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Synthesis of Macrocyclic Enaminolactams by Ring Expansion Reaction of 2-Oxocyclododecane-1-carbonitrile with Diarylcarbodiimides

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Abstract: A base promoted ring expansion reaction of 2-oxocyclododecane-1-carbonitrile (**6**) with several diarylcarbodiimides gives 14-membered α-enaminolactams (**12-17**), whereas *N*-alkyl-*N'*-aryl- and *N,N'*-dialkylcarbodiimides do not react at all. This new process seems to occur by a similar mechanism as some recently reported analogue reactions of heterocumulenes with cycloalkanones. All relevant molecular structures were confirmed by X-ray analysis.

INTRODUCTION

In the course of our progressing work on ring enlargement strategies towards new procedures that can efficiently accomplish transformations of readily available carbocyclic precursors into heterocyclic systems along with concomitant introduction of useful functionality, we discovered that suitably substituted cycloalkanones react with a variety of heterocumulenes to form functionalized unsaturated heterocycles. Depending on the nature of the chosen heterocumulene, the reactions summarized in Scheme 1 lead to imides, ketones or lactams. After an initial addition of an anion of the starting cycloalkanone **1** to the *sp*-hybridized carbon atom of a heterocumulene X=C=Y (**2**), an intramolecular attack of a nucleophilic residue Y on the carbonyl group in **3** leads to a bicyclic intermediate (e. g. **4**). Its fragmentation, promoted by a driving force consisting in the release of ring strain and by the electronic influence of an activating group W, produces an expanded cyclic product of type **5**. Nitrogen nucleophiles in the case of isocyanates, isothiocyanates and carbodiimides, carbon nucleophiles in the case of ketenes, determine the type of functional group transformation. This work focuses on the reaction of cyano-substituted cycloalkanones (W = CN) with diarylcarbodiimides, and on the synthesis

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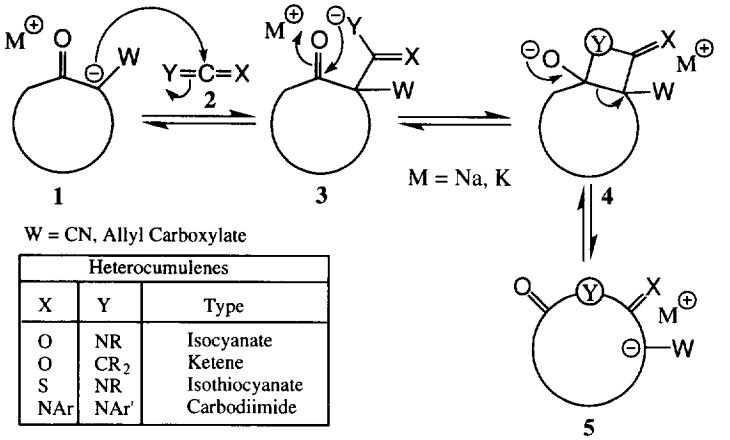
Scheme 1. Ring Expansion Reactions of Cycloalkanones with Heterocumulenes.



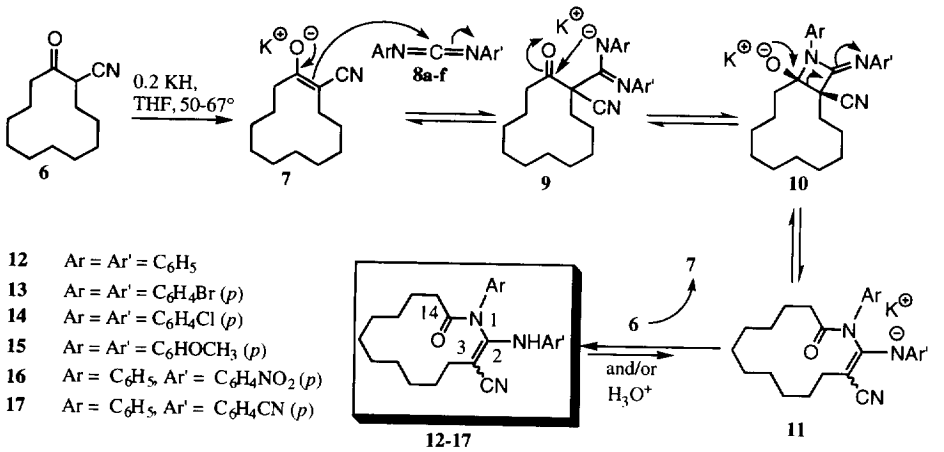
Heterocumulenes		
X	Y	Type
O	NR	Isocyanate
O	CR_2	Ketene
S	NR	Isothiocyanate
NAr	NAr'	Carbodiimide

of macrocyclic, unsaturated enaminolactams. The other three related reactions, generalized in Scheme 1, have been described previously.[1-3] Fundamentals of ring enlargement methodology have been object of exhaustive works[4] and the transformations outlined in Scheme 1 represent the more recent conceptual development of a technique based on the *X-Zip* reaction model (X = C, O, N). Moreover, the synthetic potential of carbodiimides (e. g. their suitability for cycloaddition reactions) has been demonstrated by many recent works.[5-15] We report in this paper on a new and useful reaction of an ionic type.

RESULTS AND DISCUSSION

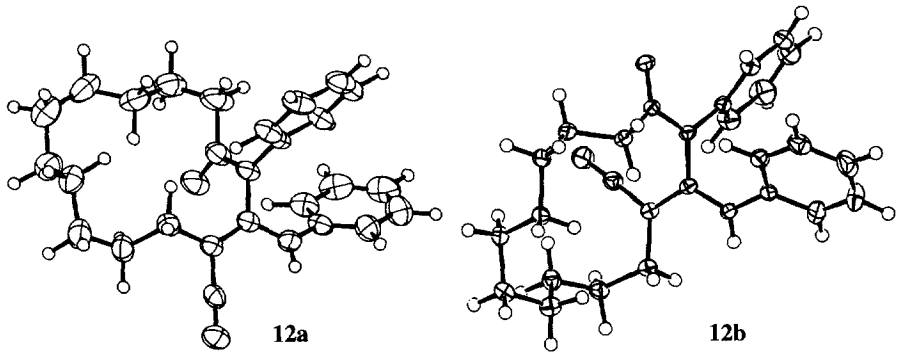
The Ring Expansion Reaction with Diarylcarbodiimides. The cyano group was preferred for the activation of the 2-position in the starting compounds[16] because of excellent results achieved erstwhile in ring expansion reactions of cyano-substituted cycloalkanones.[17] Whereas β-Keto esters[18] have been successfully used for ring enlargement reactions,[19-22] the nitro group revealed to be inadequate until now. During our efforts to test new potential building blocks for ring expansion reactions we drew attention to carbodiimides as powerful electrophiles having hidden nucleophilic nitrogen atoms. These heterocumulenes were prepared in excellent yields by the method of *Mitsunobu et al.*[23] from thioureas (commercially available or obtained by acid-catalyzed addition of anilines to thioisocyanates). The ring enlargement reaction was performed with 0.2 equivalents KH, rapidly added to the mixture of the starting materials in THF at 50-67°C. The use of only one

