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Asymmetric synthesis of (1*S*,2*R*)-2-aminocyclooctanecarboxylic acid

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ABSTRACT

A highly efficient asymmetric synthesis of (1*S*,2*R*)-2-aminocyclooctanecarboxylic acid has been completed. This asymmetric synthesis using cycloocta-1,5-diene as the starting material is achieved in 77% yield via a four-step sequence from *tert*-butyl cycloocta-1,7-dienecarboxylate **10** where the extra double bond adjacent to the unsaturated ester is essential to improve the yield. Furthermore, the Michael adduct intermediate (1*S*,2*R*,α*R*)-**14** could be used towards the synthesis of the natural product tashiromine.

1. Introduction

A range of methodologies for the asymmetric synthesis of cyclic derived β-amino acids have been devised, with much recent interest focusing around strategies for the asymmetric synthesis of the *cis*- and *trans*-diastereoisomers of 2-aminocyclopentanecarboxylic acid (cispentacin **1** and transpentacin **2,** respectively, Fig. 1). The *cis*-diastereoisomer shows potent antifungal activity,[1] while Fülöp et al. have recently demonstrated that oligomers of cispentacin adopt a sheet-type structure in DMSO.[2] Furthermore, Gellman et al. have demonstrated that short chain β-peptides derived from transpentacin and *trans*-2-aminocyclohexanecarboxylic acid adopt 12-membered helical structures both in the solid state and in solution,[3] while 3-substituted transpentacin and differently substituted cyclohexanic derivatives fold in water, which should facilitate the design of β-peptides for biological applications (Fig. 1).[4]

We have demonstrated the asymmetric synthesis of the stereoisomers of 2-amino-5-carboxymethylcyclopentane-1-carboxylate in enantiomerically pure form, via a domino reaction involving an asymmetric Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**5** to (*E*,*E*)-octa-2,6-diendioate and a subsequent 5-exotrig intramolecular cyclization.[5] Later, the versatility of this methodology was extended, and ε and ζ-functionalized α,β-unsaturated esters were shown to participate in conjugate-addition–cyclization reactions providing the synthesis of β-amino acid derivatives of cyclohexane and piperidine rings.[6]

A general asymmetric synthesis of higher cyclic compounds such as cyclooctane is desired, for instance Kaushik et al.[7] recently published the synthesis of β-amino acids containing peptides such as **3** and **4** (Fig. 1), which are shown to have antimalarial properties (IC_{50} = 3.87 and 3.64 μg/mL, respectively). Fülöp et al.[8] have reported the asymmetric synthesis of cyclic (size from 5 to 8 carbon atoms) β-amino acids by enzyme-catalyzed (lipase B from *Candida antarctica*) ring-opening resolution of unactivated alicyclic β-lactams. The β-amino acids obtained have been incorporated into different oligomers, as a way to offer a widely applicable alternative route for β-peptides and for combinatorial peptide libraries.[9]

In the retrosynthetic synthesis (Scheme 1), we proposed to accomplish the asymmetric synthesis of 2-aminocyclooctanecarboxylic acid from cyclooctadiene using lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**5** as the chiral reagent.

In addition, we report herein the asymmetric synthesis of three intermediates, which are synthetic building blocks, with the correct grouping to be applied to the synthesis of important natural bioactive products including (+)-tashiromine. Recently, Marsden et al.[10] have reported its racemic total synthesis and therein the 13 previous successful total synthesis of tashiromine are cited.

2. Results and discussion

Three intermediates **9**, **10** and **13** were synthesized (Scheme 2). The syntheses of **9** and **10** were achieved by starting with cycloocta-1,5-diene following route A. Intermediate **13** was synthesized following route B that began with cyclooctene.

Treatment of cycloocta-1,5-diene with MCPBA for 90 min provided the monoepoxide that under treatment with cyanotrimethylsilane[11] using Et_2AlCl as catalyst yielded regio and stereoselectively 2-trimethylsiloxy-cycloct-5-enocarbonitrile **6** in 100% yield (Scheme 2).

By treatment of the nitrile **6** with KOH followed by HCl addition[12] we obtained a 1:1 mixture of the acids **7** and **8** that could be resolved by column chromatography, but are best isolated by the CC at the ester stage, and are easily esterified by a normal procedure under treatment with TFAA and *tert*-butanol to obtain the

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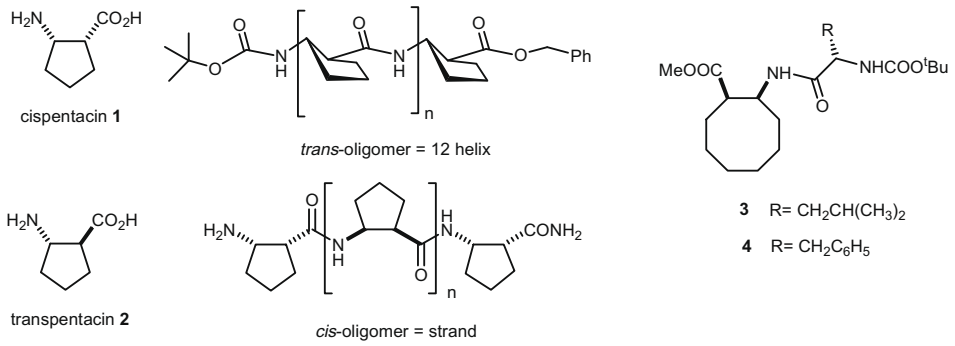
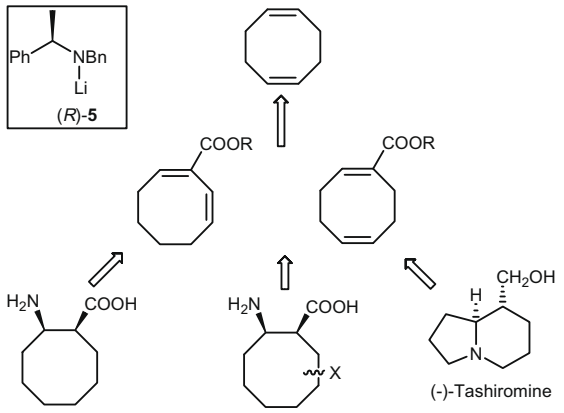


