Conjugate addition of 6-membered hydrazine to chiral *tert*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamates. Synthesis of (*S*)-celacinnine

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Two enantiomers of the bicyclic lactam, (*S*)- and (*R*)-9-phenyl-1,6-diazabicyclo[4.3.0]nonan-7-one (**6**), were synthesized stereoselectively with high optical purity (95% ee) by the asymmetric conjugate addition–cyclization of piperidazine to chiral vinyl sulfoxides, *tert*-butyl (*E*)-2-[(*R*)- and (*S*)-*p*-tolylsulfinyl]cinnamate (**4**), followed by removal of the *p*-tolylsulfinyl group with SmI_2. The subsequent reductive cleavage of the N–N bond of the bicyclic lactam **6** with sodium in liquid ammonia produced the corresponding 9-membered azalactam, (*S*)- and (*R*)-4-phenyl-1,5-diazacyclononan-2-one (**7**) with 99% and 97% ee, respectively. X-Ray crystallography showed that (*S*)-**7** exists exclusively as a *trans* conformer in the crystal state. Starting from (*S*)-**7**, naturally occurring (*S*)-celacinnine **1** was synthesized with 99% ee employing the ring-expansion reaction *via* intramolecular transamidation.

Introduction

A number of β-amino acids have been isolated in free form and show interesting pharmacological properties.[1] In addition, many classes of natural products contain β-amino acid derivatives as fragments. For example, macrocyclic lactams containing a biogenetic base such as spermine or spermidine alkaloids, which have a framework of β-amino acid-like β-phenyl-β-alanine, are of particular interest as synthetic targets in view of their broad biological activity as antibiotics and antihypertensives.[2,3] More than 30 natural products which contain a 13-membered ring system, built up from spermidine and a fatty acid unit, have been extracted from plants. Due to the unsymmetrical structure of spermidine, two constitutional ring systems are possible for the 13-membered alkaloids of the same composition and, in fact, both celacinnine **1** and dihydroperiphylline **2** are found in Nature (Fig. 1). Although the biomimetic pathway is not yet well understood, we believe that the first step is a conjugate addition of spermidine to cinnamic acid, followed by an intramolecular cyclization with the loss of H_2O. Recently, the synthesis of a 13-membered lactam alkaloid, (*S*)-(+)-dihydroperiphylline **2**, starting from (*S*)-(−)-β-phenyl-β-alanine, has been reported.[4,5] Asymmetric synthesis of β-amino acid derivatives using chiral vinyl sulfoxides has also proven to be useful methodology for the synthesis of chiral compounds.[6] Davis *et al.* reported the diastereoselective synthesis of β-amino esters by addition of enolate ions to chiral sulfinimines.[7]

We have recently developed an efficient method for the synthesis of β-amino acid esters employing the conjugate

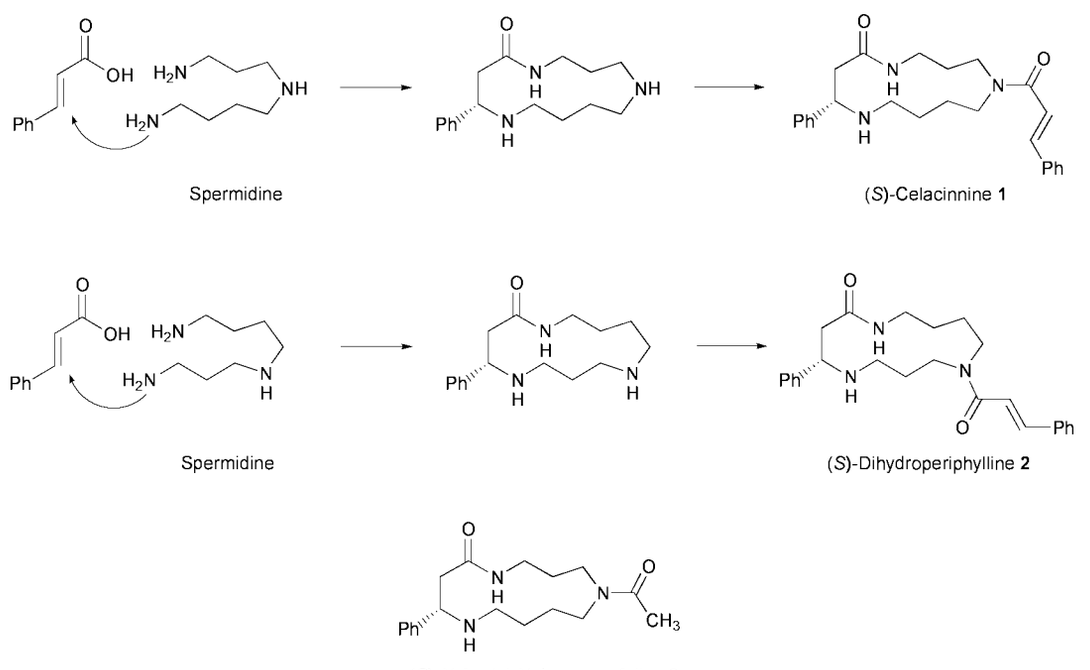

Fig. 1 Plausible reaction route to the 13-membered spermidine alkaloids: Conjugate addition of spermidine to cinnamic acid.

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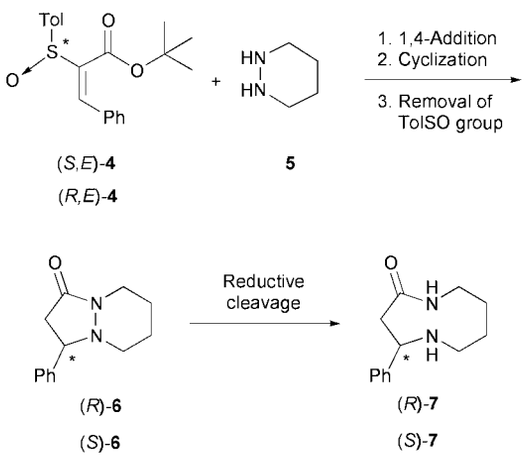
addition of nitrogen nucleophiles to chiral vinyl sulfoxides.[8] We applied this method to the synthesis of the spermine alkaloid (*S,S*)-homaline.[9]

(*S*)-(−)-Celacinnine **1** was isolated from the twigs of *Maytenus arbutifolia* (Hochst. ex A. Rich) R. Wilczek,[10] the roots *of Tripterygium wilfordii* Hook,[10] *Maytenus serrata* (Hochst. ex A. Rich) R. Wilczek,[11] *M. heteropylla* (Eckl. et Zeyher) N. Robson *subsp. heteropylla*,[11] and *Pleurostylia africana* Loes.,[12] all of which come from the plant family Celastraceae. Celacinnine **1** has a 13-membered ring formed from a naturally occurring polyamine, spermidine, and two cinnamic acid residues.

