The Macrocyclic Spermidine Alkaloid (−)-(*S*)-Neoperiphylline: Revision of the Structure Based on the Total Synthesis

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The total synthesis of the two isomeric macrocyclic enamides **2** and **17** is described. The precursor **14** was synthesized by means of template-assisted macrocyclization (*Scheme 2*). Isomerization of **14** in the presence of $[Fe(CO)_5]$ gave **2** and **17** (*Scheme 4*). Structure **2** was previously assigned to the alkaloid neoperiphylline. However, the synthetic **2** showed completely different properties compared to the earlier described data of the natural compound. Surprisingly, analytical data of the second synthetic product **17** were very close to those of the natural neoperiphylline. We conclude that the previously assigned structure of neoperiphylline is erroneous and should be corrected to that of (−)-(4*S*,12*Z*)-4-phenyl-9-[(2*E*)-3-phenylprop-2-enoyl]-1,5,9-triazacyclotridec-12-en-2-one (**17**).

Introduction. – Macrocyclic lactams derived from polyamines have attracted the interest of organic chemists due to structural diversity and broad biological activity [1]. *Hocquemiller et al.* have isolated novel spermidine alkaloids from the leaves of the New Caledonian endemic plant *Peripterygia marginata* [2]. Proposed structures of periphylline (**1**) and neoperiphylline (**2**) are shown in the *Figure*. The enamide C=C bond in these alkaloids represents an unusual structural feature. To the best of our knowledge, other macrocyclic derivatives with an enamide moiety incorporated in the macrocycle are hitherto unknown. We are interested in the structure verification and biosynthesis of these alkaloids.

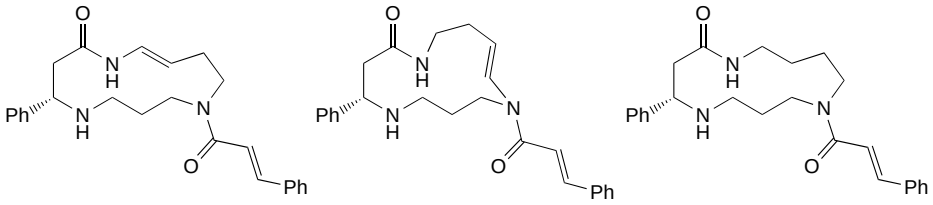


Figure. *Proposed structures of periphylline* (**1**) *and neoperiphylline* (**2**) *and structure of dihydroperiphylline* (**3**) [2].

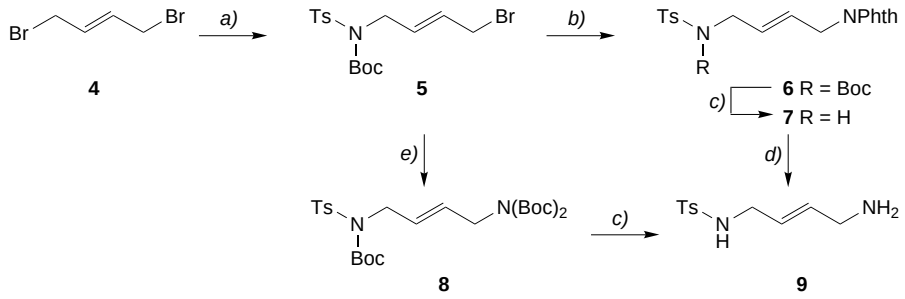
In this paper, we report the total synthesis of **2**. However, remarkable difference in the spectral properties of synthetic **2** and natural neoperiphylline [2] suggest that this structure was assigned to the natural alkaloid erroneously. We propose the alternative structure **17** for neoperiphylline (see discussion below).

[1]) Part of the Ph. D. Thesis of *S. A. S.*, University of Zürich, 2002.

Recently, we reported [3] a new method for the synthesis of the macrocyclic spermidine alkaloid dihydroperiphylline (**3**) isolated from the same plant as neoperiphylline. Dihydroperiphylline has the same C,N backbone as neoperiphylline but without an additional C=C bond in the macrocycle. The single stereogenic center in **3**, as well as in **1** and **2**, has (*S*)-configuration. For the synthetic construction of the macrocyclic moiety of neoperiphylline, we used the same strategy as in the synthesis of dihydroperiphylline.

Synthesis. – The synthesis of chiral *N*-tosylated (*S*)-*β*-phenyl-*β*-alanine **10**, based on a stereoselective *Michael* addition [4], was described previously [3]. Another necessary building block is the monotosylated (*E*)-but-2-ene-1,4-diamine **9**. (*E*)-But-2-ene-1,4-diamine itself is not commercially available although its preparation by the *Gabriel* or *Delepine* methods is described (see [5] and [6], resp.). To make the synthesis of **9** shorter and more efficient, we decided to introduce the already tosylated N-atom by nucleophilic substitution of the Br-atom in the commercially available (*E*)-1,4-dibromobut-2-ene (**4**). First, *N*-[(*tert*-butoxy)carbonyl]-4-methylbenzenesulfonamide (TsNHBoc) was alkylated with **4** to give the monobromo derivative **5** (*Scheme 1*). It should be noted that TsNHBoc could not be replaced by the extremely cheap $TsNH_2$ because of the formation of a complex mixture of polyalkylated products. Substitution of the remaining Br-atom in **5** by the phthalimido (Phth) moiety afforded fully protected diamine **6**. *N*-Boc and *N*-phthalimido groups can be successively removed by the action of CF_3COOH and hydrazine, respectively, affording the unsaturated building block **9** in good yield.

Scheme 1



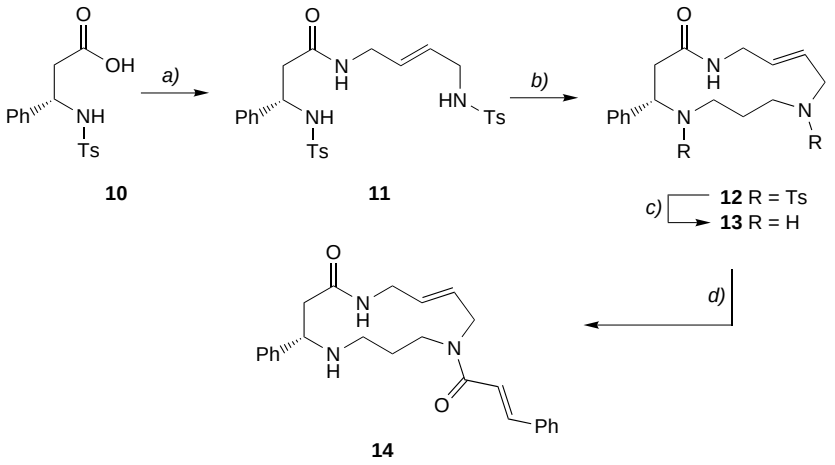
a) TsNHBoc, Cs_2CO_3, DMF, r.t.; 60%. *b*) K-phthalimide, DMF, 50°; 93%. *c*) CF_3COOH, CH_2Cl_2, r.t.; quant. *d*) $N_2H_4 \cdot H_2O$, EtOH, 50°; 82%. *e*) Boc_2NH, Cs_2CO_3, DMF, r.t.; 98%.