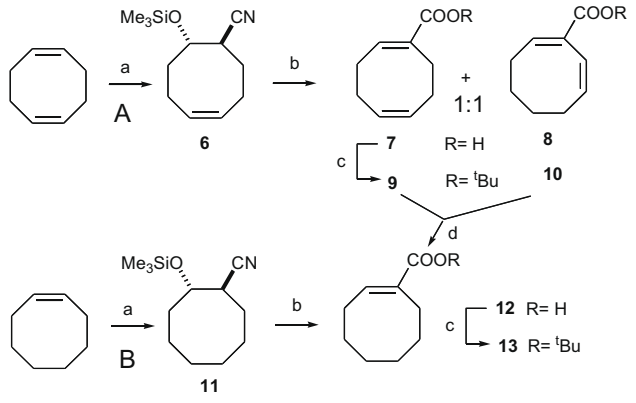
Figure 1.



Scheme 1. Proposed strategy for the synthesis of cyclooctane β-amino acid derivatives and applications.

tert-butyl ester **9** and **10**, respectively, as a 1:1 mixture. Alternatively, starting with cyclooctene, route B and following the same path of reactions: epoxidation, opening of epoxide (20%) and hydrolysis gave the compound **12** that by esterification led to the parent ester **13**. This route gave poor yield, especially in the opening of the epoxide even when we tried with different Lewis acid catalysts.[11] Nevertheless, hydrogenation of **9** and **10** separately, or as a mixture, gave compound **13** with excellent yield.

With the *tert*-butyl cyclooct-1-encarboxylates **9**, **10** and **13** in hand, we tried the protocol of asymmetric Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**5**, obtaining stereoselectively the corresponding β-amino ester derivatives: (1*S*,2*R*,α*R*)-**14**, (1*S*,2*R*,α*R*)-**15** and (1*S*,2*R*,α*R*)-**16**, respectively, in 42%, 100% and 15% yields (de >95%) (Scheme 3). Davies et al.[13] have recently published a comprehensive review in this area of chemistry covering the scope, limitations and synthetic applications of the use of enantiomerically pure lithium amides as homochiral ammonia equivalents in conjugate addition reactions.



Scheme 2. Reagents and conditions: (a) (i) MCPBA; (ii) Me_3SiCN/Et_2AlCl, 100% for **6**, 20% for **11**; (b) (i) KOH/ethylenglycol; (ii) HCl aq, quant; (c) TFAA/^{t}BuOH, 80% (15% of the acid was recovered); (d) PtO_2/H_2, EtOAc, 97%.

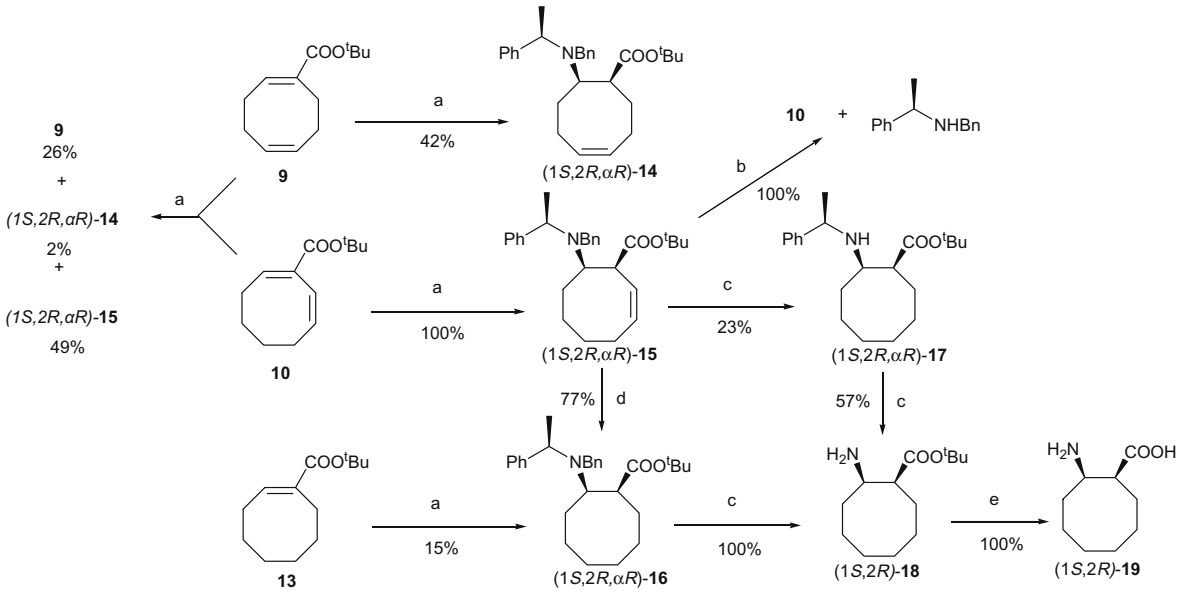
Contrary to (1*S*,2*R*,α*R*)-**14** and (1*S*,2*R*,α*R*)-**16**, that were stable in silica gel, when crude (1*S*,2*R*,α*R*)-**15** was chromatographed over silica gel, we obtained the required (1*S*,2*R*,α*R*)-**15** compound in 22% yield together with cycloocta-1,7-diencarboxylate and (*R*)-*N*-benzyl-*N*-α-methylbenzylamine. To assess this reaction, a solution of (1*S*,2*R*,α*R*)-**15** with SiO_2 in DCM was stirred for 1 h, and the retro-Michael compounds **10** and *N*-benzyl-*N*-α-methylbenzylamine were obtained quantitatively. The higher acidity of H–C-1 within (1*S*,2*R*,α*R*)-**15** related to the other Michael adduct accounts for this behaviour and could be used in the synthetic targets.[14] Nevertheless, crude (1*S*,2*R*,α*R*)-**15** could be used for further reaction or purified by crystallization in a mixture of hexane and ether. The results obtained suggest a way to differentiate the Michael acceptors **9** and **10** (Table 1). Interestingly, when a 1:1 mixture of **9** and **10** was subjected to reaction with (*R*)-**5** (1.6 equiv) (Table 1, entry 4) over 30 min (1*S*,2*R*,α*R*)-**15** was obtained together with **9** and a minute amount of (1*S*,2*R*,α*R*)-**14** that can be easily separated.