Scheme 2. Postulated Mechanism for the Ring Expansion Reaction of 2-Oxocyclododecane-1-carbonitrile (6) with Diarylcarbodiimides.



equivalent of base with a preformed ketone enolate revealed surprisingly to be unsuitable. This effect is best explained by the transformation of **11** to **12**, see Scheme 2. Anions of type **11** deprotonate the neutral cycloalkanone **6**, which is still present in the reaction mixture, and hence shift the last equilibrium step to the product side. A point concerning the influence of 4-substituents on the aryl groups should be mentioned. Both groups with donor (MeO, Br, Cl) and acceptor characteristics (CN, NO_2) were examined, but no significant effect on yields or reaction times could be realized. As predicted, a less electrophilic carbodiimide like di(4-methoxyphenyl)carbodiimide (**8d**, Scheme 2) required more vigorous conditions, increasing the risk of polymerization and decomposition. Anyway, the electronic influence of such substituents on the reactivity of carbodiimides in this process, which consists of nucleophilic addition and fragmentation reactions, is still an unclosed question. The use of a 4-nitrophenyl-substituted carbodiimide (**8e**) was the only critical entry, because of methodological constraints in that particular case. All products were isolated as mixtures of *E/Z* diastereoisomers and separated into the single components by column chromatography. An interesting manifestation of diastereoselectivity in this transformation process emerged from the unique feature that (2*Z*) diastereoisomers show also the *s-cis*-lactam moiety, (2*E*) diastereoisomers the *s-trans*-lactam group, while no other diastereoisomer was detected. To remove any unambiguity X-ray single crystal analysis of **12a** and **12b** (Figure 1), **15a** and **17a** were successfully performed. Although structural and stereochemical aspects of similar systems have recently been reviewed,[24] a considerable need exists for further progress in this field.

Figure 1. ORTEP Drawing of the Single Crystal Structure of *s-trans*-(2*E*)-14-Oxo-1-phenyl-2-(phenylamino)-1-azacyclotetradec-2-ene-3-carbonitrile (12a) and its *s-cis*-(2*Z*) Diastereoisomer 12b.[27]

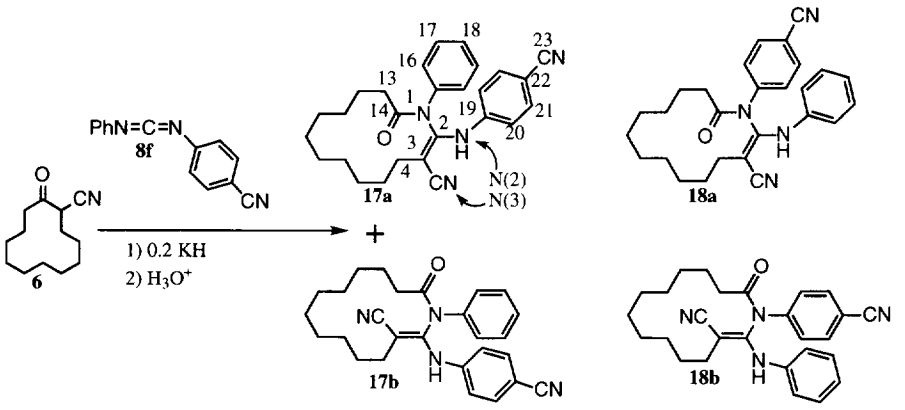


All structures were established by ^{1}H and ^{13}C NMR, IR, UV, electron impact (EI), chemical ionization (CI) and electrospray ionization (ESI) MS, collisionally induced dissociation (CID), X-ray and microanalysis. In the cases of the enaminolactams **16** and **17** a problem of regioselectivity arose from the fact that the unsymmetric substitution of the carbodiimides in question doubles the maximum number of isomers (Scheme 3). In agreement with our previous results only two diastereoisomers were isolated from the reaction of ketone **6** with *N*-(4-cyanophenyl)-*N'*-phenylcarbodiimide (**8f**) and their structures established as **17a** and **17b**. No trace of the other possible diastereoisomeric structures **18a** and **18b** (Scheme 3) could be detected. Molecular structures were assigned on the basis of the single crystal X-ray analysis of **17a** and ^{13}C NMR data. Comparison of the NMR data for **17a** and **17b** (electronwithdrawing group in the aromatic part) with those for the unsubstituted **12a** and **12b** and those for **15a** and **15b** (4-methoxy-substituted aryl groups) showed a visible difference in the shifts of the enamine carbon atoms C(2) and C(3) of these compounds (Table 1). The electronic density is shifted from the enamine group to the acceptor substituent in the 4-position of the aniline ring (compare **17** and **16**), since the NMR resonances for C(3) are shifted 5-7 ppm downfield relative to those of **12** and **15**. The same is true for the C(2) resonance of **17**, which is shifted upfield by 2-9 ppm relative to the other enaminolactams. If a substituted aryl group is located on the lactam nitrogen atom, no perceptible variance should be seen for the enamine moiety compared to the data of compounds **12** and **15**. Therefore the structures **18a** and **18b** can be excluded from further discussion. For a report on structure and physical properties of enamines and ene-1,1-diamines, including ^{13}C NMR data, see recent treatises of enamine chemistry.[25,26] This ring expansion reaction proceeds in a regioselective fashion with the more nucleophilic nitrogen atoms of the diarylcarbodiimide attacking intramolecularly the carbonyl group at the stage of intermediate **9** (Scheme 2).

Table 1. ^{13}C NMR Signals (ppm) for Compounds 12a, 12b, 15a, 17a and 17b.

C-ATOMS	12a	12b	15a	17a	17b
14	173.4	173.3	173.2	174.4	173.6
1	120.3	119.9	119.5	119.0	118.9
2	150.0	149.8	149.0	146.0	147.4
3	87.1	88.0	88.9	97.1	94.2

Scheme 3. Regioselectivity of the Reaction with Unsymmetrically Substituted Carbodiimides.



Mass Spectrometrical Evidence for a "*Retro* Reaction" in the Gas Phase. The enaminolactams **12-17** showed interesting spectrometric features. EI and CI spectra, principally in the case of compounds **13-17**, display intensive signals that can only derive from the formation of carbodiimide ions of type $[ArNCNAr']^{+\bullet}$ (**19**) or $[ArNCNAr'+H]^+$ (**20**). The experiments are summarized in Scheme 4, whereby the mechanisms of ion formation have not yet been elucidated. ESI spectra of the methanol solutions of these lactams revealed only $[M+Na]^+$ ions without trace of possible carbodiimide impurities that would appear as protonated methanol adducts. In order to prove that these additional signals originate from the molecular ions of the enaminolactams **12-17** CID measurements[28] were performed on a Finnigan TSQ mass spectrometer by selecting the $[M+Na]^+$ ions in the first quadrupole and submitting them to CID by impact on argon atoms in the second quadrupole. Daughter ion mode scanning of the third quadrupole allowed to record spectra with carbodiimide ions of type $[ArNCNAr'+H]^+$ (**20**) or $[ArNCNAr'+Na]^+$ (**21**) as pointed out in Figure 2. These results can be interpreted in terms of an unusual rearrangement leading to a *retro* reaction, which yields a carbonyl component (signal at m/z = 230, Figure 2) and a charged carbodiimide derivative.