Alternatively, di(*tert*-butyl) imidodicarbonate Boc_2NH can be used for the introduction of the second amino group. Application of this reagent in the synthesis of amines from halides represents an excellent alternative to the traditional *Gabriel* method [7]. Alkylation of Boc_2NH with **4** provided derivative **8** in excellent yield (*Scheme 1*). The use of Cs_2CO_3 as a phase-transfer catalyst allowed us to avoid the preparation of the potassium salt of Boc_2NH, as required by the original method of *Grehn* and *Ragnarsson* [8]. Finally, **8** was smoothly deprotected by the action of

CF_3COOH to yield the trifluoroacetate of **9**, which was used directly in the further synthesis.

The synthesis of macrocyclic intermediate **14** was performed in essentially the same manner as the synthesis of (*S*)-dihydroperiphylline [3]. The tosylated amino acid **10** was first converted to the corresponding acyl chloride. Subsequent reaction with either protected (*E*)-but-2-ene-1,4-diamine **9** or its trifluoroacetate gave the amide **11** in 73% yield (*Scheme 2*).

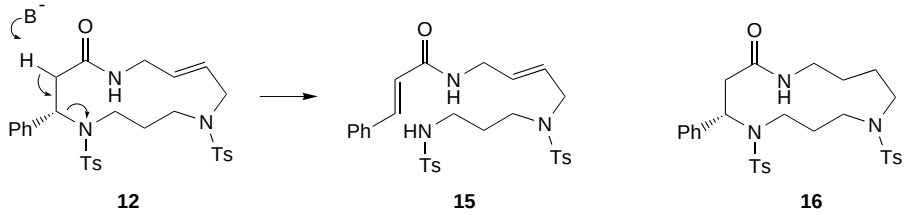
Scheme 2



a) 1. $SOCl_2$, DMF (cat.); 2. **9**, Et_3N, CH_2Cl_2, 0°; 73%. *b*) $MsO(CH_2)_3OMs$, Cs_2CO_3, DMF, r.t.; 49%. *c*) Electrolysis, EtOH/DMF; 98%. *d*) (*E*)-PhCH=CHCOCl, DMAP, CH_2Cl_2, −80°; 92%.

Cyclization of **11** with propane-1,3-diyl bis[methanesulfonate] afforded the macrocyclic derivative **12**. However, the yield was remarkably lower (49%) compared to that obtained for the saturated macrocycle **16** (78%) [3], because the formation of a significant amount of the open-chain by-product **15** was observed. Upon increasing the reaction temperature to 50°, **15** became the main product. Formation of **15** must be explained by a retro-*Michael* reaction (*Scheme 3*), which proceeds relatively easily due to higher ring strain in the macrocycle **12** compared to its saturated analog **16**.

Scheme 3

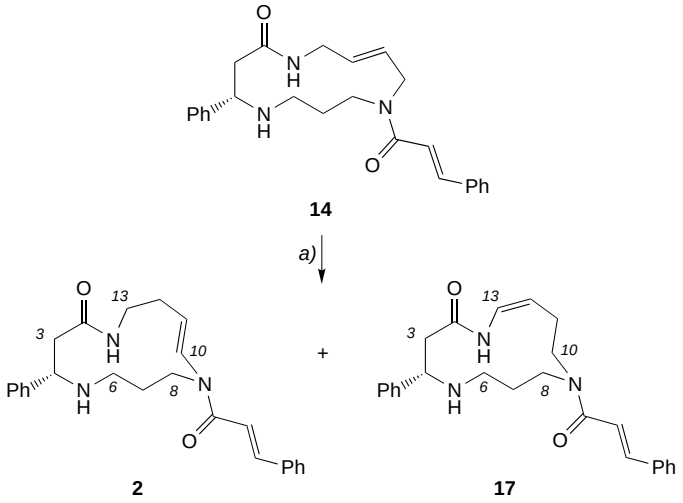


Electrochemical deprotection of **12** [3][9] gave the macrocyclic lactam **13** in almost quantitative yield. Finally, **13** was selectively acylated [3][10] with 1 equiv. of 3-

phenylprop-2-enoyl chloride in the presence of *N*,*N*-(dimethyl)pyridin-4-amine (DMAP) at low temperature to afford the unsaturated macrocyclic precursor **14** in 92% yield.

Recently, we reported [11] that *N*-(prop-1-enyl)amides can be easily prepared by the isomerization of the corresponding *N*-allylamides in the presence of $[Fe(CO)_5]$. We used this method to perform the double bond shift in **14**. Heating **14** with $[Fe(CO)_5]$ in PhCl caused complete isomerization of the starting material after 12 h (TLC). Workup and column chromatography of the reaction mixture gave two new compounds **2** and **17** (*Scheme 4*).

Scheme 4



a) $[Fe(CO)_5]$, PhCl, 120°; 20% **2**, 36% **17**.

Structure of Neoperiphylline: Analytical Data and Discussion. – In the ^{1}H-NMR spectra of both **2** and **17** in $CDCl_3$, many signals were broad at room temperature due to restricted rotation in the disubstituted amide, and in ^{13}C-NMR spectra many signals were either broad or doubled. This problem could be overcome by recording the NMR spectra in (D_6)DMSO at 363–383 K. By means of two-dimensional ^{1}H,^{1}H (COSY) experiments and ^{1}H,^{13}C correlation spectra (HMBC, HSQC), we could unambiguously assign all ^{1}H- and ^{13}C-signals in the spectra of **2** and **17** (see *Exper. Part*).