The ^{1}H NMR of (1*S*,2*R*,α*R*)-**14** shows an NOE effect between H–C-1 and H–C-2 confirming a *cis* relationship, which was anticipated by the established way of addition of lithium amide (*R*)-**5**,[15] and when the acceptor has an α-alkyl substituent,[16] as applied by Davies et al. to the synthesis of cispentacin.[17] The configuration of the newly formed stereogenic centre was confirmed to be (1*S*,2*R*) through single-crystal X-ray structure analysis (Fig. 2), in the case of (1*S*,2*R*,α*R*)-**15** product,[18] and corroborated the stereochemistry of related compounds.

The cyclooctene ring is not conformationally stable so the major planarity provided by the extra double bond adjacent to the conjugate ester must account for the excellent yield.[19]

Hydrogenolysis of (1*S*,2*R*,α*R*)-**15** gave the monodebenzylated compound (1*S*,2*R*,α*R*)-**17** in poor yield (23%), probably due to retro-Michael reaction, but the strategy of hydrogenation to give (1*S*,2*R*,α*R*)-**16** (77%), followed by hydrogenolysis (100%), provided (1*S*,2*R*)-**18** with an excellent overall 77% yield in four steps. Treatment of (1*S*,2*R*)-**18** with trifluoroacetic acid gave rise to the β-amino acid (1*S*,2*R*)-**19** quantitatively, $[\alpha]_D^{26} = -16.5$ (*c* 0.7, H_2O); {lit.[8a] for (1*R*,2*S*)-**19** $[\alpha]_D^{25} = +17.8$ (*c* 0.4, H_2O)}.

Interestingly, compound (1*S*,2*R*,α*R*)-**14** has the right functional groups to be used in the asymmetric synthesis of tashiromine, further work is being undertaken to improve the yield and to oxidize the remaining double bond. In due course a range of different substituted β-amino cyclooctanecarboxylic acid derivatives will be available.



Scheme 3. Reagents and conditions: (a) lithium *N*-benzyl-*N*-α-methylbenzylamide ((*R*)-**5**, 3.2 equiv), THF, −78 °C, 2 h; (b) SiO_2, DCM, quant; (c) Pd/C, H_2, AcOH, 4 atm, 24 h; (d) PtO_2, H_2, EtOAc, 3 h, 77%; (e) TFA, quant.

Table 1
Resolution of the mixture of **9**:**10** by (*R*)-**5**

Entry	**9**:**10** ratio	*t* (min)	(*R*)-**5** (equiv)	**9** (%)	(1*S*,2*R*,α*R*)-**14** (%)	(1*S*,2*R*,α*R*)-**15** (%)
1	1:0	120	2.4		42	
2	0:1	120	2.4			100
3	1:3	120	2.4		10	60
4	1:1	30	1.6	26	2	49

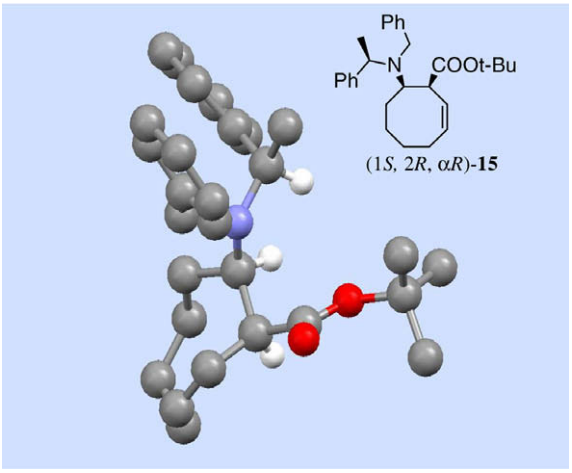


Figure 2. Representation of the X-ray crystal structure of (1*S*,2*R*,α*R*)-**15** (some H omitted for clarity).

3. Conclusions

In conclusion we have demonstrated a novel efficient diastereoselective synthesis of (1*S*,2*R*)-2-aminocycloocatanecarboxylic acid using as the key step the Michael addition of lithium amide (*R*)-**5**. This asymmetric synthesis is achieved in 77% yield via a four-step sequence from *tert*-butyl cycloocta-1,7-dienecarboxylate where cycloocta-1,5-diene is used as the starting material. The extra double bond adjacent to the conjugate ester has proved essential to improve the yield of the addition. Importantly, the analogous series of reactions deploying the enantiomers of lithium amide (*S*)-**5** in the conjugate addition step will allow simple access to (1*R*,2*S*)-**19**. Further investigation is undertaken in our group in order to obtain different substituted 2-aminocyclooctanecarboxylic acids and towards the asymmetric synthesis of tashiromine and will be published in due course.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available, and were used without further purification. IR spectra were recorded on a AVATAR 370 FT-IR Thermo Nicolet spectrophotometer. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (J) are given in Hertz. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer at 70 eV ionising voltage. HRMS were recorded using a VG Platform (Fisons) spectrometer using Chemical Ionization (ammonia as gas) or Fast Atom Bombardment (FAB) technique or a QSTAR XL spectrometer using electrospray technique. Optical rotations were determined in a Perkin–Elmer 241 polarimeter in 1 dm cells and are given in units of 10^{-1} deg cm^2 g^{-1}. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualized using iodine, UV light or 1% aqueous $KMnO_4$ solution. Column chromatography was performed with Merck Silica Gel 60 (70–230 mesh). Diethyl ether

and THF were distilled from sodium, and dichloromethane was distilled under argon from CaH_2. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analysis was performed by the microanalysis service of the 'Laboratorio de Analisis Químicos, Universidad de Salamanca'.

