3), 23.3 (CH3), 21.4 (CH3). HRMS (ESI) [M + Na]+ calc'd for C18H28N2O4Na 359.1947, found 359.1953. Anal. Calcd for C18H28N2O4: C, 64.26; H, 8.36; N, 8.24. Found: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.08; H, 8.36; N, 8.24.

Synthesis of the methyl carbamate of (+)-norsedamine (22) and its precursors 20 and 21

(2R,4R)-2-(2-oxo-2-phenylethyl)-4-(tosyloxy)-N-(methoxycarbonyl)pyrrolidine (20): Methyl triflate (490 µL, 4.5 mmol) was slowly added to a solution of 1-(p-toluenesulfonylimidazole (1020.0 mg, 4.5 mmol) in dry THF (6 mL), at 0 °C and under nitrogen atmosphere. The mixture was stirred for 0.5 h and then a solution of product [M]+ to give the tosylate 20 (1060.0 mg, 85%) as a viscous oil. [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) 

21.4 (CH3), 21.4 (CH3). HRMS (ESI) [M + Na]+ calc'd for C18H28N2O4Na 359.1947, found 359.1953. Anal. Calcd for C18H28N2O4: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.52; H, 8.21; N, 8.18.

Methyl (S)-3-(methoxycarbonyl)pyrrolidine (10-trans): Methyl triflate (490 µL, 4.5 mmol) was slowly added to a solution of 1-(p-toluenesulfonylimidazole (1020.0 mg, 4.5 mmol) in dry THF (6 mL), at 0 °C and under nitrogen atmosphere. The mixture was stirred for 0.5 h and then a solution of product 20 (1060.0 mg, 85%) as a viscous oil. [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) 

1H NMR (400 MHz, 26 °C, CD2CN): δ 7.32–7.28 (m, 4H), 7.24–7.19 (m, 1H), 5.34 (d, J = 10.0 Hz, 1H), 3.88 (ddd, J = 12.3, 10.0, 2.3 Hz, 1H), 3.69 (q, J = 6.6 Hz, 1H), 3.62 (s, 3H), 3.58 (s, 3H), 2.31–2.17 (m, 2H), 1.57–1.49 (m, 1H), 1.37–1.27 (m, 1H), 1.25 (d, J = 6.6 Hz, 3H), 1.11 (s, 3H), 1.08 (s, 3H). 13C NMR (100.6 MHz, 26 °C, CD2CN): δ 177.8 (C), 158.4 (C), 147.3 (C), 129.3 (2 × CH2), 127.7 (2 × CH2), 59.0 (CH), 55.8 (CH), 52.6 (CH3), 47.8 (C), 45.1 (CH2), 31.8 (CH2), 25.2 (CH3), 23.4 (CH3), 21.3 (CH3). HRMS (ESI) [M + Na]+ calc'd for C18H28N2O4Na 359.1947, found 359.1956. Anal. Calcd for C18H28N2O4: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.08; H, 8.36; N, 8.24.

Methyl (S)-3-(methoxycarbonyl)pyrrolidine (10-trans): Methyl triflate (490 µL, 4.5 mmol) was slowly added to a solution of 1-(p-toluenesulfonylimidazole (1020.0 mg, 4.5 mmol) in dry THF (6 mL), at 0 °C and under nitrogen atmosphere. The mixture was stirred for 0.5 h and then a solution of product 20 (1060.0 mg, 85%) as a viscous oil. [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) [α]D 20 = + 20 (c 1.0, CHCl3). IR (CHCl3) νmax: 1686, 1453, 1391, 1176, 1126 cm–1. 1H NMR (500 MHz, 70 °C, CDCl3) 