Scheme 4. Carbodiimide Ions in the Mass Spectra of the Enaminolactams 12-17 under Different Ionization Conditions.

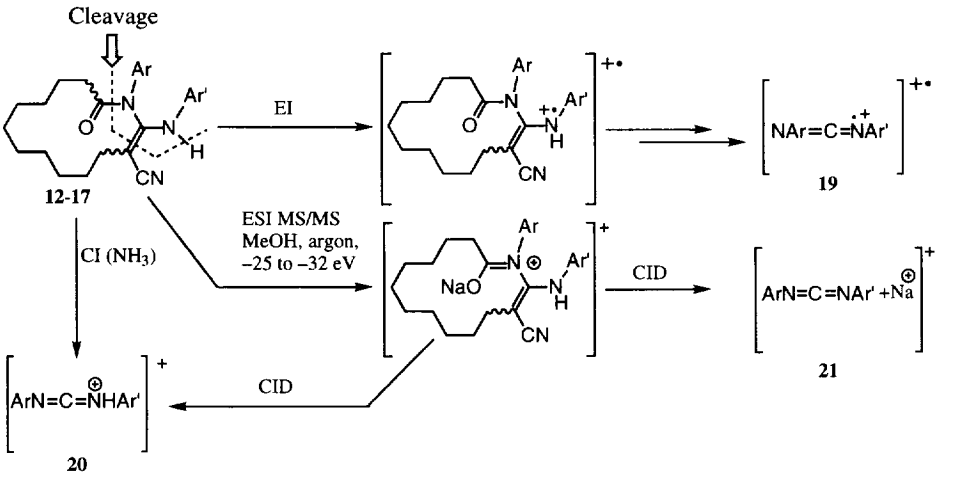
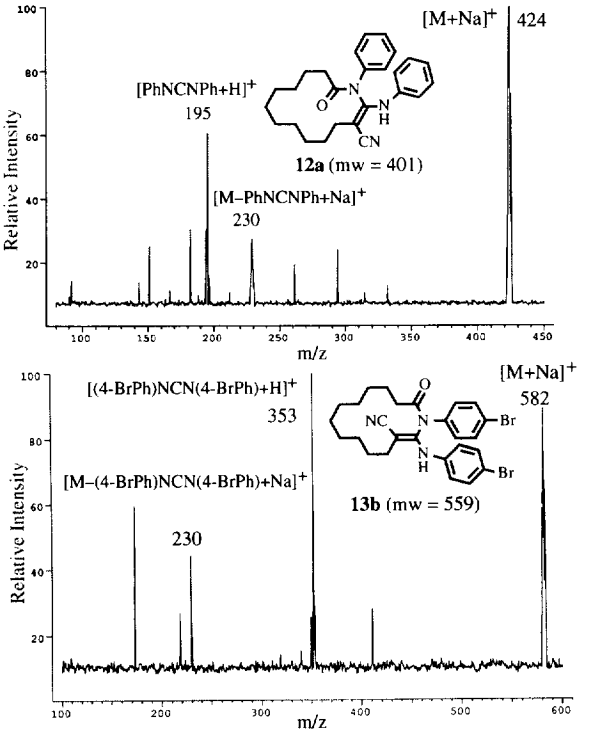
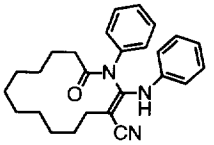


Figure 2. ESI MS/MS (CID) Spectra of the Enaminolactams 12a and 13b.

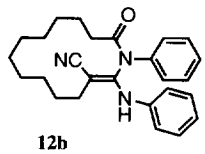


Scheme 5. *E/Z* and *s-cis/s-trans* Isomerization of the Enaminolactam 12.



12a
(*s-cis*, 2*E*)

CONDITIONS	*E/Z* RATIO
• $H^{\oplus}$(25°C, THF)	1.2
• ΔT (67°C, $CHCl_3$)	2.65
• hv (25°C, acetonitrile, λ = 308 nm)	0.87



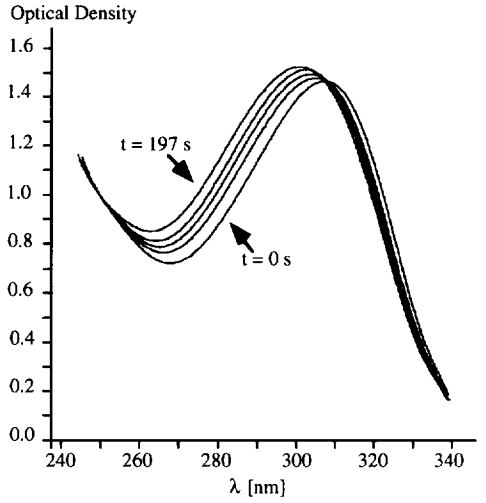
12b
(*s-trans*, 2*Z*)

In order to explore the possibility of thermal decomposition prior to ionization in the mass spectrometer, all relevant ion mass chromatograms of the EI and CI spectra were compared with the corresponding reconstructed ion current (RIC) plots. Further, compounds **15a** and **17a** were submitted to flash distillation in an evacuated glass tube. Actually, on the basis of these experiments, there is evidence that only an *E/Z* isomerization proceeds under thermal conditions, but no *retro* reaction or decomposition to carbodiimide derivatives. The root of all these observations lies probably in a rapid rearrangement of the ionized enaminolactam species before any other cleavage in the gas phase. These mass spectrometric features, encountered in the whole set of macrocyclic enaminolactams, are noteworthy as they pertain to the possibility of inverting the chemical outcome of this ground state ring expansion through an electronic or vibrational activation.