Our continuing interest in the development of synthetic pathways to the polyamine macrocycles prompted us to investigate the synthesis of the optically active 9-membered azalactam 4-phenyl-1,5-diazacyclononan-2-one[13] **7**, which could be a key intermediate in the total synthesis of 13-membered polyamine alkaloids, such as celacinnine **1**[14] and *N*(1)-acetyl-*N*(1)-deoxymayfoline **3**.[15] Our approach to **7** involves a conjugate addition–cyclization reaction of piperidazine (**5**) to chiral vinyl sulfoxides, *tert*-butyl (*E*)-2-[(*S*)- and (*R*)-*p*-tolylsulfinyl]cinnamate **4**, followed by reductive elimination of the *p*-tolylsulfinyl group from the adduct to produce (*R*)- and (*S*)-9-phenyl-1,6-diazabicyclo[4.3.0]nonan-7-one **6**. The reductive cleavage of the N–N bond of **6** leads to the almost optically pure **7** (Scheme 1).



Scheme 1

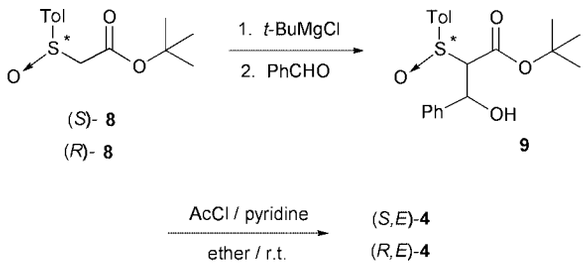
In a preliminary form we reported the synthesis of optically active celacinnine **1**.[13a] In this paper, we describe the syntheses of highly optically pure **6**, **7**, and **1** in detail.

Results and discussion

Conjugate addition–cyclization of piperidazine (5) to vinyl sulfoxide 4

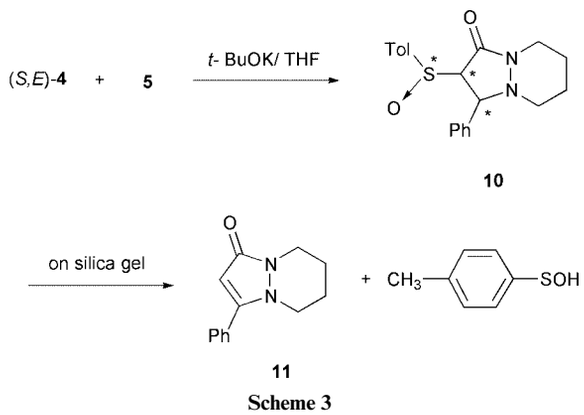
The optically active vinyl sulfoxides, *tert*-butyl (*E*)-2-[(*S*)- and (*R*)-*p*-tolylsulfinyl]cinnamate **4**, were prepared *via* **9** from *tert*-butyl (*S*)- and (*R*)-*p*-tolylsulfinylacetate[9] **8**. Addition of the carbanion derived from **8** to benzaldehyde, followed by treatment of **9** with acetyl chloride and pyridine in diethyl ether afforded optically active (*E*)-**4** [(*S*): op 91%; (*R*): op 93%] in 60% yield with a small amount of the (*Z*)-isomer (Scheme 2). The optically pure vinyl sulfoxides **4** were obtained by recrystallization, and the stereochemistry of (*R,E*)-**4** was determined by X-ray analysis.[8] The enantiomeric excess of (*E*)-**4** was determined by HPLC measurement using an optically active column (Daicel Chiralpak AS).

The conjugate addition–cyclization reaction of piperidazine (**5**) to the optically active vinyl sulfoxide (*S*)-**4** proceeded smoothly under basic conditions using potassium *tert*-butoxide in THF at room temperature to give the bicyclic compound **10**, but the elimination of toluene-*p*-sulfenic acid (*p*-TolSOH) from



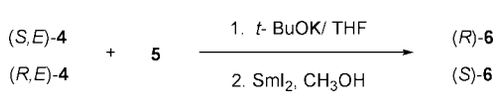
Scheme 2

10 occurred during its purification using column chromatography on silica gel, to give the unsaturated lactam **11** (Scheme 3).



Scheme 3

In order to avoid the formation of **11**, the reductive elimination of the *p*-tolylsulfinyl group from the adduct **10** with samarium(II) iodide was performed *in situ* after confirmation that (*S*)-**4** had reacted with **5** completely, giving the bicyclic lactam **6** (Scheme 4).[16] The enantiomeric excess of **6** was 95% by



Scheme 4

HPLC determination (Daicel Chiralpak AS), and the results are summarized in Table 1. Only a catalytic amount of potassium *tert*-butoxide is required for the cyclization, and the conjugate addition–cyclization of **5** to (*S,E*)-**4** and (*R,E*)-**4** proceeded successfully to give (*R*)-**6** (95% ee) and (*S*)-**6** (95% ee) in 75 and 73% yield respectively (Table 1, entries 1 and 2).[13c] When 1 equiv. of potassium *tert*-butoxide was used, the optical purity of (*R*)-**6** was 95% ee, but the yield decreased to 63% (entry 3). The conjugate addition–cyclization of **5** to (*S,E*)-**4** was also attempted in methanol. The cyclization proceeded in methanol even in the absence of *tert*-butoxide. However, the optical purity and yield of (*R*)-**6** decreased to 48% ee and 19%, respectively (entry 6). In the absence of potassium *tert*-butoxide in THF, only the conjugate addition of **5** to (*S*)-**4** proceeded, and no cyclization product was obtained (entry 8).

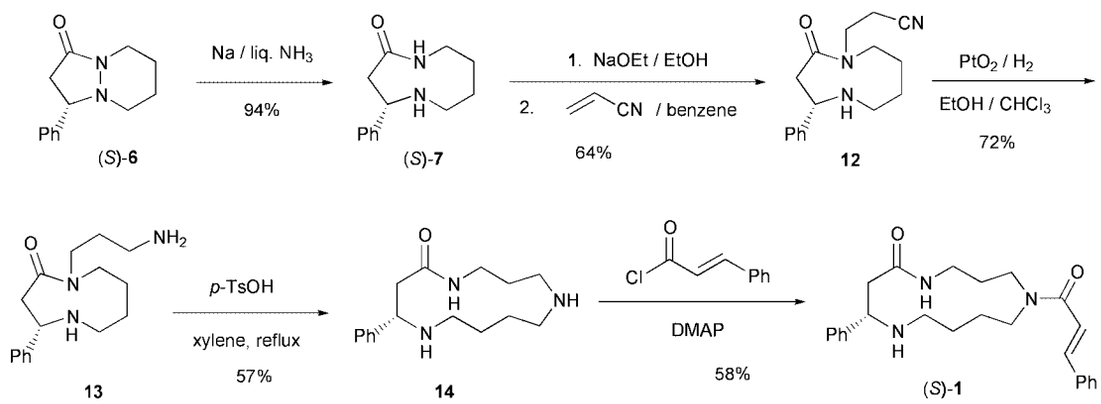
Reaction mechanism

The X-ray structure of the vinyl sulfoxide (*R,E*)-**4** was reported previously.[8] On the basis of the stereochemistry of the bicyclic lactam (*S*)-**6** obtained from the reaction of (*R,E*)-**4** with **5**, the mechanism of asymmetric conjugate addition of **5** can be explained as follows. As shown in Fig. 2, the oxygen atom of the sulfinyl group is located near the plane of the carbon–carbon double bond and the phenyl group. The *p*-tolyl group on the sulfur atom is directed below the plane and the bulky *tert*-butoxy group of the ester is also placed below the plane. Therefore, the front side of the plane is sterically less crowded as