δ 177.8 (C), 158.4 (C), 147.3 (C), 129.3 (2 × CH2), 127.7 (2 × CH2), 59.0 (CH), 55.8 (CH), 52.6 (CH3), 47.8 (C), 45.1 (CH2), 31.8 (CH2), 25.2 (CH3), 23.4 (CH3), 21.3 (CH3). HRMS (ESI) [M + Na]+ calc'd for C18H28N2O4Na 359.1947, found 359.1956. Anal. Calcd for C18H28N2O4: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.08; H, 8.36; N, 8.24.
(2S)-(2-oxo-2-phenylethyl)-N-(methoxycarbonyl)-2,5-dihydro-1H-pyrrole (21): Sodium borohydride (91.0 mg, 2.4 mmol) was added to a solution of diphenyl diselenide (394.0 mg, 1.3 mmol) in tert-butanol (10 mL) and the resulting mixture was refluxed until the disappearance of the yellow color. Then a solution of the tosyl pyrrolidine 20 was added, and the mixture was stirred under reflux for 2.5 h. Then it was cooled to room temperature, poured into water and extracted with EtOAc. The organic extract was dried over anhydrous Na2SO4 and concentrated under vacuum. The selenide was unstable and underwent elimination with further treatment. Purification by chromatography on silica gel (hexane/EtOAc 80:20) afforded the dihydropyrrole 21 (380.0 mg, 78%) as a viscous oil. [α]D20 = +110 (c 0.62, CHCl3). IR (CHCl3) νmax: 1688, 1454, 1392, 1197, 1128 cm⁻¹. 1H NMR (500 MHz, 70 °C, CDCl3) Rotamer equilibrium; two sets of signals at 26 °C, one set at 70 °C: [α]D = 3.67 (s, 3H), 3.45 (ddd, J = 11.0, 7.5, 5.0 Hz, 1H), 2.65–2.57 (m, 2H), 2.14–2.07 (m, 1H), 2.00–1.90 (m, 1H), 1.89–1.82 (m, 1H), 1.82–1.76 (m, 1H), 1.72–1.61 (m, 2H), 1.50–1.20 (m, 2H), 1.34–1.00 (m, 2H), 0.85–0.60 (m, 2H), 0.40–0.20 (m, 2H), 0.20–0.00 (m, 2H), 0.00–0.000 (m, 2H). 13C NMR (125.7 MHz, 70 °C, CDCl3): δ 198.3 (C), 155.2 (C), 137.4 (C), 133.0 (CH), 130.3 (CH), 128.6 (2 × CH), 128.2 (2 × CH), 125.3 (CH), 61.7 (CH), 53.4 (CH2), 52.2 (CH3), 43.3 (CH2). MS (EI) m/z (rel intensity) 245 (M+, 10), 105 ([PhCO]+, 100). HRMS (EI) [M]+ calcd for C14H12NO2, 142.0868; found, 142.0868; [PhCO]+ calcd for C6H5O2, 128.0712; found, 128.0716. Anal. Calcd for C14H15NO3: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.13; N, 5.99.

(2R)-2-(2-oxo-2-phenylethyl)-N-(methoxycarbonyl)pyrrolidine (22): The dihydropyrrole 21 (49.0 mg, 0.2 mmol) was dissolved in dry EtOAc (3 mL) and 10% Pd(OH)2/C (40.0 mg) was added. The resulting mixture was stirred overnight under hydrogen atmosphere (1 atm). Then it was filtered over Celite and the filtrate was concentrated under vacuum. A solution of the acid precursors following standard methodologies is described (Hernández et al. 2021). Five reactions were run in parallel and purified simultaneously to obtain the precursor for the norconiine synthesis. The synthesis of the methyl carbamate of (-)-norconiine (29): The conversion of compound 27 into the dihydropyrrole 28 is very similar to that commented for the sedamine precursor 21, and is therefore commented in the Supporting Information. The conversion of compound 28 into 29 is commented below. Although compound 29 has been reported (Wistrand and Skrinar 1991), new characterization details are commented herein.
added. The resulting mixture was stirred overnight under hydrogen atmosphere (1 atm). Then it was filtered over Celite and the filtrate was concentrated under vacuum to afford the methyl carbamate of (-)-norconiine (29) (32.4 mg, 96%) as a viscous oil. $[\alpha]_D^{20} = -22$ (c 0.34, CHCl$_3$). IR (CHCl$_3$) $\nu_{max}$: 1681, 1455, 1390, 1220, 1118 cm$^{-1}$. $^1$H NMR (500 MHz, 70 °C, CDCl$_3$) Rotamer equilibrium; two sets of signals at 26 °C, one set at 70 °C: $\delta$ 3.84–3.79 (m, 1H), 3.86 (s, 1H), 3.43 (dt, $J = 10.5, 7.5, 7.5$ Hz, 1H), 3.32 (ddd, $J = 11.0, 7.5, 5.0$ Hz, 1H), 1.95–1.87 (m, 1H), 1.88–1.82 (m, 1H), 1.72 (br b, 1H, OH), 1.67–1.63 (m, 1H), 1.35–1.27 (m, 3H), 0.93 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125.7 MHz, 70 °C, CDCl$_3$): $\delta$ 156.1 (C), 76.5/75.8 (CH), 71.2/70.7 (CH), 65.1/64.6 (CH), 53.0/52.9 (CH$_2$), 51.5/51.1 (CH$_2$), 35.9/35.3 (CH$_2$), 20.0 (CH$_2$), 14.4 (CH$_3$). MS $m/z$ (rel intensity) 204 (M$^+$ + H$^+$), 161 (M – propyl + H$^+$), 100. HRMS (EI) [M + H]$^+$ calcd for C$_9$H$_{17}$NO$_4$, 204.1236; found, 204.1238; [M – propyl + H]$^+$ calcd for C$_9$H$_{17}$NO$_4$, 161.0688; found, 161.0886. Anal. Calcd for C$_9$H$_{17}$NO$_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.32; H, 8.63; N, 6.99.