4.1.1. General procedure 1 for lithium amide reaction

n-BuLi was added dropwise to a stirred solution of secondary amine in THF at −78 °C under argon atmosphere and was stirred for 30 min prior to the addition of a solution of acceptor in THF at −78 °C. After 2 h, saturated aqueous NH_4Cl solution was added and the resultant solution was warmed to room temperature, partitioned between DCM (3 × 50 mL) and brine, dried and concentrated in vacuo. Purification by chromatography on silica gel gave the desired product. This residue was partitioned between DCM and 10% citric acid solution, organic layer washed in succession with aqueous $NaHCO_3$ solution and brine, dried and concentrated in vacuo before purification via column chromatography.

4.1.2. General procedure 2

Pd/C (10% Pd by mass) was added to β-amino ester substrate in glacial acetic acid and the resultant suspension stirred under hydrogen (5 atm) for 24 h. After filtration through Celite (eluent DCM), the organic layer was washed with saturated $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated in vacuo before purification via column chromatography.

4.1.3. General procedure 3

PtO_2 was added to a solution of unsaturated derivatives in EtOAc. The system was purge and stirred under hydrogen atmosphere for 3 h. Purification by chromatography on silica gel gave the desired product.

4.1.4. Preparation of 1,2-epoxycyclooct-5-ene

To a stirred solution of 1,5-cyclooctadiene (10.0 g, 96 mmol, 1.0 equiv) in dry DCM (150 mL) at 0 °C was added slowly MCPBA (18.5 g, 113 mmol, 1.2 equiv). The mixture was stirred for 1 h 30 min at room temperature. Then a saturated solution of $Na_2S_2O_3$ (15 mL) was added and extracted with DCM. The organic layer was washed with H_2O (2 times), saturated $NaHCO_3$ (2 times) and saturated $Na_2S_2O_3$ (2 times). The organic layer was then dried with Na_2SO_4, filtered and concentrated in vacuo. Purification of crude product by fractional distillation vacuum (15 mmHg, 65 °C) afforded the product as a liquid (8.6 g, 72%). IR (film) ν (cm^{-1}) 3050, 2955, 1655, 1229, 936, 862; δ_H (400 MHz; $CDCl_3$) 1.90–2.25 (6H, m, H-3, H-8, H-4α and H-7α), 2.30–2.55 (2H, m, H-4β and H-7β), 3.02 (2H, m, H-1 and H-2), 5.52 (2H, m, H-5 and H-6); δ_C (50 MHz; $CDCl_3$) 23.5 (CH_2), 28.0 (CH_2), 56.4 (CH), 128.7 (CH); *m/z* (CI^+) 124 (M^+, 2), 95 (14), 80 (100), 67 (100), 54 (37).

4.1.5. Reaction of 1,2-epoxycyclooct-5-ene with trimethylsilylcyanide, 6

A dry and argon-flushed flask equipped with a magnetic stirrer and a septum was charged under argon with Et_2AlCl (1.0 M in heptane) (2.30 mL, 2 mmol, 0.04 equiv) and Me_3SiCN (7.50 mL, 56 mmol, 1.2 equiv) and stirred for 30 min at room temperature. Then 1,2-epoxycyclooct-5-ene (5.72 g, 46 mmol, 1 equiv) was added dropwise to the previous solution by canula over 15 min. An exothermic reaction was observed, the mixture was stirred for 30 min. The reaction was poured onto a 200 mL mixture of ice and NaOH 3 M and extracted with ether. The organic solution was washed with saturated NaCl (2 times) and dried over Na_2SO_4, concentration of the filtrate and column chromatography (hexane–EtOAc 4:1) afforded the product **6** (10.3 g) in 100 % yield.

4.1.5.1. 2-Trimethylsiloxi-cyclooct-5-enecarbonitrile, 6. IR (film) ν (cm^{-1}) 3017, 2951, 2241, 1653, 1251, 1096, 1071, 843; δ_H (400 MHz; $CDCl_3$) 0.17 (9H, s, Me_3SiO), 1.66 (2H, m), 1.87–2.23 (6H, m), 3.03 (1H, ddd, *J* = 11.7, 7.9 and 3.9 Hz, H-1), 3.90 (1H, td, *J* = 7.9 and 3.4 Hz, H-2), 5.56 (1H, dt, *J* = 7.0 and 2.7 Hz, H-6), 5.73 (1H, dt, *J* = 10.8 and 7.0 Hz, H-5); δ_C (50 MHz; $CDCl_3$) 0.8 (3 × CH_3, Me_3SiO), 2.27 (CH_2, C-8), 23.8 (CH_2 , C-3), 28.8 (CH_2 , C-7), 35.9 (CH_2 , C-4), 37.6 (CH, C-1), 71.6 (CH, C-2), 121.5 (C, C≡N), 127.2 (CH, C-6), 131.2 (CH, C-5); *m/z* (CI^+) 223 (M^+,1), 208 (50), 195 (3), 180 (6), 167 (3), 152 (10), 126 (16), 116 (21), 101 (47), 80 (23), 73 (100), 59 (48).