Table 1 Conjugate addition–cyclization of piperidazine **5** to vinyl sulfoxides **4**[a]

Entry	Sulfoxide	Solvent	*t*-BuOK (molar amount)	Product	Yield(%)[b]	$[\alpha]_D$[c]	ee (%)[d]
1	(*S*)-**4**	THF	0.1	(*R*)-**6**	75	+153	95
2	(*R*)-**4**	THF	0.1	(*S*)-**6**	73	−155	95
3	(*S*)-**4**	THF	1.0	(*R*)-**6**	63	+150	95
4	(*S*)-**4**	THF	0.2	(*R*)-**6**	75	+149	95
5	(*R*)-**4**	THF	0.2	(*S*)-**6**	73	−145	89
6	(*S*)-**4**	MeOH	0	(*R*)-**6**	19[e]	+81	48
7	(*S*)-**4**	THF	0[f]	(*R*)-**6**	48	+145	95
8	(*S*)-**4**	THF	0	(*R*)-**6**	0[g]		

[a] The optical purity of vinyl sulfoxides **4** was determined by HPLC analysis using a chiral column (Chiralpak AS; hexane–ethanol 9 : 1). (*S*)-**4**: $[\alpha]_D$ +241 (*c* 0.90, $CHCl_3$), 98% ee; (*R*)-**6**: $[\alpha]_D$ −243 (*c* 1.00, $CHCl_3$), 99% ee. [b] Isolated yield. [c] Measured in $CHCl_3$ at 25 °C. [d] Determined by HPLC analysis using a chiral column (Chiralpak AS; hexane–ethanol 7 : 3). [e] In addition, the acyclic adduct **11** was obtained in 35% yield. [f] Reaction of **4** with **5** was carried out for 6 h in the absence of potassium *tert*-butoxide, and then potassium *tert*-butoxide was added. [g] The conjugate addition of **5** to **4** took place to give acyclic adducts in 72% yield



Scheme 5

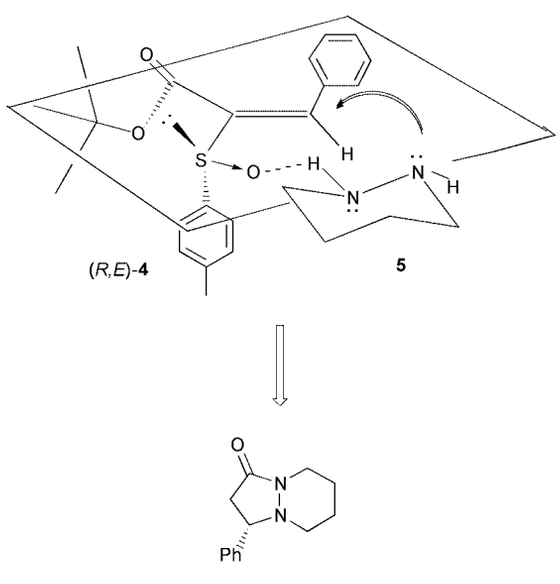


Fig. 2 Molecular structure of vinyl sulfoxide (*R*,*E*)-**4** and plausible mechanism of the addition of **5** to (*R*,*E*)-**4**.

shown in Fig. 2 and thus piperidazine **7** can attack the β-carbon atom of the double bond of (*R*,*E*)-**4** from the front side of the plane (*Re*-face). Thus, the conjugate addition–cyclization of (*R*,*E*)-**4** with **5**, followed by reduction of the *p*-tolylsulfinyl group of the resulting bicyclic compound with samarium(II) iodide, formed the bicyclic lactam (*S*)-**6**, while the reaction of (*S*,*E*)-**4** with **5** formed (*R*)-**6**. The diastereoselectivity in the conjugate addition of piperidazine **5** to the vinyl sulfoxide **4** may be controlled by not only the steric effect of the *p*-tolyl group but also hydrogen bonding between a oxygen atom of sulfoxide **4** and a hydrogen atom of piperidazine **5**.

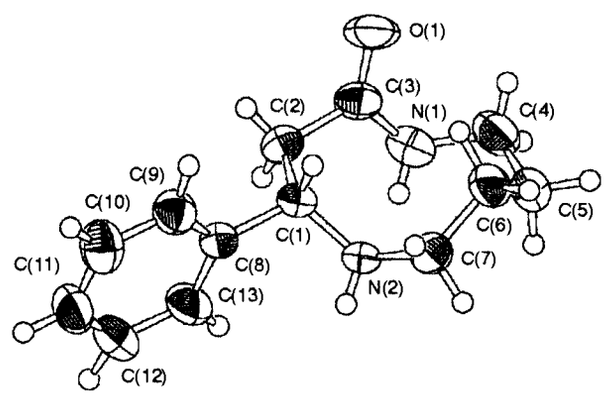


Fig. 3 ORTEP representation (50% probability ellipsoids of the X-ray molecular structure of (*S*)-**7**. Selected bond lengths (Å), bond angles (°), torsion angles (°), and intramolecular distances (Å): O(1)–C(3) 1.226(4), N(1)–C(3) 1.339(4), N(1)–C(4) 1.447(5), N(2)–C(1) 1.465(4), N(2)–C(7) 1.458(5), C(3)–N(1)–C(4) 121.8(3), O(1)–C(3)–C(2) 113.7(3), O(1)–C(3)–N(1)–C(4) 26.4(5), C(2)–C(3)–N(1)–C–(4) 149.6(3), N(1)···N(2) 2.82, N(1)···C(6) 2.91, and N(2)···C(3) 2.92.