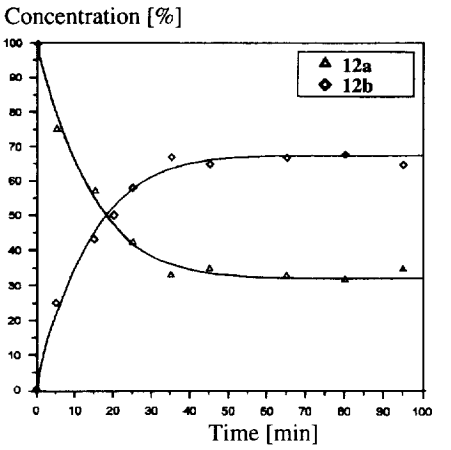
***E/Z* Isomerization Study.** In order to study its behavior the model compound **12a** was further submitted to thermal, photochemical, acidic and basic conditions. In analogy to literature precedents an especially facile *E/Z* isomerization (Scheme 5)[29,30] was observed, which holds the single diastereoisomeric couples together in an equilibrium. Under the reaction conditions of thermodynamic control a mixture of two (not four) diastereoisomers were obtained. The *E/Z* ratio of **12** ranged from 1.2 to 1.7. Therefore the *E* diastereoisomer **12a** is thermodynamically more stable, due to its *s-trans* configuration at the lactam group[31] and the less strained conformation of its 14-membered ring. The photochemical *E/Z* isomerization may lead to different directions. Direct photoisomerization (acetonitrile, at λ = 308 nm, see Figure 3 with a characteristic isosbestic point at 308 nm) gives a mixture of diastereoisomers with an *E/Z* ratio of 1:1.2 in the photostationary state, reversing therefore the equilibrium composition of the ground state. Variable *E/Z* ratios can be achieved employing photosensitizers possessing different triplet energies.[32,33] So acetone, both as sensitizer and solvent, gives a similar composition like a direct irradiation (with an *E/Z* ratio of 1:2, Figure 3), whereas the *E/Z* ratio was 2.1:1 in the case of benzophenone as sensitizer. Hence it is possible to enrich one or the other diastereoisomer in an equilibrium mixture, but not to isomerize completely one into the other.

Figure 3. *E/Z* Photoisomerization of 12a.

The Optical Density of the Analyte at Different Irradiation Times (λ = 308 nm, Acetonitrile)



Time Dependence of the **12a** and **12b** Concentrations (%) in Acetone at λ = 300 nm



CONCLUSION AND OUTLOOK

Scope and Limitations. By means of this new ring enlargement reaction interesting and functionalized *N,N'*-diaryl-substituted 14-membered, unsaturated enaminolactams (**12-17**) can be prepared from 2-oxocyclododecane-1-carbonitrile (**6**) and different diarylcarbodiimides (**8a-f**). The ring expansion reaction works successfully with big sized cycloalkanones but not with normal or medium sized rings, providing exclusively access to macrocyclic systems. Therefore *N*-alkyl groups cannot be introduced via the corresponding carbodiimides. The overall process ends up in the insertion of a CN building block into the C(1),C(2) bond of a cycloalkanone precursor, expanding the starting cycle by two atoms. Actually, on the basis of our experiments, there is evidence that only an *E/Z* isomerization takes place under thermal conditions, but no *retro* reaction or decomposition to carbodiimide derivatives, which may explain the observed signals in the mass spectra. The origin of these effects lies most likely in a rapid rearrangement of ionized enaminolactam species before any cleavage in the gas phase. Since recently isolated 14-membered natural lactams revealed potent biological activities,[34,35] the new macrocyclic compounds of this work could exhibit similar properties and shall be tested in this context.

EXPERIMENTAL

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Fresh distilled solvents were taken for chromatography and absolute solvents for reactions. All reactions were carried out in flame-dried glassware under nitrogen or argon atmosphere. Chromatographic separations were performed using silica gel 60 Merck (230-400 mesh ASTM) or 60 $F_{254+366}$. Melting points, not corrected, were measured on a Mettler FP52 apparatus (2°C and 0.2°C/min). IR spectra were determined with a Perkin Elmer 257 or 297 (characteristic frequencies in cm^{-1}). ^1H (200 or 300 MHz) and ^{13}C NMR spectra (50.4 or 75.5 MHz) were recorded on a Varian XL 200 or a Bruker ARX 300: δ in ppm relative to the solvent, coupling constants J in Hz, signal multiplicity from DEPT experiments. Mass spectrometry (EI with 70 eV, CI with NH_3 as reactand gas) was carried out on Finnigan MAT 90 and SSQ 700 mass spectrometers. The m/z values and % relative intensity are given. ESI (electrospray ionization) mass spectra were recorded with a Finnigan TSQ 700 and an electrostatic spray ion source operating at atmospheric pressure, followed by a triple stage quadrupole system. Data include the applied voltage, the solvent system used, and the flow rate followed by the m/z and RI values. Analyte concentrations ranged from 10^{-4} to 10^{-6} M. ESI MS/MS was performed on the same mass spectrometer by collisionally induced dissociation in the second quadrupole (CID) after selecting $[M+Na]^+$ ions in the first one and recording spectra through daughter ion mode scanning of the third quadrupole. The applied voltage, m/z of the selected primary ion, collision energy in eV, argon pressure, solvent system and flow rate are listed in brackets. The collision cell offset voltage varied from –20 to –50 eV. ESI mass spectra were recorded as one-scan spectra after averaging scans during 1 min at a scan time of 2 s. UV measurements were realized on Perkin Elmer 555, Perkin Elmer Lambda 9 UV/VIS/NIR and Hewlett Packard 8452 A (diode array) spectrophotometers. Photoisomerizations were carried out in quartz or Pyrex glassware (e. g. NMR tubes) using a Rayonet Photoreactor (16 fluorescent lamps, 8 Watt, at λ = 300 nm), a Dema 125 carousel or a *merry-go-round* assembly in an immersion-well apparatus with a high-pressure mercury lamp, Schott interference filters and quartz UV cells. Kinetic data for reactions were achieved by means of ^1H NMR and HPLC measurements at different irradiation times.

General Procedure for the Preparation of Carbodiimides. Carbodiimides were prepared from thioureas in 85 - 99% yields following the method of *Mitsunobu et al.*[23] Purification was achieved by distillation in *vacuo*, by crystallization in hexane at low temperatures or flash chromatography (short columns, silica gel, hexane). Since storage of such heterocumulenes is limited by their tendency to polymerize, all carbodiimides, except diphenylcarbodiimide, were immediately allowed to react with the carbonyl component 2-oxocyclododecane-1-carbonitrile, after their purity had been proven by satisfactory spectral data.

General Procedure for the Ring Enlargement Reaction of 2-Oxocyclododecane-1-carbonitrile (6) with Diarylcarbodiimides. The stirred soln. of compound **6** and the corresponding carbodiimide in THF or acetonitrile were added 0.2 equivalents of a 20% KH suspension or a 55% dispersion of NaH in mineral oil, under anhydrous conditions. The reaction was carried out between 50-80°C for 1 or 2 h and monitored by TLC (identification by UV light). Prior to work-up the reaction mixture was cooled down to 0 - 4°C. After addition of 5 ml of a 2 M NH_4Cl soln. in water, the mixture was diluted with water, poured into a separatory funnel and the water phase extracted with 3 Et_2O portions. The combined organic layers were washed with a

saturated NaCl soln. and dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude products in the organic residue were isolated by column chromatography (silica gel, hexane/Et_2O/CH_2Cl_2 4:2:1) and purified further by recrystallization or prep. TLC.