4.1.6. Hydrolysis of the nitrile, 7 and 8

The previous product (9 g, 38.6 mmol, 1 equiv) was dissolved in a solution of KOH (2.9 g) and ethane-1,2-diol (47 mL), and the mixture was refluxed at 200 °C for 20 h. The mixture was cooled with an ice bath and H_2O (50 mL) was added, the crude was extracted with ether and the organic layer was separated. The aqueous solution was made acidic by addition of HCl. The organic layer was washed with H_2O (2 times) and saturated NaCl (2 times), dried over Na_2SO_4, filtered and concentrated in vacuo to give the reaction product (5.9 g) in 100% yield. ^1H NMR of the crude shows a product **7**:**8** ratio of 1:1. A part was purified on column chromatography by elution with hexane–EtOAc 4:1 to afford the acids **7** and **8**.

4.1.6.1. Cycloocta-1,5-dienecarboxylic acid, 7. IR (film) ν (cm^{-1}) 3600–2500, 2958, 2934, 1684, 1622; δ_H (400 MHz; $CDCl_3$) 1.56 (4H, m), 2.21 (2H, m), 2.50 (2H, m), 5.85 (2H, m, H-5 and H-6), 7.28 (1H, m, H-2); δ_C (50 MHz; $CDCl_3$) 21.5 (CH_2, C-4), 25.6 (CH_2, C-7), 25.8 (CH_2, C-3), 29.8 (CH_2, C-8), 124.0 (CH, C-5), 131.0 (C, C-1), 136.8 (CH, C-6), 139.3 (CH, C-2), 173.0 (C, COOH); *m/z* (CI^+) 153 (M^+, 32), 136 (26), 124 (10), 107 (74), 89 (72), 77 (100), 69 (32), 63 (25), 1 (57). HRMS (CI^+) $C_9H_{12}O_2$ $[M]^+$, requires 152.0837; found: 152. 0817.

4.1.6.2. Cycloocta-1,7-dienecarboxylic acid, 8. IR (film) ν (cm^{-1}) 3600–2450, 3021, 2930, 2857, 1690, 1622; δ_H (400 MHz; $CDCl_3$) 1.25 (2H, m), 1.48 (2H, m), 2.13 (2H, m), 2.31 (2H, m), 5.88 (1H, dt, *J* = 11.3 and 7.2 Hz, H-7), 6.13 (1H, d, *J* = 11.3, H-8), 7.08 (1H, t, *J* = 8.0 Hz, H-2); δ_C (50 MHz; $CDCl_3$) 22.6 (CH_2), 25.5 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 122.5 (CH), 129.3 (C, C-1), 133.9 (CH), 144.9 (CH, C-2), 171.2 (C, COOH); *m/z* (CI^+) 152 (M^+, 10), 135 (9), 107 (41), 89 (36), 77 (100), 63 (23), 1 (56). HRMS (CI^+) $C_9H_{12}O_2$ $[M]^+$, requires 152.0837; found: 152. 0833.

4.1.7. Esterification of the acids mixture, 9 and 10

To a mixture (1:1) of acids **7** and **8** (5.11 g, 34 mmol, 1 equiv) was added TFAA (9 mL, 64 mmol, 1.8 equiv) at 0 °C and was stirred for 15 min. After that, the reaction mixture was cooled to 0 °C and *tert*-butanol (11 mL, 110 mmol, 3.2 equiv) was added and stirred for 4 h at room temperature. The reaction was quenched with NaOH 10% (50 mL). Ether was added and the organic layer was washed with NaOH 1 M (2 times) and saturated NaCl (2 times), dried with Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography afforded *tert*-butyl cyclooct-1,5-dienecarboxylate **9** (3.41 g, 48%) and *tert*-butyl cyclooct-1,7-dienecarboxylate **10** (2.18 g, 31%). The aqueous basic solution was acidified, and ether extraction followed by usual procedure yielded 767 mg (15%) of starting acids **7** and **8**.

4.1.7.1. *tert*-Butyl cycloocta-1,5-dienecarboxylate, 9. IR (film) ν (cm^{-1}) 2932, 1709, 1368, 1155; δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s, $COOC(CH_3)_3$), 2.06 (4H, m, H-4 and H-7), 2.33 (4H, m, H-3 and H-8), 5.69 (2H, m, H-5 and H-6), 6.92 (1H, s, H-2); δ_C (50 MHz; $CDCl_3$) 21.9 (CH_2), 24.1 (CH_2), 26.3 (CH_2), 28.2 (3 × CH_3, $COOC(CH_3)_3$), 29.8 (CH_2), 79.9 (C, $COOC(CH_3)_3$), 124.5 (CH), 133.6 (C, C-1), 135.4 (CH),

135.7 (CH, C-2), 166.0 (C, *C*OOC(CH_3)$_3$); *m/z* (Cl^+) 208 (M^+, 1), 152 (M^+-56, 36), 135 (13), 123 (6), 107 (35), 93 (5), 79 (32), 77 (13), 57 (100). HRMS (Cl^+) $C_{13}H_{20}O_2$ $[M]^+$, requires 208.1463; found: 208.1444.

4.1.7.2. *tert*-Butyl cycloocta-1,7-dienecarboxylate, 10. IR (film) *ν* (cm^{-1}) 2930, 1717, 1456, 1368, 1159; δ_H (400 MHz; $CDCl_3$) 1.49 (9H, s, COOC(CH_3)$_3$), 2.11 (4H, m, H-4 and H-5), 2.24 (4H, m, H-3 and H-6), 5.80 (1H, dt, *J* = 11.2 and 7.2 Hz, H-7), 6.09 (1H, d, *J* = 11.2 Hz, H-8), 6.85 (1H, t, *J* = 8.0 Hz, H-2); δ_C (50 MHz; $CDCl_3$) 22.4 (CH_2), 22.9 (CH_2), 28.2 (3 × CH_3, COOC(*C*H_3)$_3$), 28.3 (CH_2), 28.4 (CH_2), 80.1 (C, COO*C*(CH_3)$_3$), 123.7 (CH, C-7), 131.8 (C, C-1), 132.8 (CH, C-8), 141.3 (CH, C-2), 166.6 (C, *C*OOC(CH_3)$_3$); *m/z* (Cl^+) 208 (M^+, 1), 152 (31), 135 (12), 123 (6), 107 (32), 92 (12), 79 (41), 67 (13), 57 (100). HRMS (Cl^+) $C_{13}H_{20}O_2$ $[M]^+$, requires 208.1463; found: 208. 1458.