Synthesis and structure of 9-membered azalactam 7

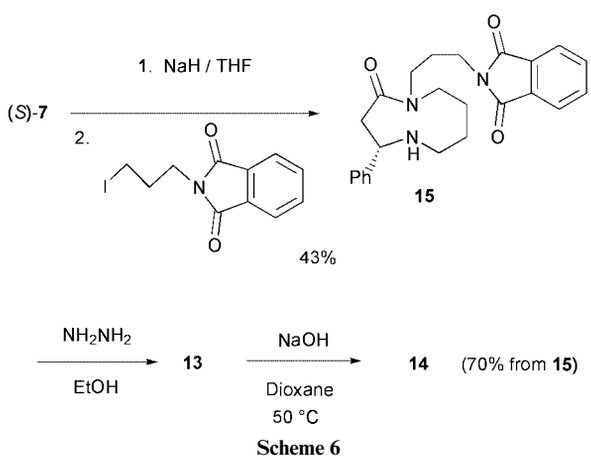
The 9-membered azalactam **7** was the key intermediate for the synthesis of racemic celacinnine **1**.[14c] We obtained the enantiomerically pure (*S*)- and (*R*)-**6** by recrystallization of the optically active product **6** (95% ee) from hexane. Reductive cleavage of the N–N bond of (*S*)-**6** (99% ee) with sodium (3.0 equiv.) in liquid ammonia for 1 h afforded the 9-membered azalactam (*S*)-**7** (99% ee) in 94% yield, and the stereochemistry of the asymmetric carbon atom of (*S*)-**6** could be retained during the reduction process. Similarly, (*R*)-**7** (97% ee) was obtained in 87% yield by the reductive cleavage of the N–N bond of (*R*)-**6** (97% ee) (Scheme 5). By crystallization from chloroform–hexane, the azalactam (*S*)-**7** formed single crystals suitable for X-ray structure analysis, and Fig. 3 shows the

molecular structure. The structure is similar to that of the racemic mixture of compound **7**.[13d] The compound has a twisted structure, and the amide linkage adopts a *trans* conformation as has been reported for azacyclononan-2-one.[17] The N(1)–C(3) bond [1.339(4) Å] is shorter than the N(1)–C(4) bond [1.447(5) Å], reflecting a partial double-bond character. Since the intramolecular N(1)···N(2) distance (2.82 Å) is 9% shorter than the sum of the van der Waals radii (3.10 Å), a weak, intramolecular hydrogen bond [N(1)–H···N(2)] is formed across the ring. The fairly distorted amide bond [the torsion angle C(2)–C(3)–N(1)–C(4) = 149.6(3)°] is favorable for the formation of the N(1)–H···N(2) hydrogen bond, because the N(1)–H bond is forced to face the inside of the ring.

The conformations of lactams of various ring sizes were studied spectroscopically by Roberts[18] and by Wilson,[19] and it was found that the lactams with eight or fewer members adopt the *cis*-conformation, while the 9-membered lactam exists as a mixture of the *cis*- and *trans*-conformations in solution. Thus, the ^{1}H NMR spectrum of (*S*)-**7** in $C_2D_2Cl_4$ at 25 °C displayed the signals revealing that two conformational isomers exist in the ratio of *ca.* 1 : 0.1 in solution. We considered that the major conformer should be the *trans* isomer, while the minor one would be the *cis* isomer. In this spectrum the signal of the *trans* amide proton is observed at lower field (δ 7.00) than that of the *cis* amide proton (δ 5.40), reflecting the existence of the weak intramolecular hydrogen bond. These signals gradually broadened with increasing temperature and coalesced at 100 °C, and showed a simple pattern at 150 °C, suggesting the occurrence of the rapid conformational change between the *trans* and *cis* isomers.

Synthesis of optically active celacinnine 1

We have synthesized naturally occurring (*S*)-celacinnine **1** starting from the optically active (*S*)-**7** as shown in Scheme 5. Selective alkylation of the amide NH group was achieved in good yield by treatment of (*S*)-**7** with sodium ethoxide in ethanol, followed by reaction with acrylonitrile to give the nitrile derivative (*S*)-**12** in 64% yield.[14a] Hydrogenation of (*S*)-**12** over PtO_2 gave the amine (*S*)-**13** in 72% yield. Intramolecular ring enlargement of the 9-membered azalactam (*S*)-**13** to 13-membered diazalactam (*S*)-**14** could be accomplished in 57% yield under acidic conditions (*p*-TsOH, industrial mixture of xylene).[14a] We also carried out another approach to (*S*)-**14** by employing alkylation of the sodium salt of (*S*)-**7** with *N*-(3-iodopropyl)phthalimide in THF as shown in Scheme 6.



Scheme 6

Treatment of (*S*)-**7** (99% ee) with 5 equiv. of sodium hydride in THF at 50 °C, followed by addition of 3 equiv. of *N*-(3-iodopropyl)phthalimide produced the phthalimide derivative (*S*)-**15** in 43% yield. Removal of the phthalimide group of (*S*)-**15** with 10 equiv. of hydrazine in ethanol afforded the amine (*S*)-**13** which was converted directly to the 13-membered diazalactam (*S*)-**14** in 70% overall yield from (*S*)-**15** *via* intramolecular transamidation in the dilute sodium hydroxide solution (1 M NaOH, 1,4-dioxane).[13b] The optically active (*S*)-celacinnine **1** was obtained in 58% yield by the regioselective acylation, with *trans*-cinnamoyl chloride, of the 13-membered diazalactam (*S*)-**14** according to the reported method.[14d] The (*S*)-celacinnine (**1**) thus obtained exhibited identical spectral data as those of natural (−)-celacinnine.[11,14a]

In summary, the conjugate addition–cyclization of piperidazine (**5**) to optically active vinyl sulfoxides **4** proceeded smoothly in THF at room temperature in the presence of potassium *tert*-butoxide as base. The diastereoselectivity of the conjugate addition was high (95% ee) and optically active bicyclic lactam **6** was obtained. Optically active 4-phenyl-1,5-diazabicyclononan-2-one (**7**), which is a key intermediate in the synthesis of celacinnine **1**, could be synthesized by the reductive cleavage of the N–N bond of optically active bicyclic lactam **6**. The synthesis of optically active (*S*)-celacinnine **1** was achieved starting from the optically active (*S*)-**7**.

Experimental

All melting points are uncorrected. NMR spectra were recorded in a $CDCl_3$ or 1,1,2,2-tetrachloroethane-d_2 solution at 500 or 400 MHz (^{1}H), and 125 or 100 MHz (^{13}C). Chemical shifts are given in ppm relaive to TMS. Specific optical rotations $[\alpha]_D$ are given in deg cm^2 g^{-1} at 25 °C, and concentrations (*c*) are expressed in g per 100 mL. IR absorption spectra were recorded for KBr discs or liquid films, and only noteworthy absorptions (cm^{-1}) are given. The mass spectra and high-resolution mass spectra were taken at an ionizing voltage of 70 eV. The enantiomeric excess of optically active compounds was measured by HPLC using a chiral column (Daicel Chemical, Chiralpak AD and Chiralpak AS, 0.46 cm × 25 cm). Gel-permeation liquid chromatography (GPLC) was performed with liquid chromatography using Jaigel-1H columns (20 mm × 600 mm × 2) and chloroform as eluent. TLC was performed with Merck Kieselgel (Merck Art. 5554). Column chromatography was performed with silica gel [Wakogel C-200, Daisogel IR-60 (60/210 mesh), and Kanto silica gel (100/200 mesh)]. All solvents were dried and purified by the usual procedures: diethyl ether and THF were distilled from sodium diphenylketyl; methanol and ethanol were distilled over dimethoxy- and diethoxymagnesium, respectively; dichloromethane, acetonitrile, and *N,N*-dimethylformamide (DMF) were distilled over calcium hydride. The optically active vinyl sulfoxides, *tert*-butyl (*E*)-2-[(*S*)- and (*R*)-*p*-tolylsulfinyl]-cinnamate (**4**), were prepared from *tert*-butyl (*S*)- and (*R*)-tolylsulfinylacetate (**8**) *via* **9**.[9]