(2E/Z)-14-Oxo-1-phenyl-2-(phenylamino)-1-azacyclotetradec-2-ene-3-carbonitrile (**12**, as a mixture of two diastereoisomers). The mixture of 289 mg (1.4 mmol) ketone **6** and 274 mg (1.4 mmol) diphenylcarbodiimide (**8a**) in acetonitrile reacted upon treatment with 13 mg NaH (0.3 mmol) to give 337 mg **12** (0.84 mmol, 60% yield, *E/Z* ratio 1.2:1) as a mixture of diastereoisomers. The diastereoisomeric **12a** and **12b** were separated and purified as described above.

s-trans-(2E)-14-Oxo-1-phenyl-2-(phenylamino)-1-azacyclotetradec-2-ene-3-carbonitrile (**12a**), colorless crystals (hexane/Et_2O/EtOH), m.p. 151.0 - 152.4°C. IR (KBr): 3320, 2196, 1675, 1615, 1600. ^{1}H NMR (200 MHz): 7.24-7.16 (*m*, 5 H); 7.08-7.03 (*m*, 1 H); 6.81 (*d*, *J* = 7.4, 2 H); 6.59 (*d*, *J* = 7.1, 2 H); 6.23 (*s*, 1 H); 2.40-2.20 (*m*, 1 H); 2.16-2.13 (*m*, 2 H); 1.89 (*m*, 2 H); 1.49-1.21 (*m*, 15 H). ^{13}C NMR (50.4 MHz): 173.4, 150.0, 138.9, 138.5 (4 *s*); 129.0, 128.5, 126.8, 125.9, 124.2, 121.3 (6 *d*, 10 C); 120.3, 87.1 (2 *s*); 33.4, 27.4, 26.7, 26.6, 25.5, 25.3, 25.2, 24.2, 23.7, 23.1 (10 *t*). CI MS (NH_3): 402 (100, $[M+H]^+$). EI MS: 401 (100, $[M]^{+\bullet}$); 332 (7); 309 (8); 304 (15); 291 (8); 248 (77); 235 (10); 234 (13); 223 (30); 209 (9); 194 (5); 173 (10); 155 (30); 130 (6); 119 (6); 98 (10); 93 (21); 77 (56). ESI MS/MS (–3 kV, DAU 424, –31 eV, 2 mTorr argon, MeOH/MeCN, 2 µl/min): 424 (100, $[M+Na]^+$); 332 (10); 294 (24); 261 (20); 230 (27, [*M*–PhNCNPh+Na]$^+$); 195 (60, [PhNCNHPh]$^+$); 182 (30); 151 (25); 92 (10). Anal. calc. for $C_{26}H_{31}N_3O$ (401.55): C 77.77, H 7.78, N 10.46, O 3.98; found: C 77.97, H 7.98, N 10.70, O 3.35.

s-cis-(2Z)-14-Oxo-1-phenyl-2-(phenylamino)-1-azacyclotetradec-2-ene-3-carbonitrile (**12b**), colorless crystals (hexane/ Et_2O/EtOH), m.p. 152.9 - 155.3°C. IR (KBr): 3330, 2196, 1665, 1620, 1590. ^{1}H NMR (200 MHz): 7.24-7.13 (*m*, 5 H); 7.08-7.04 (*m*, 3 H); 6.75 (*d*, *J* = 7.7, 2 H); 6.06 (*s*, 1 H); 3.00-2.90 (*m*, 1 H); 2.49-2.39 (*m*, 1 H); 2.23-2.18 (*m*, 2 H); 2.14-1.89 (*m*, 1 H); 1.79-1.34 (*m*, 15 H). ^{13}C-NMR (50.4 MHz): 173.3, 149.8, 139.1, 138.5 (4 *s*); 129.3, 128.7, 127.0, 126.1, 124.5, 121.2 (6 *d*, 10 C); 119.9, 88.0 (2 *s*); 33.5, 27.8, 26.9, 26.7, 25.6, 25.3, 24.4, 24.1, 23.9, 23.3 (10 *t*). CI MS (NH_3): 419 (14, $[M+NH_4]^+$); 402 (100, $[M+H]^+$). EI MS: 401 (66, $[M]^{+\bullet}$); 332 (9); 309 (13); 304 (20); 291 (11); 279 (5); 248 (97); 235 (22); 234 (25); 223 (46); 209 (12); 194 (10); 173 (16); 155 (62); 130 (9); 117 (8); 104 (15); 93 (46); 92 (14); 77 (100). Anal. calc. for $C_{26}H_{31}N_3O$ (401.55): C 77.77, H 7.78, N 10.46, O 3.98; found: C 77.65, H 7.87, N 10.65, O 3.83.

(2E/Z)-1-(4-Bromophenyl)-2-(4-bromophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**13**, as a mixture of two diastereoisomers). The reaction of 0.647 g (3.12 mmol) **6**, 1.099 g (3.12 mmol) di(4-bromophenyl)carbodiimide (**8b**) and 0.125 g of KH suspension for 2 h at 50° C in THF, after work-up and column chromatography, yielded 888 mg (50.9%) of the (2*E*) diastereoisomer **13a** and 561 mg (32.1%) of (2*Z*)-**13b**, for a total yield of 83% (*E/Z* ratio 1.6).

s-trans-(2E)-1-(4-Bromophenyl)-2-(4-bromophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**13a**), colorless solid, m.p. 169.7 - 172.5°C. IR (KBr): 3450, 3280, 2197, 1695, 1640, 1590. ^{1}H NMR (300 MHz): 7.39-7.33 (*m*, 4 H); 6.72 (*d*, *J* = 8.4, 2 H); 6.51 (*d*, *J* = 7.3, 2 H); 6.17 (*s*, 1 H); 2.14-1.30 (*m*, 20 H). CI MS (NH_3): 558 (17, $[M+H]^+$); 378 (60); 351(50). EI MS: 557 (26, $[M]^{+\bullet}$); 460 (5); 446 (6); 404 (16); 391 (9); 379 (18); 350 (6); 324 (16); 299 (5); 275 (17); 274 (5); 261 (10); 249 (7); 233 (91); 221 (10); 208 (10); 207 (9); 195 (17); 181 (9); 180 (7); 171 (60); 155 (91); 143 (15); 91 (56); 90 (24); 81 (21); 79 (13); 77 (37).