(2S,3S,4R)-3,4-dihydroxy-2-propyl-N-(methoxycarbonyl)pyrrolidine (31): 3-Chloroperbenzoic acid (122.0 mg, 0.7 mmol) was added to a solution of the olefin ent-28b (185.1052; found, 185.1051; [M – propyl]$^+$ calcd for C$_9$H$_{17}$NO$_4$, 142.0504; found, 142.0498. Anal. Calcd for C$_9$H$_{17}$NO$_4$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.49; H, 8.12; N, 7.47.

(2S,3S,4S)-3-Hydroxy-4-phenylthio-2-propyl-N-(methoxycarbonyl)pyrrolidine (32): The epoxide 31 (18.5 mg, 0.1 mmol) was dissolved in dry acetone (5 mL) and treated with PhSH (31 µL, 33.0 mg, 0.3 mmol) and Et$_3$N (42 µL, 30.3 mg, 0.3 mmol). The mixture was stirred at 50 °C for 72 h. Then it was poured into H$_2$O and extracted with CH$_2$Cl$_2$. The organic extract was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 85:15) to give the epoxide 31 (81.6 mg, 75%) as a viscous oil: $[\alpha]_D^{19} = +42$ (c 0.67, CHCl$_3$). IR (CHCl$_3$) $\nu_{max}$: 3594, 1688, 1454, 1391, 1204, 1123 cm$^{-1}$. $^1$H NMR (500 MHz, 70 °C, CDCl$_3$) Rotamer equilibrium; two sets of signals at 26 °C, one set at 70 °C: $\delta$ 4.23–4.18 (m, 1H), 3.88 (dd, $J = 4.0, 2.5$ Hz, 1H), 3.68–3.63 (m, 1H), 3.67 (s, 3H), 3.48 (dd, $J = 11.3, 6.3$ Hz, 1H), 3.36 (dd, $J = 11.2, 6.1$ Hz, 1H), 1.71–1.63 (m, 1H), 1.47–1.34 (m, 3H), 0.93 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (125.7 MHz, 26 °C, CD$_2$OD): $\delta$ 158.0/157.8 (C), 76.5/75.8 (CH), 71.2/70.7 (CH), 65.1/64.6 (CH), 53.0/52.9 (CH$_2$), 51.5/51.1 (CH$_2$), 35.9/35.3 (CH$_2$), 20.0 (CH$_2$), 14.4 (CH$_3$). MS $m/z$ (rel intensity) 204 (M$^+$ + H$^+$), 6, 161 (M – propyl + H$^+$), 100. HRMS (EI) [M + H]$^+$ calcd for C$_9$H$_{17}$NO$_4$, 204.1236; found, 204.1238; [M – propyl + H]$^+$ calcd for C$_9$H$_{17}$NO$_4$, 161.0688; found, 161.0886. Anal. Calcd for C$_9$H$_{17}$NO$_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.32; H, 8.63; N, 6.99.
1H), 3.70 (s, 3H), 3.50 (ddd, J = 8.3, 11.8 Hz, 1H), 3.28 (dd, J = 8.0, 7.5 Hz, 1H), 2.99–2.85 (m, 1H), 1.73–1.65 (m, 1H), 1.44–1.36 (m, 2H), 0.96 (t, J = 7.5 Hz). 13C NMR (100.6 MHz, 26 °C, CDCl3) δ 156.4/155.4 (C), 133.9 (C), 131.6 (CH), 129.2 (2 × CH), 127.5 (2 × CH), 80.4/79.6 (CH), 65.1/64.6 (CH), 52.4/51.9 (CH2), 51.0 (CH3), 34.9/34.4 (CH), 29.7 (CH3), 18.6 (CH3), 14.0 (CH3). MS m/z (rel intensity) 295 (M+*, 13), 186 ([M – SPh]+*, 100). HRMS (EI) [M]+ calcd for C15H21 NO3S, 295.1242; found, 295.1237; [M – SPh]+ calcd for C9H16NO3, 186.1130; found, 186.1125. Anal. Calcd for C15H21NO3S: C, 61.39; H, 7.21; N, 4.67; S, 10.85. Found: C, 61.39; H, 7.21; N, 4.66; S, 10.99.

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Declarations

Conflict of interest There are no conflicts of interest to declare. All the studies were performed in accordance with ethical standards.

Informed consent No experiments involving human participants or animals were carried out, so informed consent is not required.

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