Preparation of compound 6 using potassium *tert*-butoxide. Typical procedure for Table 1

Piperidazine **7** (127 mg, 1.48 mmol) was added to a solution of a sulfoxide **4** (100 mg, 0.29 mmol) and potassium *tert*-butoxide (3.3 mg, 0.029 mmol) in dry THF (5 mL). The mixture was stirred for 6 h at room temperature under nitrogen. Then, the solution was cooled under ice–water, and samarium(II) iodide in THF (0.1 M, 17.4 mL, 1.74 mmol) and methanol (0.5 mL) were added. After stirring had been continued for 30 min, saturated aq. sodium carbonate (10 mL) was added, and the product was extracted with dichloromethane (100 mL × 3). After the organic layer was concentrated, (*S*)-(−)-**6** {46 mg, 0.21 mmol, $[\alpha]_D$ −155 (*c* 0.460, $CHCl_3$, 95% ee)} was obtained in 73% yield by column chromatography on silica gel (ethyl acetate as eluent) (Table 1, entry 2).

Compound (***S***)-(−)-**6** showed mp 98.8–101.0 °C; ν_{max} ($CHCl_3$) 1677 (C=O); δ_H ($CDCl_3$) 7.27–7.41 (5 H, m, phenyl), 4.17 (1 H, d, *J* 11.2, 5-CH), 3.85 (1 H, dd, *J* 11.2, 8.3, 9-CH), 3.06 (1 H, d, *J* 10.0, 2-CH), 2.98 (1 H, dd, *J* 12.4, 11.6, 5-CH),

2.88 (1 H, dd, *J* 16.4, 8.8, 8-CH), 2.52 (1 H, dd, *J* 16.4, 11.4, 8-CH), 2.26 (1 H, td, *J* 11.2, 2.4, 2-CH), 1.70–1.79 (2 H, m, 3-CH_2), 1.59–1.67 (1 H, m, 4-CH), 1.37–1.48 (1 H, m, 4-CH); δ_C ($CDCl_3$) 168.5 (C=O), 139.0 (phenyl C), 128.7 and 127.5 (*o*- and *m*-phenyl C), 128.1 (*p*-phenyl C), 67.4 (9-C), 55.4 (2-C), 42.0 (5-C), 39.9 (8-C), 23.9 (3-C), 22.7 (4-C); *m*/*z* 216 (100%, M^+), 173 (7), 138 (13), 130 (8), 104 (20), 85 (28), 56 (20) (Calc. for $C_{13}H_{16}N_2O$: *M*, 216.1263 Found: M^+, 216.1273); $[a]_D$ −167 (*c* 1.30, $CHCl_3$, 99% ee, after recrystallization from hexane); optically active column [Daicel Chiralpak AD, retention time, t_R 18.1 min: 99.5% (*S*-form), t_R = 20.4 min: 0.5% (*R*-form), hexane–propan-2-ol 19 : 1; flow rate 1 mL min^{-1}; detection, UV 254 nm].

(*R*)-(+)-**6**: R_f (hexane–ethyl acetate 2 : 1) 0.10; mp 95.5–96.5 °C; ν_{max} (KBr) 1665 (CO); δ_H ($CDCl_3$) 7.28–7.41 (5 H, m, phenyl), 4.17 (1 H, d, *J* 11.2, 5-CH), 3.85 (1 H, dd, *J* 11.2, 8.3, 9-CH), 3.06 (1 H, d, *J* 11.5, 2-CH), 2.98 (1 H, dd, *J* 12.7, 11.2, 5-CH), 2.88 (1 H, dd, *J* 16.6, 8.3, 8-CH), 2.52 (1 H, dd, *J* 16.6, 11.2, 8-CH), 2.26 (1 H, td, *J* 11.5, 2.0, 2-CH), 1.40–1.77 (4 H, m, 3- and 4-CH_2); δ_C ($CDCl_3$) 168.5 (C=O), 139.1 (phenyl C), 128.7 and 127.5 (*o*- and *m*-phenyl C), 128.1 (*p*-phenyl C), 67.5 (9-C), 55.4 (2-C), 42.1 (5-C), 39.9 (8-C), 23.9 (3-C), 22.8 (4-C); *m*/*z* 216 (79%, M^+), 173 (12), 162 (41), 131 (100), 103 (81), 91 (13), 85 (54), 77 (49), 55 (56) (Calc. for $C_{13}H_{16}N_2O$: *M*, 216.1263. Found: M^+, 216.1283); $[a]_D$ +163 (*c* 1.60, $CHCl_3$, 97% ee, after recrystallization from hexane); optically active column [Daicel Chiralpak AD, retention time, t_R = 18.9 min: 1.7% (*S*-form), t_R = 21.1 min: 98.3% (*R*-form), hexane–propan-2-ol 19 : 1; flow rate 1 mL min^{-1}; detection, UV 254 nm].

(*S*)- and (*R*)-4-Phenyl-1,5-diazacyclononan-2-one 7

In a 200-mL three-necked flask equipped with a Dewar condenser cooled with solid CO_2 was placed *ca.* 50 mL of liquid ammonia at −78 °C under nitrogen. A solution of (*S*)-(−)-**6** {164 mg, 0.76 mmol, $[a]_D$ −167 (*c* 1.50, $CHCl_3$), 99% ee} in dry THF (5 mL) was added to the flask, and then sodium metal (3 equiv.) was added until the color of the solution turned to dark blue. After stirring of the mixture for 1 h, solid ammonium chloride was added until the blue color of the solution disappeared. Then the Dewar condenser and cooling bath were removed, and liquid ammonia was distilled off. The residue was dissolved in a mixture of dichloromethane (50 mL) and water (50 mL), and the product was extracted with dichloromethane (100 mL × 4). After the solution had been concentrated, (*S*)-**7** (156 mg, 0.72 mmol) was obtained in 94% yield by column chromatography on silica gel (eluent hexane–ethyl acetate 1 : 1). Similarly, (*R*)-**7** (198 mg, 0.91 mmol) was prepared in 87% yield by the reduction of the N–N bond of (*R*)-**6** {226 mg, 1.05 mmol, $[a]_D$ +163 (*c* 1.20, $CHCl_3$), 97% ee}. The ^1H NMR spectrum of (*S*)-**7** at room temperature indicated the product to be a mixture of major and minor isomers in the ratio 1 : 0.1. The major and minor isomers were assigned to the *trans*- and *cis*-conformer, respectively. These signals gradually broadened with increasing temperature and coalesced at 100 °C. The simplified ^1H NMR chemical shifts at 125 °C and those of the major isomer at room temperature are given here.