The characteristic signal at δ 5.58 (*dt*, $J = 14.0, 7.0$ Hz) in the ^{1}H-NMR spectrum of **2** ((D_6)DMSO, 363 K) clearly indicates the presence of the *N*-enylamide functionality. The value of coupling constant (14 Hz) confirms the (*E*)-configuration of the endocyclic double bond. The signal of the CH=C*H*N group appears at δ 6.95 as a sharp *d* ($J = 14$ Hz). The (*Z*)-configuration of the endocylic C=C bond in **17** can be judged from the value of the coupling constant between H–C(12) and H–C(13) ($J = 8.5$ Hz).

The synthesized cyclic enamide **2** has a structure that was suggested [2] for natural neoperiphylline based on the following arguments. EI-MS of natural neoperiphylline has the molecular mass 403, and typical signals at δ 4.97 and 6.75 in ^{1}H-NMR spectra

($CDCl_3$, room temperature) indicate the presence of the *N*-enylamide moiety (*Table*). In addition, hydrogenation of periphylline (**1**), dihydroperiphylline (**3**), and neoperiphylline afforded the same derivative [2]. The structure of dihydroperiphylline (**3**) was later confirmed by total synthesis [3][10][12]. This undoubtedly established that neoperiphylline contains the same 13-membered lactam ring, derived from dicinnamoylspermidine as **1** and **3**, and only the position of the endocyclic C=C bond is uncertain. *A priori*, four positions are possible for this C=C bond: HC(6)=HC(7), HC(7)=HC(8), HC(10)=HC(11), and HC(12)=HC(13). The structures with H(6)=C(7)H and H(7)=C(8)H must be excluded, since they require the signal of two CH_2 groups at 1.5–2.0 ppm. In the two remaining cases, the *N*-enylamide C=C bond can have either (*E*)- or (*Z*)-configuration. The structure with (*E*)-HC(12)=HC(13) corresponds to periphylline (**1**), isolated from the same plant. Based on the assumption that the endocyclic C=C bond in the molecule of neoperiphylline also has the (*E*)-configuration, *Hocquemiller et al.* [2] deduced structure **2** as the only possibility for neoperiphylline.

Table. *Comparison of* $[\alpha]_D$ *Values and* ^{1}*H-NMR Spectra* ($CDCl_3$, r.t.) *of the Natural Neoperiphylline* [2] *and the Synthetic Isomeric Compounds* **2**, **17**.

	Natural neoperiphylline [2]	Synthetic **2** (this work)	Synthetic **17** (this work)
$[\alpha]_D$	−34 ($c = 0.5$, $CHCl_3$)	+130.5 ($c = 0.84$, $CHCl_3$)	−34.7 ($c = 0.91$, $CHCl_3$)
$NCH_2CH_2CH_2N$, PhCHN*H*	1.50–1.95 (*m*, 3 H)	1.45–1.95 (*m*, 3 H)	1.50–2.00 (*m*, 3 H)
$NCH_2CH_2CH_2N$		2.25–2.70 (*m*, 6 H)	
CH_2CO	2.40–2.85 (*m*, 6 H)	3.05–3.15 (*m*, 1 H)	2.20–2.80 (*m*, 6 H)
$NCH{=}CHCH_2CH_2$	3.25–4.10 (*m*, 5 H)	3.60–3.95 (*m*, 3 H)	3.05–4.30 (*m*, 5 H)
PhC*H*NH		4.10–4.20 (*m*, 1 H)	
C*H*=CHN	4.97 (*m*, 1 H)	5.45–5.60 (*m*, 1 H)	4.85–5.00 (*m*, 1 H)
CH=C*H*N	6.75 (*m*, 1 H)	6.73 (*d*, $J = 13.6$, 1 H)	6.75–7.00 (*m*, 2 H)
PhCH=C*H*CO	6.85 (*d*, $J = 15.5$, 1 H)	6.85 (*d*, $J = 15.5$, 1 H)	
2 Ph	7.35 (*m*, 10 H)	7.15–7.40 (*m*, 8 H)	7.15–7.35 (*m*, 8 H)
		7.50–7.66 (*m*, 2 H)	7.47–7.54 (*m*, 2 H)
PhC*H*=CHCO	7.70 (*d*, $J = 15.5$, 1 H)	7.66 (*d*, $J = 15.5$, 1 H)	7.68 (br. *d*, $J \approx 15$, 1 H)

However, synthetic **2** showed completely different properties compared to those reported for natural neoperiphylline [2]. First, the value of optical rotation of the synthetic material is +130.5 instead of − 34 for the natural compound. Then, in the ^{1}H-NMR spectra of **2** ($CDCl_3$, room temperature), the characteristic *m* of *CH*=CHN is shifted by *ca.* 0.5 ppm downfield compared to natural neoperiphylline (see *Table*). We concluded that the structure **2** was assigned to neoperiphylline erroneously.

Surprisingly, the properties of the second synthetic product **17** were very similar to those of the natural neoperiphylline. The value of the optical rotation of the synthetic **17** was identical to that of the natural product. Comparison of ^{1}H-NMR spectra of synthetic **17** and the natural neoperiphylline in $CDCl_3$ at room temperature exhibited only minor differences in the chemical shifts of most signals (*Table*), which can be explained by different measuring conditions. Finally, the assumption about the (*E*)-configuration of the endocyclic C=C bond in natural neoperiphylline was apparently incorrect. Determination of coupling constants from ^{1}H-NMR spectra in $CDCl_3$ at

room temperature is hardly possible because of line broadening (see above). Unfortunately, the authentic sample of natural compound was not available, and direct comparison of spectral data was not possible.

In summary, we conclude that the structure of neoperiphylline suggested in [2] is erroneous and should be corrected to the (−)-(4*S*,12*Z*)-4-phenyl-9-[(2*E*)3-phenylprop-2-enoyl]-1,5,9-triazacyclotridec-12-en-2-one (**17**).

We thank Mr. *A. Guggisberg* for electrochemical experiments and the *Swiss National Science Foundation* for financial support.