s-cis-(2Z)-1-(4-Bromophenyl)-2-(4-bromophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**13b**), colorless solid, m.p. 174.4 - 177.2°C. IR ($CHCl_3$): 3410, 2200, 1692, 1620. ^1H NMR (300 MHz): 7.40-7.31 (*m*, 4 H); 6.95 (*d*, *J* = 8.8, 2 H); 6.62 (*d*, *J* = 8.8, 2 H); 5.95 (*s*, 1 H); 2.90-2.70 (*m*, 1 H); 2.40-1.20 (*m*, 19 H). ^{13}C NMR (50.4 MHz): 173.4, 148.9, 137.7, 137.5 (4 *s*); 132.2, 131.8, 127.5, 122.6 (4 *d*, 8 C); 120.7, 119.8, 117.2, 88.7 (4 *s*); 33.3, 27.5, 26.6, 25.5, 25.4, 25.2, 24.3, 23.7, 23.1 (9 *d*, 10 C). CI MS (NH_3): 558 (57, $[M+H]^+$); 351 (6). EI MS: 557 (26, $[M]^{+\bullet}$); 404 (16); 393 (17); 388 (8); 380 (15); 379 (12); 366 (13); 350 (19); 324 (10); 311 (12); 278 (11); 264 (13); 251 (10); 250 (9); 233 (64); 223 (12); 208 (10); 195 (21); 181 (10); 171 (82); 155 (82); 143 (16); 91 (37); 90 (56); 81 (22); 79 (21); 77 (25); 76 (57); 75 (48); 69 (38); 55 (100). ESI MS (–3 kV, MeOH/$CHCl_3$, 2 µl/min): 582 ($[M+Na]^+$); 1142 ($[2M+Na]^+$); 1700 ($[3M+Na]^+$). ESI MS/MS (–3 kV, DAU 582, –28 eV, 2 mTorr argon, MeOH/$CHCl_3$, 2 µl/min): 582 (90, $[M+Na]^+$); 411 (30); 353 (100, [(4-BrPh)NCNH(4-BrPh)]$^+$); 230 (44, [*M*–(4-BrPh)NCN(4-BrPh)+Na]$^+$); 218 (27); 174 (60).

(2E/Z)-1-(4-Chlorophenyl)-2-(4-chlorophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**14**, as a mixture of two diastereoisomers). The mixture of 0.959 g (4.625 mmol) **6**, 1.217 g (4.625 mmol) di-(4-chloroophenyl)carbodiimide **8c** gave upon treatment with 0.185 g of a KH suspension for 1 h at 67°C 0.634 g (1.35 mmol, 29.1%) of the (2*E*) diastereoisomer **14a** and 0.483 g (22.2%) of the other diastereoisomer **14b**, after work-up and column chromatography, total yield 51.3% (*E/Z* ratio 1.3).

s-trans-(2E)-1-(4-Chlorophenyl)-2-(4-chlorophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**14a**), colorless solid, m.p. 188 - 189°C. IR ($CHCl_3$): 3410, 3290, 2200, 1680, 1637, 1598. ^1H NMR (300 MHz): 7.29-7.23 (*m*, 4 H); 6.82 (*d*, *J* = 8.3, 2 H); 6.62 (*d*, *J* = 7.9, 2 H); 6.32 (*s*, 1 H); 3.57-3.50 (*m*, 1 H); 2.34-1.11 (*m*, 19 H). ^{13}C NMR (75.5 MHz): 173.2, 149.0, 137.3, 136.9, 132.8, 129.9 (6 *s*); 129.4, 128.9, 127.2, 122.3 (4 *d*, 8 C); 119.5, 88.9 (2 *s*); 33.3, 29.0, 27.7, 26.7, 26.6, 25.5, 25.2, 24.3, 23.8, 23.1 (10 *t*). CI MS (NH_3): 470 (43, $[M+H]^+$); 436 (9, [*M*–Cl+2H]$^+$); 263 (100, [(4-ClPh)NCN(4-ClPh)+H]$^+$). EI MS: 469 (14, $[M]^{+\bullet}$); 343 (9); 372 (9); 343 (28); 320 (51); 316 (28); 303 (11); 302 (11); 291 (11); 280 (8); 262 (100); 245 (8); 229 (13); 218 (9); 207 (18); 202 (36); 200 (35); 189 (80); 178 (78); 164 (11); 163 (10); 151 (24); 137 (14); 127 (49); 111 (78); 99 (24); 90 (25); 75 (93).

s-cis-(2Z)-1-(4-Chlorophenyl)-2-(4-chlorophenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**14b**), colorless waxy solid. IR ($CHCl_3$): 3410, 3300, 2200, 1685, 1640, 1598. ^1H NMR (300 MHz): 7.31-7.21 (*m*, 4 H); 7.03 (*d*, *J* = 8.8, 2 H); 6.71 (*d*, *J* = 8.8, 2 H); 6.08 (*s*, 1 H); 2.60-1.11 (*m*, 20 H). ^{13}C-NMR (75.5 MHz): 174.0, 147.2 (2 *s*); 138.2 (*s*, 2 C); 134.3 (*s*); 129.4, 129.1 (2 *d*, 4 C); 129.1 (*s*); 128.4, 121.9 (2 *d*, 4 C); 119.4, 90.6 (2 *s*); 33.6, 29.0, 27.7, 26.7, 25.7, 25.4, 25.1, 24.9, 24.0 (9 *t*, 10 C). CI MS (NH_3): 470 (45, $[M+H]^+$); 263 (100, [(4-ClPh)NCN(4-ClPh) +H]$^+$). EI MS: 469 (34, $[M]^{+\bullet}$); 400 (12); 372 (13); 359 (9); 343 (13); 320 (25); 316 (69); 303 (27); 291 (26); 280 (13); 262 (98); 245 (5); 232 (10); 229 (7); 218 (8); 207 (15); 203 (30); 200 (13); 189 (92); 178 (23); 164 (17); 153 (27); 151 (21); 138 (16); 127 (78); 111 (76); 99 (23); 90 (35); 75 (100).

(2E/Z)-1-(4-Methoxyphenyl)-2-(4-methoxyphenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**15**, as a mixture of two diastereoisomers). To a solution of ketone **6** (1.2 g, 5.78 mmol) and 1.47 g (5.78 mmol) di(4-methoxyphenyl)carbodiimide (**8d**) were added 0.275 g (1.375 mmol) of a KH suspension and heated for 9 h at 67°C. After work-up and column chromatography 0.886 g (33.2%) of the (2*E*) lactam **15a** and 0.605 g (22.7%) of (2*Z*)-**15b** were isolated (55.9% total yield, *E/Z* ratio 1.5).