Compound (***S***)-(−)-**7** showed mp 90.1–91.0 °C; δ_H (tetrachloroethane-d_2; 125 °C) 7.31 (2H, m, phenyl), 7.29 (3 H, m, phenyl), 3.63 (2 H, m, 4- and 9-CH), 2.79–2.85 (3H, m, 6-CH_2 and 9-CH), 2.47 (1 H, m, 3-CH), 2.35 (1 H, d, *J* 11, 3-CH), 1.84 (1 H, m, 7-CH), 1.53 (5 H, m, NH, 7- and 8-CH_2); δ_H ($CDCl_3$; 24.5 °C) (signals of the major isomer) 7.24–7.37 (5 H, m, phenyl), 6.98 (1 H, d, *J* 9.2, amide NH), 3.70–3.78 (1 H, m, 9-CH), 3.57 (1 H, dd, *J* 12.0, 2.8, 4-CH), 2.83–2.90 (2H, m, 6- and 9-CH), 2.75 (1 H, td, *J* 12.0, 2.8, 6-CH), 2.51 (1 H, t, *J* 12.0, 3-CH), 2.36 (1 H, dd, *J* 11.6, 2.8, 3-CH), 1.89–1.97 (1 H, m, 7-CH), 1.86 (1 H, br s, NH), 1.59–1.68 (1 H, m, 8-CH), 1.36–1.54 (2 H, m, 7- and 8-CH); δ_C ($CDCl_3$; 24.5 °C) (signals of the major isomer) 176.4 (C=O), 144.7 (phenyl C), 129.1 and 125.9 (*o*- and *m*-phenyl C), 127.6 (*p*-phenyl C), 61.5 (4-C), 51.5 (6-C), 46.3 (3-C), 40.4 (9-C), 29.3 (7-C), 25.8 (8-C); δ_C (signals of the minor isomer) 176.48 (C=O), 146.19, 128.89, 127.41, 125.58, 60.01, 48.99, 45.39, 42.32, 29.88, 22.51; *m*/*z* 218 (4%, M^+), 159 (8), 146 (5), 132 (37), 118 (8), 105 (100), 91 (6), 77 (75), 51 (32) (Calc. for $C_{13}H_{18}N_2O$: *M*, 218.1420. Found: M^+, 218.1401); $[a]_D$ −149 (*c* 1.20, $CHCl_3$, 99% ee); optically active column [Daicel Chiralpak AD, t_R = 29.2 min: 99.5% (*S*-form), t_R = 33.2 min: 0.5% (*R*-form), hexane–propan-2-ol 95 : 5 containing 0.1% diethylamine, flow rate 1 mL min^{-1}, detection UV 254 nm].

Isomer (***R***)-(+)-**7**: showed R_f (ethyl acetate) 0.42; mp 70–71 °C; ν_{max} (KBr) 1560, 1640 (CO), 3310 (NH); δ_H ($CDCl_3$) (signals of the major isomer) 7.24–7.36 (5 H, m, phenyl), 7.00 (1 H, d, *J* 10.3, amide NH), 3.74 (1 H, d, *J* 10.3, 9-CH), 3.57 (1 H, dd, *J* 11.7, 3.7, 4-CH), 2.80–2.95 (2 H, m, 6- and 9-CH), 2.74 (1 H, td, *J* 11.9, 2.4, 6-CH), 2.49 (1 H, dd, *J* 11.7, 11.7, 3-CH), 2.35 (1 H, dd, *J* 11.7, 3.7, 3-CH), 1.87–2.00 (2 H, m, 7-CH and NH), 1.56–1.80 (1 H, m, 8-CH), 1.34–1.56 (2 H, m, 7- and 8-CH); δ_C ($CDCl_3$) (signals of the major isomer) 176.3 (C=O), 144.6 (phenyl C), 129.0 and 125.8 (*o*- and *m*-phenyl C), 127.5 (*p*-phenyl C), 61.5 (4-C), 51.4 (6-C), 46.3 (3-C), 40.3 (9-C), 29.2 (7-C), 25.7 (8-C); *m*/*z* 218 (22%, M^+), 190 (6), 159 (39), 146 (61), 132 (51), 118 (81), 112 (26), 104 (100), 91 (80); $[a]_D$ +142 (*c* 1.20, $CHCl_3$, 97% ee) (Calc. for $C_{13}H_{18}N_2O$: *M*, 218.1420. Found: M^+, 218.1401); optically active column [Daicel chiralpak AD, t_R = 30.0 min: 1.7% (*S*-form), t_R = 31.4 min: 98.3% (*R*-form), hexane–propan-2-ol 95 : 5 containing 0.1% diethylamine, flow rate 1 mL min^{-1}, detection UV 254 nm].

(*S*)-4-Phenyl-1-(2′-cyanoethyl)-1,5-diazacyclononan-2-one 12

To a solution of (*S*)-**7** {127 mg, 0.58 mmol, $[a]_D$ −149 (*c* 1.20, $CHCl_3$, 99% ee} in dry ethanol (1 mL) was added sodium ethoxide (44 mg, 0.65 mmol) and the mixture was irradiated with ultrasonic apparatus (Yamato 2200) in a water-bath until dissolution (for *ca.* 10 min) was observed. The solution was evaporated to dryness under vacuum. The remaining salt was dissolved in dry benzene (2 mL), and then acrylonitrile (2.3 mL, 35.0 mmol) was added to the solution under argon at 20 °C in an ice-bath. The addition of acrylonitrile was stopped when all the starting material had been consumed (by TLC) and the mixture was stirred for 12 h at room temperature before being poured into water and extracted with dichloromethane (100 mL × 3). After chromatographic separation on silica gel, nitrile (*S*)-**12** (104 mg, 0.38 mmol) was obtained in 64% yield. The ^1H NMR spectrum revealed that product (*S*)-**12** consisted of only one isomer. (*S*)-(−)-**12**: R_f ($CHCl_3$–MeOH 95 : 5) 0.50; ν_{max} (liquid film) 3300–3600 (NH), 2248 (CN), 1628 (CO); δ_H ($CDCl_3$) 7.23–7.35 (5 H, m, phenyl), 4.92 (1 H, td, *J* 13.6, 3.9, 9-CH), 3.97 (1 H, m, 1′-CH), 3.75 (1 H, d, *J* 10.0, 4-CH), 3.39 (1 H, dd, *J* 13.2, 4.8, 9-CH), 3.19 (1 H, dd, *J* 12.2, 10.0, 3-CH), 3.13 (1 H, ddd, *J* 13.2, 8.4, 6.0, 1′-CH), 2.96 (1 H, dt, *J* 12.4, 3.2, 6-CH), 2.85 (1 H, ddd, *J* 16.8, 8.4, 6.8, 2′-CH), 2.78 (1 H, td, *J* 12.4, 4.8, 6-CH), 2.57–2.64 (2 H, m, 3- and 2′-CH), 1.85–1.94 (1 H, m, 8-CH), 1.85 (1H, br s, NH), 1.55–1.64 (1 H, m, 8-CH), 1.29–1.47 (2 H, m, 7-CH_2); δ_C ($CDCl_3$) 174.5 (C=O), 146.3 (phenyl C), 129.0 and 125.5 (*o*- and *m*-phenyl C), 127.3 (*p*-phenyl C), 118.6 (CN), 61.1 (4-C), 49.5 (6-C), 49.0 (9-C), 46.5 (1′-C), 41.3 (3-C), 26.4 (8-C), 21.8 (7-C), 16.1 (2′-C); *m*/*z* 271 (49%, M^+), 228 (32), 159 (100), 146 (94), 132 (65), 123 (41), 119 (92), 104 (62), 91 (38) (Calc. for $C_{16}H_{21}N_3O$: *M*, 271.1686. Found: M^+, 271.1678); $[a]_D$ −85.4 (*c* 1.00, $CHCl_3$).