Experimental Part

General. All chemicals and solvents were obtained from commercial sources (*Fluka*, *Aldrich*, *Merck*) and used without further purification unless stated otherwise. Technical grade solvents were distilled before use. DMF was stored over flame-dried molecular sieves (4 Å). Reactions were carried out under dry N_2 or Ar. (3*S*)-3-{[(4-Methylphenyl)sulfonyl]amino}-3-phenylpropanoic acid (**10**) [3] and propane-1,3-diyl bis[methanesulfonate] [13] were prepared according to the published procedures. Column chromatography (CC): SiO_2, *Merck 60* (40–63 μm). TLC: precoated SiO_2 plates, *Merck 60* F_{254}; detection by UV at 254 nm, *Fluram* reagent (*Fluka*) in acetone, fluorescence at 366 nm (for primary amines), *Schlittler* reagent [14] (for amines and polyamines), or $KMnO_4$ (for unsaturated compounds). M.p.: *Mettler FP-5*. Optical rotations: *Perkin-Elmer 241* polarimeter. IR (cm^{-1}): *Perkin-Elmer Spectrum One*; KBr pellets or neat substance. NMR: *Bruker ARX-300* (300 (^{1}H) or 75 MHz (^{13}C)) or *AMX-600* (600 (^{1}H) or 150 MHz (^{13}C)); chemical shifts δ in ppm rel. to Me_4Si as internal standard, *J* values in Hz. ^{13}C multiplicities from DEPT experiments. CI-MS (NH_3 as reactant gas): *Finnigan MAT 90*. ESI-MS (NaI/MeOH/CH_2Cl_2): *Finnigan TSQ 700*; in *m/z* (rel. intensity in % of base peak).

tert-*Butyl [(2*E*)-(4-Bromobut-2-enyl][(4-methylphenyl)sulfonyl]carbamate* (**5**). A mixture of BocNHTs (10.8 g, 0.04 mol), (2*E*)-1,4-dibromobut-2-ene (**4**; 25.7 g, 0.12 mol), Cs_2CO_3 (13.1 g, 0.04 mol), and DMF (100 ml) was stirred for 16 h at r.t. The DMF was evaporated, the residue dissolved in CH_2Cl_2 (150 ml), the mixture filtered, and the filtrate evaporated. CC of the residue (hexane/CH_2Cl_2 1:1, then pure CH_2Cl_2) afforded **5** (9.7 g, 60%). Colorless oil. R_f (CH_2Cl_2) 0.54. IR (neat): 2981*m*, 2929*m*, 1784*w*, 1731*s*, 1598*m*, 1495*m*, 1435*m*, 1395*m*, 1357*s*, 1291*s*, 1257*m*, 1207*m*, 1042*m*, 1019*m*, 968*m*, 915*w*, 847*m*, 815*m*, 771*w*, 720*m*, 675*s*. ^{1}H-NMR ($CDCl_3$): 1.36 (*s*, Me_3C); 2.44 (*s*, Me); 3.97 (*d*, *J* = 7.2, CH_2N); 4.45 (*d*, *J* = 5.8, CH_2Br); 5.88 (*dt*, *J* = 15.2, 5.8, CH=C*H*CH_2Br); 5.97 (*dt*, *J* = 15.2, 7.2, CH=C*H*CH_2N); 7.31 (*d*, *J* = 8.2, 2 H of Ts); 7.80 (*d*-like *m*, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.5 (*q*, Me); 27.8 (*q*, *Me*$_3$C); 31.5 (*t*, CH_2Br); 47.1 (*t*, CH_2N); 84.4 (*s*, Me_3C); 128.1, 129.1 (2*d*, 2 × 2 arom. CH); 130.0 (2 overlapping *d*, CH=CH); 136.9, 144.2 (2*s*, 2 arom. C); 150.5 (*s*, C=O). CI-MS: 421, 423 (13, 13, $[M+NH_4]^+$), 365, 367 (98, 100, $[(M-C_4H_8)+NH_4]^+$), 321, 323 (15, 15, $[(M-C_4H_8-CO_2)+NH_4]^+$).

tert-*Butyl [(2*E*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-2-enyl][(4-methylphenyl)sulfonyl]carbamate* (**6**). A mixture of **5** (4.81 g, 11.9 mmol), potassium phthalimide (2.20 g, 11.9 mmol), and DMF (30 ml) was stirred at 50° for 12 h. The mixture was allowed to reach r.t. and poured into ice/H_2O (200 ml). The precipitate was filtered, washed with H_2O, and dried *in vacuo*: **6** (5.19 g, 93%). White solid. R_f (CH_2Cl_2/AcOEt 10:1) 0.78. M.p. 123–124.5°. IR (KBr): 2990*m*, 2937*m*, 1771*s*, 1720*s*, 1612*w*, 1596*m*, 1468*m*, 1429*m*, 1391*s*, 1352*s*, 1260*m*, 1152*m*, 1121*s*, 1086*m*, 1027*m*, 971*m*, 907*m*, 848*m*, 820*m*, 794*w*, 770*m*, 753*m*, 720*s*, 673*s*. ^{1}H-NMR ($CDCl_3$): 1.30 (*s*, Me_3C); 2.42 (*s*, Me); 4.31 (*d*, *J* = 4.1, CH_2N); 4.41 (*d*, *J* = 4.7, CH_2N); 5.75–5.87 (*m*, CH=CH); 7.29 (*d*, *J* = 8.0, 2 H of Ts); 7.68–7.76 (*m*, 2 H of Ts, 2 H of Phth); 7.83–7.90 (*m*, 2 H of Phth). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, Me); 27.6 (*q*, *Me*$_3$C); 38.7, 47.2 (2*t*, 2 CH_2N); 84.1 (*s*, Me_3C); 123.1 (*d*, 2 arom. CH); 127.9 (2 overlapping *d*, 2 arom. CH, CH=); 128.3 (*d*, CH=); 129.2 (*d*, 2 arom. CH); 133.9 (*s*, 2 arom. C); 136.9 (*s*, arom. C); 137.0 (*d*, 2 arom. CH); 144.0 (*s*, arom. C); 150.5 (*s*, C=O of Boc); 167.6 (*s*, 2 C=O of Phth). CI-MS: 488 (67, $[M+NH_4]^+$), 432 (59, $[(M-C_4H_8)+NH_4]^+$), 388 (100, $[(M-C_4H_8-CO_2)+NH_4]^+$).