4.1.8. Preparation of *tert*-butyl cyclooct-1-enecarboxylate, 13

Upon subjecting 500 mg of cyclooctene to the series of reaction described above the following compounds were obtained: epoxycyclooctene (100%), 2-trimethylsiloxy-cyclooctanecarbonitrile **11** (20%), cyclooctenecarboxylic acid **12** (85%) and *tert*-butyl cyclooct-1-enecarboxylate **13** (80%) together with **12** (15%).

4.1.9. Hydrogenation reactions of 9 and 10, 13

Following general procedure 3 and as starting material (270 mg, 1.3 mmol) **9**, **10** or a mixture (1:1) of both for a one-hour period, compound **13** was obtained (263 mg, 97%).

4.1.10. Preparation of *tert*-butyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cyclooct-5-enecarboxylate, (1*S*,2*R*,α*R*)-14

Following general procedure 1, **9** (233 mg, 1.1 mmol) in THF (3 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (541 mg, 2.6 mmol) in THF (10 mL) and *n*-BuLi (1.6 M, 1.6 mL, 2.5 mmol) gave after chromatographic purification on silica (hexane–Et_2O 9:1) (1*S*,2*R*,α*R*)-**14** (194 mg, 42%).

$[\alpha]_D^{26} = +98.0$ (*c* 1.2, $CHCl_3$); $C_{28}H_{37}NO_2$ requires C, 80.2; H, 8.9; N, 3.3; found C, 80.0; H, 8.5; N, 3.2; IR (film) *ν* (cm^{-1}) 3854, 3752, 3677, 2932, 1653, 1700, 1559; δ_H (400 MHz; $CDCl_3$) 1.37 (9H, s, COOC(CH_3)$_3$), 1.45 (3H, d, *J* = 6.8 Hz, C(α)*Me*), 1.5–2.4 (8H, m, H-3, H-4, H-7, H-8), 2.50 (1H, m, H-1), 3.85 (1H, m, H-2), 3.85 (1H, AB, J_{AB} = 17.1 Hz, NCH_AH$_B$Ph), 4.10 (1H, AB, J_{AB} = 17.1 Hz, NCH$_A$CH_BPh), 4.25 (1H, q, *J* = 6.8 Hz, C(α)*H*), 5.80 (1H, m, H-5), 6.05 (1H, m, H-6), 7.30 (10H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 13.2 (CH_3, C(α)*Me*), 25.8 (CH_2), 27.5 (CH_2, C-8), 27.9 (C, COOC(*C*H_3)$_3$), 30.1(CH_2), 30.6 (CH_2), 51.7 (CH_2, NCH_2), 53.5 (CH, C-1), 54.7 (CH, CH(α)), 56.5 (CH, C-2), 80.0 (COO*C*(CH_3)$_3$), 126.5–129.9 (10 × CH, Ar), 128.0 (CH, C-5), 129.6 (CH, C-6), 141.9 (C, C_{ipso}), 144.1 (C, C_{ipso}), 174.9 (C, *C*OOC(CH_3)$_3$); *m/z* (Cl^+) 419 (M^+, 19), 258 (21),205 (8), 172 (11), 136 (6), 105 (100), 77 (33). HRMS (Cl^+) $C_{28}H_{37}NO_2$ $[M]^+$, requires 419.2824; found: 419.2843.

4.1.11. Preparation of *tert*-butyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cyclooct-7-enecarboxylate (1*S*,2*R*,α*R*)-15

Following general procedure 1, **10** (242 mg, 1.2 mmol) in THF (3 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (633 mg, 3 mmol) in THF (10 mL) and *n*-BuLi (1.6 M, 1.8 mL, 2.9 mmol) gave crude (1 S,2*R*,α*R*)-**15** (503 mg, 100%). We used it without further purification or by crystallization from a mixture of hexane–ether. Mp = 119 °C.

After chromatographic purification of crude (1*S*,2*R*,α*R*)-**15** (100 mg) on silica gel (hexane–Et_2O 9:1), **10** (30 mg, 60%), (1*S*,2*R*,α*R*)-**15** (22 mg, 22%) together with (*R*)-*N*-benzyl-*N*-α-methylbenzylamine were obtained.

$[\alpha]_D^{26} = -4.7$ (*c* 0.96, $CHCl_3$); $C_{28}H_{37}NO_2$ requires C, 80.2; H, 8.9; N, 3.3; found C, 79.9; H, 8.5; N, 3.1%; IR (film) *ν* (cm^{-1}) 2939, 1717, 1651, 1541, 1493, 1456, 1368, 1248, 1155, 1030, 783, 750, 700; δ_H (400 MHz; $CDCl_3$) 1.17 (3H, d, *J* = 7.0 Hz, C(α)Me); 1.56 (9H, m, COOC(*C*H_3)$_3$); 1.65–1.75 (4H, m, H-4 and H-5); 1.90–2.10 (5H, m, H-1, H-3 and H-6); 3.61 (1H, AB, J_{AB} = 15.2 Hz, NCH_ACH$_B$); 3.65 (1H, m, H-2); 3.77 (1H, AB, J_{AB} = 15.2 Hz, NCH$_A$CH_B); 4.08 (1H, q, *J* = 7.0 Hz, C(α)H); 5.74 (1H, m, H-7); 5.85 (1H, t, *J* = 10.1 Hz, H-8); 7.26 (10H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 20.7 (CH_3, C(α)*Me*); 26.3 (CH_2); 27.3 (CH_2); 27.5 (CH_2); 28.4 (CH_3 × 3, COOC(*C*H_3)$_3$); 30.2 (CH_2); 48.1 (CH, C-1); 50.8 (CH_2, CH_2Ph); 63.2 (CH, CH(α)); 65.8 (CH, C-2); 80.5 (C, COO*C*(CH_3)$_3$); 126.4 (CH); 128.6 (CH) 126.5–128.3 (10 × CH, *o,m,p-Ph*); 143.2 (C, C_{ipso}); 144.0 (C, C_{ipso}); 173.1 (C, *C*OOC(CH_3)$_3$). *m/z* (Cl^+) 420 (M^+, 70), 258 (22), 154 (52), 105 (100). HRMS (Cl^+) $C_{28}H_{37}NO_2$ $[M]^+$, requires 419.2824; found: 419.2819.