(*S*)-(−)-4-Phenyl-1-(3′-aminopropyl)-1,5-diazacyclononan-2-one 13

To a solution of nitrile (*S*)-**12** (121 mg, 0.45 mmol) in dry ethanol (10 mL) containing chloroform (0.2 mL) was added platinum(IV) oxide (30 mg). Then, gaseous H_2 was introduced with a balloon into the reaction flask, and the reaction mixture was stirred for 14 h. The insoluble material was filtered off, and

the filtrate was concentrated. The product was purified by preparative TLC (PLC) ($CHCl_3$–MeOH–2-aminopropane 5 : 5 : 1, R_f = 0.10). Compound (*S*)-**13** (88 mg, 0.32 mmol) was obtained in 72% yield. On the basis of the ^1H NMR spectrum, product (*S*)-**13** consisted of only one isomer. (*S*)-(−)-**13**: ν_{max} 3363 (N-H), 1618 (C=O); δ_H ($CDCl_3$) 7.20–7.35 (5 H, m, phenyl), 4.73 (1 H, t, *J* 12.0, 9-CH), 3.93 (1 H, dt, *J* 13.6, 7.2, 1′-CH), 3.78 (1 H, d, *J* 10.4, 4-CH), 3.26 (1 H, dd, *J* 14.0, 3.6, 9-CH), 3.16 (1 H, t, *J* 11.2, 3-CH), 2.85–3.00 (2 H, m, 6- and 1′-CH), 2.67–2.85 (3 H, m, 6-CH, 3′-CH_2), 2.59 (1 H, d, *J* 12.4, 3-CH), 1.87–2.02 (1 H, m, 2′-CH), 1.62–1.85 (1 H, m, 7-CH), 1.51–1.62 (1 H, m, 2′-CH), 1.36–1.51 (4 H, m, 7- and 8-CH and NH_2), 1.10–1.36 (1 H, m, 8-CH), 0.879 (1 H, br s, NH); δ_C ($CDCl_3$) 174.1 (C=O), 146.5 (phenyl C), 128.9 and 125.6 (*o*- and *m*-phenyl C), 127.2 (*p*-phenyl C), 61.1 (4-C), 49.4 (9-C), 47.3 (6-C), 46.3 (3-C), 41.0 (1′-C), 39.1 (3′-C), 29.7 (7-C), 26.2 (2′-C), 22.0 (8-C); *m*/*z* 275 (14%, M^+), 258 (100), 232 (7), 205 (9), 160 (18), 146 (28), 131 (25), 126 (21), 98 (24), 84 (36), 70 (49) (Calc. for $C_{16}H_{25}N_3O$: *M*, 275.2000. Found: M^+ 275.2019); $[\alpha]_D$ −32.5 (*c* 0.88, $CHCl_3$).

2-Phenyl-1,5,9-triazacyclotridecan-4-one 14

To a solution of (*S*)-**13** (100 mg, 0.36 mmol) in dry xylene (5 mL) was added *p*-TsOH·H_2O (55 mg, 0.29 mmol) and the solution was refluxed for 3 h. Upon cooling, aq. NaOH was added to the mixture until it turned basic, and the mixture was extracted with dichloromethane. The extracts were dried (sodium sulfate), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–25% aq. NH_3 7 : 3 : 1, R_f 0.50) to afford compound (*S*)-**14** (57 mg, 57%) as a colorless, amorphous solid. The ^1H and ^{13}C NMR spectra of product (*S*)-**14** showed that the 13-membered ring preferred only one conformation. (*S*)-(−)-**14**: R_f ($CHCl_3$–MeOH–25% aq. NH_3 7 : 3 : 1) 0.50; ν_{max} (liquid film) 3120–3600 (NH), 1650 (CO); δ_H ($CDCl_3$) 8.66 (1 H, br s, amide NH), 7.20–7.40 (5 H, m, phenyl), 4.14 (1 H, d, *J* 11.7, 2-CH), 3.84 (1 H, m, 6-CH), 3.27 (2H, m, 6- and 10-CH), 3.11 (1H, m, 8-CH), 3.02 (1H, m, 10-CH), 2.87–2.96 (2H, m, 13- and 3- or 13-CH), 2.61 (1H, dd, *J* 11.6, 9.5, 8-CH), 2.52 (1H, dd *J* 13.1, 3.7, 3-CH), 2.32 (1H, dd, *J* 12.2, 6.7, 13- or 3-CH), 2.20 (1H, m), 2.13, 1.86, 1.65 and 1.60 (2H, 1H, 1H, and 1H, each m, 7; 11- and 12-CH), the signals of two NH protons were not observed; δ_C ($CDCl_3$) 172.5 (C=O), 141.5 (phenyl C), 128.9 and 126.8 (*o*- and *m*-phenyl C), 127.7 (*p*-phenyl C), 59.9 (2-C), 49.5 (13-C), 49.2 (10-C), 45.2 (8-C), 45.0 (3-C), 38.8 (6-C), 26.8 (7-C), 26.7 (11- or 12-C), 26.0 (12- or 11-C); *m*/*z* 275 (21%, M^+), 258 (100) (Calc. for $C_{16}H_{25}N_3O$: *M*, 275.1999. Found: M^+, 275.1997); $[\alpha]_D$ −39.1 (*c* 0.17, $CHCl_3$).