N-*[(2*E*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-but-2-enyl]-4-methylbenzenesulfonamide* (**7**). A stirred soln. of **6** (5.17 g, 11 mmol) in CH_2Cl_2 (40 ml) was treated with CF_3COOH (3.8 ml, 0.05 mol) in one portion and stirred for 4 h at r.t. The soln. was evaporated and the residue dried *in vacuo:* **7** (3.49 g, 100%). White solid. M.p. 141–142°. R_f (CH_2Cl_2/AcOEt 10:1) 0.52. IR (KBr): 3275*s*, 3050*m*, 2930*m*, 2854*m*, 1774*s*, 1720*s*, 1614*m*, 1595*m*, 1493*m*, 1466*m*, 1456*m*, 1434*s*, 1396*s*, 1320*s*, 1265*m*, 1188*m*, 1155*s*, 1089*s*, 1067*m*, 1022*m*, 972*s*, 922*m*, 884*m*, 820*m*, 790*m*, 720*s*, 702*s*. ^{1}H-NMR ($CDCl_3$): 2.38 (*s*, Me); 3.55 (*d*, *J* = 4.2, CH_2N); 4.17 (*d*, *J* = 4.3, CH_2N); 4.82 (br.,

NH); 5.53–5.67 (*m*, CH=CH); 7.25 (*d*, *J* = 8.0, 2 H of Ts); 7.65–7.75 (*m*, 2 H of Ts, 2 H of Phth); 7.77–7.85 (*m*, 2 H of Phth). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, Me); 38.6, 44.4 (2*t*, 2 CH_2N); 123.2 (*d*, 2 arom. CH); 126.8 (*d*, CH=); 127.0 (*d*, 2 arom. CH); 128.4 (*d*, CH=); 129.6 (*d*, 2 arom. CH); 131.9 (*s*, 2 arom. C); 134.0 (*d*, 2 arom. CH); 136.8, 143.3 (2*s*, 2 arom. C); 167.6 (*s*, 2 C=O). CI-MS: 388 (100, $[M+NH_4]^+$), 371 (6, $[M+1]^+$).

Di(tert-*butyl*) N-*{(2*E*)-4-[[*(tert-*Butoxy)carbonyl][(4-methylphenyl)sulfonyl]amino}but-2-enyl}imidodicarbonate* (**8**). A mixture of **5** (5.90 g, 14.6 mmol), Boc_2NH (3.47 g, 16 mmol), Cs_2CO_3 (5.22 g, 15 mmol), and DMF (50 ml) was stirred for 16 h at r.t. The DMF was evaporated, the residue distributed between CH_2Cl_2 (100 ml) and H_2O (50 ml), and the org. phase washed with H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated: **8** (7.70 g, 98%). Colorless oil. R_f (CH_2Cl_2/AcOEt 20:1) 0.58. IR (neat): 2980*m*, 2935*m*, 1788*m*, 1732*s*, 1695*s*, 1598*m*, 1478*m*, 1456*m*, 1367*s*, 1298*s*, 1257*m*, 1225*s*, 1151*s*, 973*w*, 852*m*, 814*w*, 771*w*, 720*m*, 673*m*. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, Me_3C); 1.49 (*s*, 2 Me_3C); 2.43 (*s*, Me); 4.19 (*d*, *J* = 4.3, CH_2N); 4.42 (*d*, *J* = 4.7, CH_2N); 5.69–5.83 (*m*, CH=CH); 7.31 (*d*, *J* = 8.2, 2 H of Ts); 7.78 (*d*, *J* = 8.2, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, Me); 27.8 (*q*, *Me*$_3$C); 27.9 (*q*, 2 *Me*$_3$C); 47.1, 47.5 (2*t*, 2 CH_2N); 82.3 (*s*, 2 Me_3*C*); 84.0 (*s*, Me_3*C*); 127.3 (*d*, CH=); 128.0, 129.1 (2*d*, 2 × 2 arom. CH); 129.8 (*d*, CH=); 137.1, 143.9 (2*s*, 2 arom. C); 150.6 (*s*, C=O); 152.1 (*s*, 2 C=O). ESI-MS: 563 ($[M+Na]^+$).

N-*[(2*E*)-4-Aminobut-2-enyl]-4-methylbenzenesulfonamide* (**9**). *Method A.* A stirred soln. of **7** (3.49 g, 11 mmol) in EtOH (60 ml) was treated in one portion at 50° with $N_2H_4 \cdot H_2O$ (4.0 ml, *ca.* 0.08 mol). Stirring was continued for 1 h. Then the soln. was cooled to r.t., the precipitate filtered off, the filtrate evaporated, and the residue redissolved in CH_2Cl_2 (100 ml). The soln. was filtered, the filtrate evaporated, and the residue dried *in vacuo*: **9** (2.16 g, 82%). White solid. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 80:12:2) 0.28. M.p. 95–96.5°. IR (KBr): 3355*m*, 3027*m*, 2922*m*, 2858*m*, 2768*m*, 2691*m*, 1647*w*, 1590*m*, 1478*m*, 1466*m*, 1447*m*, 1395*m*, 1322*s*, 1230*w*, 1152*s*, 1108*m*, 1091*m*, 1031*m*, 974*m*, 908*m*, 829*s*, 810*s*, 761*m*, 706*w*, 661*s*. ^{1}H-NMR ($CDCl_3$): 2.42 (*s*, Me); 3.20 (*dd*, *J* = 5.6, 1.3, CH_2N); 3.53 (*dd*, *J* = 6.0, 1.5, CH_2N); 5.46 (*dtt*, *J* = 15.2, 6.0, 1.5, CH=); 5.68 (*dtt*, *J* = 15.2, 5.6, 1.3, CH=); 7.29 (*d*, *J* = 8.4, 2 H of Ts); 7.74 (*d*, *J* = 8.4, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.5 (*q*, Me); 43.2, 44.8 (2*t*, 2 CH_2N); 124.9 (*d*, CH=); 127.2, 129.7 (2*d*, 2 × 2 arom. H); 134.6 (*d*, CH=); 137.3, 143.3 (2*s*, 2 arom. C). CI-MS: 241 ($[M+1]^+$).

Method B. A stirred soln. of **8** (5.40 g, 10 mmol) in CH_2Cl_2 (20 ml) was treated with CF_3COOH (7.6 ml, 0.1 mol) in one portion and stirred for 4 h at r.t. The soln. was evaporated and the residue dried *in vacuo* to give *ca.* 3.4 g of crude **9** · CF_3COOH, which was used without further purification. ^{1}H-NMR (CD_3OD): 2.41 (*s*, Me); 3.42–3.52 (*m*, 2 CH_2N); 5.63–5.89 (*m*, CH=CH); 7.35 (*d*, *J* = 8.2, 2 H of Ts); 7.70 (*d*, *J* = 8.2, 2 H of Ts). ^{13}C-NMR (CD_3OD; signals of CF_3COO^- not given): 21.3 (*q*, Me); 41.6, 44.9 (2*t*, 2 CH_2N); 124.4 (*d*, CH=); 128.0, 130.7 (2*d*, 2 × 2 arom. H); 134.6 (*d*, CH=); 138.7, 144.8 (2*s*, 2 arom. C).