4.1.12. Treatment of a mixture of 9:10 with lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide

Following general procedure 1, a mixture (1:1) of **9** and **10** (362 mg, 1.75 mmol) in THF (3 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (591 mg, 2.8 mmol) in THF (10 mL) and *n*-BuLi (1.6 M, 1.7 mL, 2.9 mmol) stirred for 30 min gave a reaction crude that by ^{1}H NMR analysis shows the following composition: (1*S*,2*R*,α*R*)-**15** (49%), (1*S*,2*R*,α*R*)-**14** (2%) and **9** (26%). Compounds were purified by crystallization of (1*S*,2*R*,α*R*)-**15** or by Kugelrohr distillation of **9**.

Accordingly the mixture (1:3) of **9** and **10** described in Table 1, entry 3 gave the results shown.

4.1.13. Preparation of *tert*-butyl (1*S*,2*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-cyclooctanecarboxylate, (1*S*,2*R*,α*R*)-16

Following general procedure 1, **13** (500 mg, 2.4 mmol) in THF (3 mL), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.8 mmol) in THF (10 mL) and *n*-BuLi (1.6 M, 3.6 mL, 5.7 mmol) gave after chromatographic purification on silica (hexane–Et_2O 9:1) (1*S*,2*R*,α*R*)-**16** (152 mg, 15%). Following general procedure 3, (1*S*,2*R*,α*R*)-**15** (338 mg, 0.8 mmol) in EtOAc (20 mL), PtO_2 (93 mg, 0.4 mmol) gave crude (1*S*,2*R*,α*R*)-**16** (261 mg, 77%) and 23% of staring material was recovered. This compound was purified by crystallization from a mixture of hexane–ether. Mp = 110 °C.

$[\alpha]_D^{26} = +109$ (*c* 1.0, $CHCl_3$); $C_{28}H_{39}NO_2$ requires C, 79.8; H, 9.3; N, 3.3; found C, 80.1; H, 9.5; N, 3.0; IR (film) *ν* (cm^{-1}) 2970, 2927, 2852, 1719, 1455, 1370, 1148; δ_H (400 MHz; $CDCl_3$) 1.26 (3H, d, *J* = 7 Hz, C(α)*Me*); 1.41 (9H, s, COOC(*C*H_3)$_3$); 1.57–1.62 (8H, m); 2.24 (2H, m); 2.50 (2H, m); 3.12 (1H, m, H-1); 3.15 (1H, m, H-2); 3.85 (1H, AB, J_{AB} = 14.0 Hz, NCH_ACH$_B$); 3.90 (1H, AB, J_{AB} = 14.0 Hz, NCH$_A$CH_B); 3.96 (1H, q, *J* = 6.5 Hz, C(α)H).; δ_C (50 MHz; $CDCl_3$) 17.0 (CH_3, C(α)*Me*); 24.3 (CH_2); 26.1 (CH_2 × 2); 28.2 (CH_3 × 3, COOC(*C*H_3)$_3$); 28.3 (CH_2); 29.5 (CH_2); 29.6 (CH_2); 49.7 (CH, C-1); 51.6 (CH_2, CH_2Ph); 54.8 (CH, C-2); 58.7 (CH, CH(α)); 80.2 (C, COO*C*(CH_3)$_3$); 126.5 (CH, *o*-Ph); 126.8 (CH, *o*-Ph); 128.0 (CH, *m*-Ph) 128.2 (CH, *m-Ph*); 128.2 (CH, *p*-Ph); 128.2 (CH, *p*-Ph); 143.2 (C, C_{ipso}); 145.3 (C, C_{ipso}); 176.3 (C, *C*OOC(CH_3)$_3$). HRMS (Cl^+) $C_{28}H_{40}NO_2$ $[M+H]^+$, requires 422.3054; found: 422.3039.

4.1.14. Preparation of *tert*-butyl (1*S*,2*R*,α*R*)-2-*N*-α-methylbenzylamino-cyclooctanecarboxylate, (1*S*,2*R*,α*R*)-17

Following general procedure 2. (1*S*,2*R*,α*R*)-**15** (67 mg, 0.2 mmol) in glacial acetic acid (3 mL), Pd/C (10% Pd by mass, 35 mg) and H_2 (4 atm) for 24 h, gave after purification by column chromatography (hexane–EtOAc 1:1) (1*S*,2*R*,α*R*)-**17** (12 mg, 23%).