(*S*)-4-Phenyl-1-(3′-phthalimidopropyl)-1,5-diazacyclononan-2-one 15

In a 10-mL round-bottomed flask were placed (*S*)-**7** (70 mg, 0.32 mmol, 99% ee) and THF (2 mL), and then sodium hydride (60 mg, 1.5 mmol, 60% in oil), previously washed with dry hexane, was added. After the solution had been refluxed for 30 min, *N*-(3-iodopropyl)phthalimide (300 mg, 0.95 mmol) was added and the solution was refluxed for 2 days. After cooling of the solution, saturated aq. ammonium chloride (10 mL) was added, and the product was extracted with a mixture of diethyl ether (50 mL) and dichloromethane (50 mL). The organic layer was dried (sodium sulfate) and concentrated. The product (*S*)-**15** (56 mg, 0.14 mmol, 43%) was purified by column chromatography on silica gel (hexane–ethyl acetate 1 : 1), and (*S*)-**7** (9 mg, 0.04 mmol) was recovered. Product (***S***)-(−)-**15** showed ν_{max} (liquid film) 3100–3700 (NH), 1700, 1615 (CO); δ_H ($CDCl_3$) 7.84 (2H, dd, *J* 5.4, 2.9, phthalimide), 7.71 (2H, dd, *J* 5.4, 2.9, phthalimide), 7.21–7.38 (5H, m, phenyl), 4.78 (1H, td, *J* 11.7, 3.9, 6-CH), 3.94 (1H, dt, *J* 13.5, 7.3, 9-CH), 3.81 (1H, d, *J* 10.3, 4-CH), 3.73 (2H, td, *J* 7.3, 2.9, 1′-CH_2), 3.31 (1H, dd, *J* 14.4, 3.7, 6-CH), 3.22 (1H, dd, *J* 12.7, 10.5, 3-CH), 2.86–2.98 (2H, m, 3′-CH_2), 2.75–2.82 (1H, m), 2.60 (1 H, d, *J* 12.7), 1.88–2.01 (4H, m), 1.49–1.52 (1H, m), 1.42 (2H, m); δ_C ($CDCl_3$) 173.8, 168.4 (C=O), 145.9 (phenyl C), 133.9 and 123.2 (phthalimide), 132.1 (substituted phthalimide), 129.0 and 125.8 (*o*- and *m*-phenyl C), 127.4 (*p*-phenyl C), 61.3 (4-C), 49.4 (3′-C), 47.2 (6-C), 46.0 (3-C), 41.7 (9-C), 36.0 (1′-C), 26.3 (7-C), 26.1 (8-C), 21.7 (2′-C); *m*/*z* 405 (29%, M^+), 377 (13), 362 (7), 301 (7), 287 (14), 259 (18), 245 (30), 217 (16), 188 (39), 159 (100), 146 (42) (Calc. for $C_{24}H_{27}N_3O_3$: *M*, 405.2052. Found: M^+, 405.2057); $[\alpha]_D$ −58 (*c* 0.9, $CHCl_3$).

Alternative preparation of (*S*)-14

The phthalimide (*S*)-**15** (56 mg, 0.14 mmol, 99% ee) was added to a solution of hydrazine monohydrate (75 mg, 1.5 mmol) in ethanol (2 mL), and the solution was refluxed for 12 h. A white solid precipitated during the reflux. After the reaction mixture had cooled to room temperature, 25% ammonium hydroxide (1 mL) was added to the solution, which was then stirred for 30 min at room temperature. After removal of the solvent, the product was extracted with dichloromethane (10 mL × 3). The organic layer was dried and concentrated under reduced pressure. The residual oil was dissolved in a mixture of 1,4-dioxane (5 mL) and 1 M aq. sodium hydroxide (5 mL), and the mixture was stirred at 50 °C for 18 h. The solvent was removed and the product was extracted with dichloromethane (10 mL × 3). Macrocycle (*S*)-**14** (27 mg, 0.10 mmol) was obtained in 70% yield by PLC on silica gel (developer $CHCl_3$–MeOH–25% NH_3 7 : 3 : 1, R_f 0.50). The product (*S*)-**14** thus obtained exhibited identical spectral data with those of (*S*)-**14** described above.

(*S*)-Celacinnine 1

A solution of (*S*)-(−)-**14** (54 mg, 0.20 mmol) and 4-(dimethylamino)pyridine (DMAP) (76 mg, 0.62 mmol) in dry dichloromethane (5 mL) was cooled to −78 °C under nitrogen, and a solution of *E*-cinnamoyl chloride (56 mg, 0.28 mmol) in dichloromethane (4 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, then at −20 °C for 5 h. The reaction was quenched by the addition of 14% aq. ammonia (6 mL) and the product was extracted with dichloromethane (50 mL × 3). (*S*)-(−)-Celacinnine **1** (46 mg, 0.104 mmol, 58%) was obtained by purification using column chromatography on silica gel (eluent $CHCl_3$–MeOH 15 : 1), R_f ($CHCl_3$–MeOH 9 : 1) 0.32; δ_H ($CDCl_3$) 7.58 (1H, d, *J* 15.2, PhC*H*=CH), 7.20–7.46 (11H, m, phenyl H and amide NH), 6.82 (1H, d, *J* 15.2, PhCH=C*H*), 3.97 (1H, t, *J* 7.4, 2-CH), 3.11–3.76 (6H, m, 6-, 8- and 10-CH_2), 2.68 (1 H, *J* 12.0, 3-CH), 2.32–2.54 (3 H, m, 3-CH and 13-CH_2), 1.24–2.17 (7 H, m, 10-, 11- and 12-CH_2 and NH); *m*/*z* 405 (51%, M^+), 274 (100), 260 (19), 160 (25), 159 (13), 146 (34), 131 (99), 103 (63) (Calc. for $C_{25}H_{31}N_3O_2$: *M*, 405.2416. Found: M^+, 405.2399); $[\alpha]_D$ −19.0 (*c* 0.43, $CHCl_3$) {lit.,[11] $[\alpha]_D$ −20.0 (*c* 0.13, $CHCl_3$); lit.,[14a] $[\alpha]_D$ −20.7 (*c* 0.61, $CHCl_3$)}.

Crystallographic structural determination of (*S*)-7†

Single crystals of (*S*)-**7** were obtained by slow recrystallization of a solution in chloroform–hexane; a colorless prism of crystal size 0.66 × 0.44 × 0.40 mm was used. X-Ray data collection was carried out on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å) and a rotating anode generator: $C_{13}H_{18}N_2O$, *M* = 218.30, monoclinic, space group $P2_1$ (No. 4), *a* = 6.794(5), *b* = 8.125(6), *c* = 11.675(4) Å, β = 103.60(4)°, *V* = 626.4(7) Å^3, *Z* = 2, D_{calc} = 1.157 g cm^{-3}, *R* = 0.045, R_W = 0.065 using 957 reflections with $I > 3.00\sigma(I)$. Structural parameters of non-hydrogen atoms were refined anisotropically according to the full-matrix least-squares

† CCDC reference number 170583. See http://www.rsc.org/suppdata/p1/b1/b107443c/ for crystallographic data in .cif or other electronic format.

technique, and all hydrogen atoms were located at calculated positions. The absolute configuration of this molecule is indeterminate from the crystallography experiment and has been assumed from the synthesis.

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