*(−)-(3*S*)-3-[[(4-Methylphenyl)sulfonyl]amino]-*N*-[(2*E*)-4-[[(4-methylphenyl)sulfonyl]amino}but-2-enyl]-3-phenylpropanamide* (**11**). To **10** (2.87 g, 10 mmol) was added $SOCl_2$ (10 ml) followed by DMF (*ca.* 0.05 ml). The resulting mixture was stirred at r.t. for 2 h. The excess of $SOCl_2$ was evaporated, and the obtained chloride was dissolved in CH_2Cl_2 (30 ml) and added dropwise to a stirred soln. of **9** · CF_3COOH (3.4 g, 10 mmol) and Et_3N (6.9 ml, 50 mmol) in CH_2Cl_2 (100 ml) at 0°. Stirring was continued for 30 min at 0° and for another 30 min at r.t. The resulting soln. was washed with 10% aq. citric acid (50 ml), H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated. Crystallization of the residue from $CHCl_3$ afforded **11** (3.95 g, 73%). White solid. R_f (CH_2Cl_2/AcOEt 1:1) 0.32. $[\alpha]_D = -18.7$ (*c* = 1.17, MeOH). M.p. 149–149.5°. IR (KBr): 3336*s*, 3276*s*, 3032*w*, 2922*w*, 1917*w*, 1643*s*, 1598*m*, 1536*s*, 1495*w*, 1458*m*, 1446*m*, 1430*m*, 1380*w*, 1325*s*, 1288*m*, 1244*w*, 1211*w*, 1156*s*, 1091*m*, 1067*m*, 1048*m*, 1013*w*, 975*m*, 922*w*, 848*m*, 814*m*, 760*w*, 704*s*, 673*s*, 609*w*. ^{1}H-NMR ($CDCl_3$): 2.06, 2.29 (2*s*, 2 Me); 2.53 (*dd*, *J* = 14.3, 5.2, 1 H, CH_2CO); 2.64 (*dd*, *J* = 14.3, 8.3, 1 H, CH_2CO); 3.38–3.44 (*m*, C*H*$_2$NHTs); 3.60–3.70 (*m*, C*H*$_2$NHCO); 4.72–4.77 (*m*, CHN); 5.37 (*dt*, *J* = 15.5, 5.4, CH=); 5.49 (*dt*, *J* = 15.5, 5.0, CH=); 5.58 (*t*, *J* = 5.8, NH); 6.61 (*t*, *J* = 5.7, NH); 6.82 (*d*, *J* = 6.1, CHN*H*Ts); 7.00–7.10 (*m*, 5 H of Ph, 2 H of Ts); 7.25 (*d*, *J* = 8.0, 2 H of Ts); 7.46 (*d*, *J* = 8.3, 2 H of Ts); 7.71 (*d*, *J* = 7.8, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.4, 21.5 (2*q*, 2 Me); 40.5, 43.5, 44.7 (3*t*, 3 CH_2); 55.6 (*d*, CHN); 126.5–129.7 (several *d*, 13 arom. CH, CH=CH); 136.6, 137.5, 139.8, 142.9, 143.5 (5*s*, 5 arom. C); 170.3 (*s*, C=O). ESI-MS: 564 ($[M+Na]^+$).

*(+)-(4*S*,11*E*)-5,9-Bis[(4-methylphenyl)sulfonyl]-4-phenyl-1,5,9-triazacyclotridec-11-en-2-one* (**12**). A stirred suspension of Cs_2CO_3 (1.14 g, 3.5 mmol) in dry DMF (20 ml) was treated dropwise with a soln. of **11** (0.811 g, 1.5 mmol) and propane-1,3-diyl bis[methanesulfonate] (0.348 g, 1.5 mmol) in dry DMF (40 ml) during 2 h. After the addition was completed, stirring was continued for 120 h. Then the DMF was evaporated and the residue partitioned between CH_2Cl_2 (50 ml) and H_2O (20 ml). The org. layer was washed with H_2O (2 × 20 ml), dried ($MgSO_4$), and evaporated. CC of the residue (CH_2Cl_2/AcOEt 5:1) afforded **12** (0.424 g, 49%). White solid. M.p. 119–120°. R_f (CH_2Cl_2/AcOEt 1:1) 0.64. $[\alpha]_D = +79.0$ (*c* = 1.05, $CHCl_3$). IR (KBr): 3385*m*, 3030*w*, 2928*m*, 2247*w*, 1733*w*, 1668*s*, 1598*m*, 1526*m*, 1495*m*, 1453*m*, 1335*s*, 1208*w*, 1155*s*, 1107*m*, 1089*m*, 1033*w*, 969*m*, 923*m*,

839*w*, 816*m*, 764*m*, 736*s*, 690*m*, 654*m*. ^{1}H-NMR ($CDCl_3$): 2.00–2.12 (*m*, 2 H–C(7)); 2.23, 2.41 (2*s*, 2 Me); 2.56 (*dd*, *J* = 13.6, 3.3, 1 H–C(3)); 2.97–3.11 (*m*, 2 H–C(8), 1 H–C(10)); 3.18–3.30 (*m*, 2 H–C(6), 1 H–C(13)); 3.73 (*dd*, *J* = 13.6, 12.4, 1 H–C(3)); 4.12 (*dd*, *J* = 12.4, 4.8, 1 H–C(10)); 4.23–4.28 (*m*, 1 H–C(13)); 4.81 (*dd*, *J* = 12.4, 3.3, H–C(4)); 5.64 (*ddd*, *J* = 14.9, 9.7, 5.0, H–C(12)); 5.98 (*ddd*, *J* = 14.9, 9.8, 5.1, H–C(11)); 6.70 (*dd*, *J* = 8.2, 4.7, NH); 6.87 (*d*, *J* = 8.2, 2 H of Ts); 6.95 (*d*, *J* = 8.4, 2 H of Ts); 7.07–7.20 (*m*, 5 H of Ph); 7.31 (*d*, *J* = 8.0, 2 H of Ts); 7.68 (*d*, *J* = 8.2, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.1, 21.3 (2*q*, 2 Me); 30.1 (*t*, C(7)); 40.2 (*t*, C(13)); 41.6 (*t*, C(3)); 46.3 (*t*, C(8)); 49.4 (*t*, C(6)); 53.3 (*t*, C(10)); 63.7 (*d*, C(4)); 126.8–129.6 (several *d*, 13 arom. CH); 130.1 (*d*, C(12)); 131.5 (*d*, C(11)); 135.3, 136.9, 137.0, 142.4, 143.1 (5*s*, 5 arom. C); 170.8 (*s*, C=O). ESI-MS: 604 (100, $[M+Na]^+$), 582 (45, $[M+1]^+$).