s-trans-(2E)-1-(4-Methoxyphenyl)-2-(4-methoxyphenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**15a**), colorless crystals (hexane/Et_2O/EtOH, $CHCl_3$), m.p. 114.4 - 116.4°C. IR (KBr): 3300, 2190, 1680, 1630. ^1H NMR (300 MHz): 6.77-6.69 (*m*, 4 H); 6.64 (*d*, *J* = 8.8, 2 H); 6.40 (*d*, *J* = 8.7, 2 H); 6.12 (*s*, 1 H); 3.73 (*s*, 3 H); 3.71 (*s*, 3 H); 2.28-1.11 (*m*, 20 H). ^{13}C NMR (75.5 MHz): 174.3, 159.1, 156.8, 149.5, 132.5, 132.3 (6 *s*); 128.4, 123.8 (2 *d*, 4 C); 120.3 (*s*); 114.1 (*d*, 4 C); 85.9 (*s*); 55.4 (*q*, 2 C); 33.2, 27.6, 26.8, 25.7, 25.4, 24.9, 24.2, 24.0 (8 *t*, 10 C). CI MS (NH_3): 462 (39, $[M+H]^+$); 255 (100, [(4-MeOPh)NCN(4-MeOPh)+H]$^+$). EI MS: 461 (100, $[M]^{+\bullet}$); 339 (24); 314 (16); 311 (10); 308 (46); 296 (7); 283 (17); 254 (32); 239 (17); 231 (6); 228 (11); 217 (11); 203 (28); 185 (41); 149 (11); 147 (9); 134 (10); 123 (79); 108 (24); 92 (17); 77 (32); 57 (10); 55 (19).

s-cis-(2Z)-1-(4-Methoxyphenyl)-2-(4-methoxyphenylamino)-14-oxo-1-azacyclotetradec-2-ene-3-carbonitrile (**15b**), waxy solid. IR ($CHCl_3$): 3410, 3310, 2195, 1675, 1630. ^1H NMR (300 MHz): 6.93 (*d*, *J* = 9.0, 2 H); 6.77-6.71 (*m*, 6 H); 5.75 (*s*, 1 H); 3.76 (*s*, 3 H); 3.74 (*s*, 3 H); 2.85-3.05 (*m*, 1 H); 2.40-1.11 (*m*, 19 H). ^{13}C NMR (75.5 MHz): 173.3, 158.2, 157.1, 151.0, 131.9, 131.1 (6 *s*); 127.4, 124.2 (2 *d*, 4 C); 120.5 (*s*); 114.3, 113.8 (2 *d*, 4 C); 85.2 (*s*); 55.4, 55.2 (2 *q*); 33.3, 27.3, 26.9, 26.6, 25.5, 25.4, 25.3, 24.3, 23.8, 23.2 (10 *t*). CI MS (NH_3): 462 (14, $[M+H]^+$); 255 (100, [(4-MeOPh)NCN(4-MeOPh)+H]$^+$). EI MS: 461 (8, $[M]^{+\bullet}$); 254 (100); 239 (79); 224 (5); 211 (6); 196 (7); 92 (10); 77 (14).

s-trans-(2E)-2-(4-Nitrophenylamino)-14-oxo-1-phenyl-1-azacyclotetradec-2-ene-3-carbonitrile (**16a**). From the reaction of 0.763 g (3.7 mmol) **6**, 0.88 g (3.7 mmol) *N*-(4-nitrophenyl)-*N'*-phenylcarbodiimide (**8e**) and 0.147 g of a KH suspension, after refluxing in THF for 2 h, only one diastereoisomer (**16a**, 0.170 g, 0.38 mmol, 10.3%, waxy solid) was isolated by column chromatography. Comparing the chromatographic behavior on silica gel (hexane/Et_2O/CH_2Cl_2) and the spectral data of the other derivatives, a (2*E*) configuration and the position of the nitro-substituted phenyl ring were assigned. The second diastereoisomer **16b** could not be isolated from this rather complex reaction mixture.

IR ($CHCl_3$): 3410, 2210, 1670, 1620, 1600. ^1H NMR (300 MHz): 8.10 (*d*, *J* = 9.0, 2 H); 7.30-7.25 (*m*, 3 H); 6.84 (*d*, *J* = 9.4, 2 H); 6.80-6.71 (*m*, 2 H); 6.35 (*s*, 1 H); 2.35-1.20 (*m*, 20 H). ^{13}C NMR (75.5 MHz): 174.4, 146.3 (2 *s*); 142.3 (*s*, 2 C); 139.2 (*s*); 129.6, 127.1, 125.4 (3 *d*, 7 C); 118.5 (*s*); 117.7 (*d*, 2 C); 98.0 (*s*); 33.7, 28.1, 26.7, 25.7, 25.4, 24.9, 24.0 (7 *t*, 10 C). CI MS (NH_3): 464 (64, $[M+NH_4]^+$); 447 (72, $[M+H]^+$); 417 (100, $[M-NO+H]^+$); 257 (80, [(4-NO_2Ph)NCNPh+NH_4]$^+$); 195 (39, [(4-NO_2Ph)NCNPh–CN+2H]$^+$); 156 (37); 194 (46, $[PhNH_3]^+$). EI MS: 446 (5, $[M]^{+\bullet}$); 309 (10); 293 (16); 280 (6); 273 (9); 268 (9); 262 (8); 239 (100); 209 (19); 194 (17); 193 (14); 164 (6); 155 (11); 119 (11); 93 (10); 90 (21); 77 (37). ESI MS (–3.3 kV, DAU 469, –31 eV, 2 mTorr argon, MeOH/$CHCl_3$, 2 µl/min): 469 (90, $[M+Na]^+$); 468 (100, $[M-H+Na]^{+\bullet}$); 435 (18); 414 (26); 326 (18); 305 (25); 274 (10); 260 (18); 240 (38, [(4-NO_2Ph)NCNPh]$^+$); 194 (20); 174 (56); 162 (18).

(2E/Z)-2-(4-Cyanophenylamino)-14-oxo-1-phenyl-1-azacyclotetradec-2-ene-3-carbonitrile (**17**, mixture of two diastereoisomers). A solution of 0.77 g (3.7 mmol) **6**, 0.79 g (3.7 mmol) *N*-(4-cyanophenyl)-*N'*-phenylcarbodiimide (**8g**) and 0.176 g of a KH suspension was stirred for 1 h at 67°C. Work-up and chromatographic separation afforded 0.948 g (2.2 mmol, 60%) of a (1:1)-distereoisomeric mixture of the (2*E*) lactam **17a** and the (2*Z*) **17b**, along with 0.3 g (39%) of the starting ketone **6**.