IR (film) *ν* (cm^{-1}) 2973, 2924, 2856, 1723, 1452, 1367, 1151; δ_H (400 MHz; $CDCl_3$) 1.34 (3H, d, *J* = 6.2 Hz, C(α)*Me*); 1.49 (9H, s, COOC(CH_3)$_3$); 1.20–1.70 (10H, m); 1.80–1.95 (2H, m); 2.75 (1H, m, H-1); 2.95 (1H, m, H-2); 3.90 (1H, m, N-C(α)H); 7.26 (5H, m, H-Ar); δ_C (50 MHz; $CDCl_3$) 24.6 (CH_3, C(α)*Me*) 24.8 (CH_2); 25.5 (CH_2); 26.0 (CH_2); 27.1 (CH_2); 27.5 (CH_2); 28.4 (CH_3 × 3,

$COOC(CH_3)_3$); 32.3 (CH_2); 46.7 (CH, C-1); 54.3 (CH, C(α)); 55.4 (CH, C-2); 80.5 (C, $COOC(CH_3)_3$); 126.9 (CH × 2, *o*-Ph); 127.1 (CH × 2, *m*-Ph); 128.5 (CH, *p*-Ph); 146.5 (C, C_{ipso}); 174.9 (C, $COOC(CH_3)_3$). HRMS (ESI) $C_{21}H_{34}NO_2$ $[M+H]^+$, requires 332.2584; found: 332.2572.

4.1.15. Hydrogenolysis of (1*S*,2*R*,α*R*)-16 and (1*S*,2*R*,α*R*)-17. Preparation of *tert*-butyl (1*S*,2*R*)-2-amino-cyclooctanecarboxylate, (1*S*,2*R*)-18

Following general procedure 2. (1*S*,2*R*,α*R*)-**16** (67 mg, 0.2 mmol) in glacial acetic acid (4 mL), Pd/C (10% Pd by mass, 35 mg) and H_2 (4 atm) for 24 h after, gave after purification by column chromatography (1*S*,2*R*)-**18** (45 mg, 100%). (1*S*,2*R*,α*R*)-**17** (11 mg, 0.03 mmol) gave (1*S*,2*R*)-**18** (4.3 mg, 57%).

4.1.15.1. *tert*-Butyl (1*S*,2*R*)-2-amino-cyclooctanecarboxylate, (1*S*,2*R*)-18. $[\alpha]_D^{26} = -11.2$ (*c* 1.2, $CHCl_3$); IR (film) *ν* (cm^{-1}) 3375, 2922, 2847, 1724, 1464, 1370, 1153; δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s, $COOC(CH_3)_3$; 1.53–1.65 (6H, m); 1.75–1.90 (6H, m, H-4, H-8, H-3); 2.62 (1H, m, H-1); 3.27 (1H, m, H-2); δ_C (50 MHz; $CDCl_3$) 23.6 (CH_2); 23.8 (CH_2); 25.9 (CH_2); 26.7 (CH_2); 28.2 (CH_2); 28.3 (CH_3 × 3, $COOC(CH_3)_3$); 33.8 (CH_2); 47.6 (CH, C-1); 51.7 (CH, C-2); 80.4 (C, $COOC(CH_3)_3$); 175.6 (C, $COOC(CH_3)_3$). HRMS (ESI) $C_{13}H_{26}NO_2$ $[M+H]^+$, requires 228.1958; found: 228.1941.

4.1.16. Preparation of (1S,2*R*)-2-amino-cyclooctanecarboxylic acid by hydrolysis of the β-amino ester, (1*S*,2*R*)-19

The β-amino ester (1*S*,2*R*)-**18** (34 mg, 0.2 mmol) was dissolved in CF_3COOH (0.5 mL, 7 mmol) and was stirred for 1 h 30 min at room temperature. The solution was concentrated in vacuo, and organic impurities were washed with EtOAc, and dried to give (1*S*,2*R*)-**19** (29 mg, 100%). $[\alpha]_D^{26} = -16.5$ (*c* 0.7, H_2O); δ_H (400 MHz; D_2O) 1.49–1.52 (4H, m, H-5, H-6); 1.60–1.74 (4H, m, H-4, H-7); 1.86–1.88 (4H, m, H-3, H-8); 3.04 (1H, ddd, J = 8.5, 5.0 and 3 Hz, H-1); 3.73 (1H, ddd, J = 9, 6.3 and 3 Hz, H-2); δ_C (50 MHz; D_2O) 23.0 (CH_2, C-5); 24.4 (CH_2, C-6); 25.0 (CH_2, C-4); 25.7 (CH_2, C-7); 26.5 (CH_2, C-8); 28.7 (CH_2, C-3); 42.7 (CH, C-1); 50.9 (CH, C-2); 177.6 (C, C-9). HRMS (ESI) $C_9H_{18}NO_2$ $[M+H]^+$, requires 172.1332; found: 172.1336.

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18. A single crystal of (1*S*,2*R*,α*R*)-**15** compound was subjected to X-ray diffraction studies on a Seifert 3003 SC four-circle diffractometer (Cu Kα radiation, graphite monochromator) at 293(2) K. Crystal data for **1**: $C_{28}H_{37}N_1O_2$, M = 419.59, monoclinic, space group $P2_1$ (no. 4), a = 10.202(2) Å, b = 10.819(2) Å, c = 11.253(2) Å, β = 90.87(3)°, V = 1241.9(4) Å^3, Z = 2, D_c = 1.122 Mg/m^3, m = (Cu Kα) = 0.535 mm^{-1}, F(000) = 456. 5148 reflections were collected at $3.80 \leqslant 2\theta \leqslant 60.00$ and merged to give 1947 unique reflections, of which 1885 with $I > 2\sigma I$ were considered to be observed. The structure was solved by direct method and the non-hydrogen atoms were refined anisotropically by full-matrix least squares. H atoms attached to methyl groups were positioned geometrically and the rest of the hydrogen atoms were located in a difference Fourier map. The final R factors were R_1 = 0.0293 and ωR_2 = 0.0721 for a total of 407 parameters. Crystallographic data (excluding structure factors) for this structure have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. CCDC 705369.
19. The addition of (*R*)-5 to methyl (*R*)-6-methyl-cyclohex-1,3-dienecarboxylate with 86% yield in the formal synthesis of (−)-pumiliotoxin C has been reported: Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595–1596.