(+)-(4S,11E)-4-Phenyl-1,5,9-triazacyclotridec-11-en-2-one (**13**). A soln. of **12** (995 mg, 1.71 mmol) in a minimal amount of DMF was added to 0.1M Me_4NCl in EtOH (100 ml). The resulting soln. was subjected to electrolysis under Ar at −2.25 V in a three electrode cell with a Hg cathode, graphite rod anode, and standard calomel electrode as reference electrode (see [9] for detailed procedure). After the electrolysis was completed, the solvents were evaporated, the residue dissolved in 20% aq. K_2CO_3 soln. (10 ml), and the soln. extracted with CH_2Cl_2 (4 × 75 ml). The combined extracts were dried ($MgSO_4$) and evaporated: **13** (457 mg, 98%). Colorless oil. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 70:30:3) 0.46. $[\alpha]_D = +14.2$ (*c* = 0.97, $CHCl_3$). IR (KBr): 3425*m*, 3285*m*, 3055*m*, 3020*m*, 2932*m*, 2845*m*, 1643*s*, 1546*s*, 1495*m*, 1452*m*, 1430*m*, 1356*m*, 1310*m*, 1255*w*, 1222*w*, 1190*w*, 1130*w*, 1074*w*, 974*m*, 763*m*, 703*s*. ^{1}H-NMR ($CDCl_3$): 1.38–1.48, 1.52–1.60 (2*m*, 2 H–C(7)); 1.98 (br. *s*, 2 NH); 2.34–2.55 (*m*, 2 H–C(3), 2 H–C(6)); 2.62–2.79 (*m*, 2 H–C(8)); 3.05–3.35 (*m*, 2 H–C(10)); 3.48–3.54 (*m*, 1 H–C(13)); 3.92 (*dd*, *J* = 10.0, 4.4, H–C(4)); 4.00–4.08 (*m*, 1 H–C(13)); 5.76–5.91 (*m*, CH=CH); 7.20–7.35 (*m*, 5 arom. H); 7.50 (br. *s*, CONH). ^{13}C-NMR ($CDCl_3$): 28.9 (*t*, C(7)); 39.7 (*t*, C(13)); 41.4 (*t*, C(8)); 42.8 (*t*, C(6)); 45.5 (*t*, C(3)); 49.0 (*t*, C(10)); 61.1 (*d*, C(4)); 126.3 (*d*, 2 arom. CH); 127.3 (*d*, arom. CH); 128.6 (*d*, 2 arom. CH); 130.2, 133.1 (2*d*, CH=CH); 143.1 (*s*, arom. C); 171.7 (*s*, C=O). CI-MS: 274 ($[M+1]^+$).

(−)-(4S,11E)-4-Phenyl-9-[(2E)-3-phenylprop-2-enoyl]-1,5,9-triazacyclotridec-11-en-2-one (**14**). A stirred soln. of **13** (435 mg, 1.59 mmol) and DMAP (585 mg, 4.80 mmol) in CH_2Cl_2 (25 ml) was cooled to −80° and treated dropwise with a soln. of cinnamoyl chloride (265 mg, 1.59 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 1 h at −80°, allowed to reach r.t., washed with H_2O (2 × 10 ml), and evaporated. CC of the residue (CH_2Cl_2/MeOH 10:1) afforded **14** (588 mg, 92%). Colorless amorphous solid. R_f (CH_2Cl_2/MeOH 10:1) 0.61. $[\alpha]_D = -73.5$ (*c* = 1.15, $CHCl_3$). IR (KBr): 3425*m*, 3295*s*, 3060*m*, 3025*m*, 2927*s*, 2855*m*, 1645*s*, 1595*s*, 1545*m*, 1495*m*, 1425*s*, 1360*m*, 1304*m*, 1204*m*, 1160*m*, 1115*m*, 1072*w*, 1030*w*, 975*m*, 853*w*, 763*s*, 702*s*. ^{1}H-NMR ((D_6)DMSO, 373 K): 1.53–1.63, 1.72–1.82 (2*m*, 2 H–C(7)); 2.28–2.30 (*m*, 2 H–C(3), 1 H–C(6)); 2.58 (*ddd*, *J* = 12.7, 7.6, 4.8, 1 H–C(6)); 2.90 (br. *s*, NH); 3.37–3.45 (*m*, 1 H–C(8)); 3.55–3.66 (*m*, 1 H–C(8), 1 H–C(13)); 3.78–3.85 (*m*, 1 H–C(13)); 3.91 (*dd*, *J* = 14.7, 5.8, 1 H–C(10)); 4.02 (*t*, *J* = 7.3, H–C(4)); 4.33 (*dd*, *J* = 14.7, 5.8, 1 H–C(10)); 5.82–6.00 (*m*, H–C(11), H–C(12)); 7.03 (*d*, *J* = 15.5, CH=C*H*CO); 7.19–7.22 (*m*, 1 arom. CH); 7.24–7.43 (*m*, 7 arom. CH); 7.49 (*d*, *J* = 15.5, CH=C*H*Ph); 7.58–7.63 (*m*, 2 arom. CH); 7.96 (br. *s*, CONH). ^{13}C-NMR ((D_6)DMSO, 373 K): 28.5 (*t*, C(7)); 38.5 (*t*, C(13)); 43.5 (2 overlapping *t*, C(6), C(8)); 44.8 (*t*, C(3)); 48.1 (*t*, C(10)); 59.8 (*d*, C(4)); 119.4 (*d*, CH=*C*HCO); 125.6 (*d*, 2 arom. CH); 125.8 (*d*, C(11)); 126.8 (*d*, 2 arom. CH); 127.3 (*d*, arom. CH); 127.4, 127.8 (2*d*, 2 x 2 arom. CH); 128.3 (*d*, arom. CH); 130.2 (*d*, C(12)); 135.0 (*s*, arom. C); 139.6 (*d*, CH=*C*HPh); 143.8 (*s*, arom. C); 165.3 (*s*, CH=CH*C*=O); 170.1 (*s*, CONH). CI-MS: 404 ($[M+1]^+$).

(+)-(4S,10E)-4-Phenyl-9-[(2E)-3-phenylprop-2-enoyl]-1,5,9-triazacyclotridec-10-en-2-one (**2**) and *(−)-(4S,2Z)-4-Phenyl-9-[(2E)-3-phenylprop-2-enoyl]-1,5,9-triazacyclotridec-12-en-2-one* (**17**). A mixture of **14** (285 mg, 0.71 mmol), $[Fe(CO)_5]$ (0.1 ml, ca. 1 mmol), and PhCl (1 ml) was stirred for 12 h at 120°. Volatile materials were evaporated, and the residue was dissolved in $CHCl_3$/acetone 5:1 (ca. 20 ml). The soln. was filtered through Celite, the filtrate evaporated, and the residue purified by CC (CH_2Cl_2/AcOEt 1:1, then CH_2Cl_2/acetone 2:1, and then CH_2Cl_2/acetone 1:1): **17** (first-eluted; 104 mg, 36%) and **2** (58 mg, 20%).

Data of **2**. Colorless oil. R_f (CH_2Cl_2/acetone 1:1) 0.42. $[\alpha]_D = +130.5$ (*c* = 0.84, $CHCl_3$). IR (KBr): 3292*m*, 3059*m*, 3026*m*, 2926*m*, 1957*w*, 1888*w*, 1645*s*, 1606*m*, 1547*m*, 1494*m*, 1450*m*, 1404*m*, 1356*m*, 1336*m*, 1253*w*, 1203*m*, 1187*m*, 1110*w*, 1070*w*, 976*m*, 951*m*, 912*w*, 857*w*, 763*m*, 701*m*. ^{1}H-NMR ((D_6)DMSO, 363 K): 1.52–1.62, 1.80–1.90 (2*m*, 2 H–C(7)); 2.26–2.52 (*m*, 2 H–C(3), 2 H–C(8), 2 H–C(12)); 3.00 (br. *s*, NH); 3.21–3.28, 3.43–3.50 (2*m*, 2 H–C(13)); 3.69–3.88 (*m*, 2 H–C(6)); 3.98 (*dd*, *J* = 10.8, 3.2, H–C(4)); 5.58 (*dt*, *J* = 14.0, 7.0, H–C(11)); 6.95 (*d*, *J* = 14.0, H–C(10)); 7.08 (*d*, *J* = 15.5, CH=C*H*CO); 7.19–7.22 (*m*, 1 arom. CH); 7.29–7.43 (*m*, 7 arom. CH); 7.53 (*d*, *J* = 15.5, CH=C*H*Ph); 7.63–7.69 (*m*, 2 arom. CH); 7.84 (br. *s*, CONH). ^{13}C-NMR ((D_6)DMSO, 363 K): 27.8 (*t*, C(7)); 29.0 (*t*, C(12)); 36.8 (*t*, C(13)); 42.5 (*t*, C(6)); 43.2 (*t*, C(8)); 45.7 (*t*, C(3)); 59.4 (*d*, C(4)); 115.6 (*d*, C(11)); 118.7 (*d*, CH=*C*HCO); 126.0 (*d*, 2 arom. CH); 126.2 (*d*, arom. CH); 127.4, 127.7, 128.2 (3*d*, 3 × 2 arom. CH); 129.0 (*d*, arom. CH); 129.8 (*d*, C(10)); 134.7 (*s*, arom. C); 141.5 (*d*, CH=*C*HPh);

143.6 (*s*, arom. C); 163.7 (*s*, CH=CH*C*=O); 170.0 (*s*, CONH). ESI-MS: 426 (100, $[M+Na]^+$), 404 (25, $[M+1]^+$).

Data of **17**. Colorless oil. R_f (CH_2Cl_2/acetone 1:1) 0.73. $[\alpha]_D = -34.7$ ($c = 0.91$, $CHCl_3$). IR (KBr): 3440*m*, 3269*m*, 3140*m*, 3082*m*, 3059*m*, 2938*m*, 2861*m*, 1955*w*, 1887*w*, 1731*w*, 1685*s*, 1648*s*, 1601*s*, 1520*s*, 1495*m*, 1453*m*, 1423*s*, 1377*m*, 1327*m*, 1258*m*, 1195*m*, 1166*m*, 1119*m*, 1072*m*, 1030*w*, 976*m*, 946*w*, 895*m*, 868*m*, 825*w*, 763*s*, 702*s*, 685*m*, 644*m*, 618*w*. ^{1}H-NMR ((D_6)DMSO, 383 K): 1.61–1.70, 1.80–1.90 (2*m*, 2 H–C(7)); 2.26 (*dd*, $J = 15.9$, 2.2, 1 H–C(3)); 2.30–2.56 (*m*, 2 H–C(11), 2 H–C(6)); 2.74 (*dd*, $J = 15.9$, 11.4, 1 H–C(3)); 2.85 (br. *s*, NH); 3.40–3.48 (*m*, 1 H–C(10)); 3.66–3.81 (*m*, 2 H–C(8), 1 H–C(10)); 3.94 (*dd*, $J = 11.4$, 2.2, H–C(4)); 4.91 (*dt*, $J = 8.5$, 7.8, H–C(12)); 6.71–6.78 (*m*, H–C(13)); 7.04 (*d*, $J = 15.5$, CH=C*H*CO); 7.23–7.42 (*m*, 8 arom. CH); 7.49 (*d*, $J = 15.5$, CH=C*H*Ph); 7.62 (*m*, 2 arom. CH); 10.70 (br. *d*, CONH). ^{13}C-NMR ((D_6)DMSO, 383 K): 23.7 (*t*, C(11)); 30.0 (*t*, C(7)); 41.8 (*t*, C(8)); 42.6 (*t*, C(6)); 43.1 (*t*, C(3)); 44.5 (*t*, C(10)); 58.8 (*d*, C(4)); 105.1 (*d*, C(12)); 118.8 (*d*, CH=*C*HCO); 123.7 (*d*, C(13)); 125.8 (*d*, 2 arom. CH); 126.4 (*d*, arom. CH); 127.0, 127.7, 130.0 (3*d*, 3 x 2 arom. CH); 128.5 (*d*, arom. CH); 134.9 (*s*, arom. C); 140.2 (*d*, CH=*C*HPh); 142.6 (*s*, arom. C); 165.0 (*s*, CH=CH*C*=O); 167.7 (*s*, CONH). ESI-MS: 426 (100, $[M+Na]^+$), 404 (33, $[M+1]^+$).

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