s-trans-(2E)-2-(4-Cyanophenylamino)-14-oxo-1-phenyl-1-azacyclotetradec-2-ene-3-carbonitrile (**17a**), colorless crystals (hexane/Et_2O/EtOH), m.p. 169 - 171°C. IR ($CHCl_3$): 3410, 3290, 2230, 2205, 1680, 1620, 1605. ^1H NMR (300 MHz): 7.49 (*d*, *J* = 8.6, 2 H); 7.28-7.15 (*m*, 4 H); 6.83 (*d*, *J* = 8.2, 2 H); 6.75-6.69 (*m*, 2 H); 6.38 (*s*, 1 H); 2.40-2.10 (*m*, 3 H); 1.80 (*m*, 2 H); 1.80-1.20 (*m*, 15 H). ^{13}C NMR (75.5 MHz): 174.4, 146.0, 144.3, 139.3 (4 *s*); 133.3, 129.5 (2 *d*, 4 C); 128.8, 127.1 (2 *d*, 3 C); 119.0, 118.7 (2 *s*); 118.4 (*d*, 2 C); 105.2, 97.0 (2 *s*); 33.7, 28.0, 26.7, 25.7, 25.4, 24.9, 24.0 (7 *t*, 10 C). CI MS (NH_3): 427 (20, $[M+H]^+$); 237 (100, [(4-CNPh)NCNPh+NH_4]$^+$); 220 (10, [(4-CNPh)NCNPh+H]$^+$); 195 (10). EI MS: 426 (77, $[M]^{+\bullet}$); 357 (11); 329 (21); 315 (7); 309 (8); 304 (7); 273 (84); 260 (23); 248 (48); 244 (32); 235 (10); 234 (8); 219 (100); 198 (23); 194 (15); 180 (8); 173 (10); 155 (20); 144 (8); 119 (9); 102 (79); 93 (29); 77 (35). ESI MS/MS (–3.3 kV, DAU 449, –30 eV, 2 mTorr argon, MeOH/$CHCl_3$, 2 µl/min): 449 (45, $[M+Na]^+$); 448 (45, $[M-H+Na]^+$); 431 (10); 350 (20); 317 (10); 303 (22); 242 (100, [(4-CNPh)NCNPh+Na]$^+$); 201 (25); 187 (10); 140 (60).

s-cis-(2Z)-2-(4-Cyanophenylamino)-14-oxo-1-phenyl-1-azacyclotetradec-2-ene-3-carbonitrile (**17b**), a waxy solid. IR ($CHCl_3$): 3410, 3290, 2230, 2205, 1685, 1625, 1605. ^1H NMR (300 MHz): 7.40 (*d*, *J* = 8.6, 2 H); 7.18-7.05 (*m*, 6 H); 6.70 (*d*, *J* = 8.6, 2 H); 3.05-2.85 (*m*, 1 H); 2.60-2.40 (*m*, 1H); 2.40-1.10 (*m*, 18 H). ^{13}C NMR (75.5 MHz): 173.6, 147.4, 143.6, 138.6 (4 *s*); 133.3, 129.0, 127.6, 126.2 (4 *d*, 7 C); 118.9, 118.6 (2 *s*); 118.4 (*d*, 2 C); 105.5, 94.2 (2 *s*); 33.2, 29.0, 28.4, 26.6, 25.6, 25.2, 24.3, 23.8, 23.1 (9 *t*, 10 C). CI MS (NH_3): 444 (8, $[M+NH_4]^+$); 427 (12, $[M+H]^+$); 237 (100, [(4-CNPh)NCNPh+NH_4]$^+$); 220 (9, [(4-CNPh)NCNPh +H]$^+$). EI MS: 426 (5, $[M]^{+\bullet}$); 273 (22); 248 (15); 219 (100); 194 (10); 155 (8); 118 (9); 91 (21); 77 (35). ESI MS (–3.3 kV, MeOH/$CHCl_3$, 2 µl/min): 449 ([M+Na]$^+$); 876 ([2M+Na]$^+$).

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REFERENCES

1. Ognyanov, V.; Hesse, M. *Helv. Chim. Acta* **1989**, *72*, 1522-1526.
2. Ognyanov, V.; Hesse, M. *Helv. Chim. Acta* **1990**, *73*, 272-276.
3. Koch, T.; Ognyanov, V.; Hesse, M. *Helv. Chim. Acta* **1992**, *75*, 62-68.
4. Hesse, M. *Ring Enlargement in Organic Chemistry*; Verlag Chemie: Weinheim. 1991.
5. Saito, T.; Ohmori, H.; Furuno, E.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 22-24.
6. Jochims, J. C.; Lubberger, H.-J.; Dahlenburger, L. *Chem. Ber.* **1990**, *123*, 499-503.
7. Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929-939.
8. Molina, P.; Diáz, I.; Tárraga, A. *Tetrahedron* **1995**, *51*, 5617-5630.
9. Trifonov, L. S.; Christova, N. I.; Dimitrov, V. S.; Orahovats, A. S. *Helv. Chim. Acta* **1992**, *75*, 1262-1266.

10. Sankhavasi, W.; Kohmoto, S.; Yamamoto, M.; Nishio, T.; Iida, I.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 935-937.
11. Baeg, J.-O.; Alper, H. *J. Org. Chem.* **1992**, *57*, 157-162.
12. Fujiwara, M.; Baba, A.; Matsuda, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1069-1073.
13. Cristau, H.-J.; Perraud-Darcy, A.; Ribeill, Y. *Tetrahedron Lett.* **1992**, *33*, 2693-2696.
14. Ojima, I.; Higuchi, H.; Sata, Y.; Yamamoto, H.; Koizumi, T.; Iyoda, M.; Yamamoto, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2111-2120.
15. Augustin, M.; Günther, E. *Z. Chem.* **1990**, 169-170.
16. Föhlisch, B.; Herter, R.; Wolf, E.; Stezowski, J. J.; Eckle, E. *Chem. Ber.* **1982**, *115*, 355-380.
17. Süsse, M.; Hájicek, J.; Hesse, M. *Helv. Chim. Acta* **1985**, *68*, 1986-1997.
18. Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613-616.
19. Shimizu, I.; Ishii, H. *Tetrahedron* **1994**, *50*, 487-495.
20. Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77-90.
21. Xie, Z.-F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820-826.
22. Koch, T., Dissertation Thesis, University of Zurich 1994.
23. Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* **1970**, *26*, 5731-5736.
24. Cervinka, O. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; J. Wiley & Sons: Chichester, 1994; Vol. 1, pp. 219-254.
25. Huang, Z.-T.; Wang, M.-X. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; J. Wiley & Sons: New York, 1994; Vol. 2, pp. 1303-1364.
26. Chiara, J. L.; Gomez-Sanchez, A. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; J. Wiley & Sons: Chichester, 1994; Vol. 1, pp. 279-404.
27. The atomic coordinates are deposited at the Cambridge Crystallographic Data Center, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EW, England.
28. Busch, K. L.; Glish, G. L.; McLuckey, S. A. *Mass Spectrometry/Mass Spectrometry*; Verlag Chemie: New York. 1988.
29. Siegel, M. G.; Winkler, J. D. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; J. Wiley & Sons: Chichester, 1994; Vol. 1, pp. 637-680.
30. Chiacchio, U.; Musumarra, G.; Purrello, G. *J. Chem. Soc., Perkin Trans. II* **1988**, 1591-1593.
31. Robin, M. B.; Bovey, F. A.; Basch, H. In *The Chemistry of Amides*; Zabicky, J., Ed.; J. Wiley & Sons: London, 1970; Vol. pp. 1-72.
32. Klessinger, M.; Michl, J. *Lichtabsorption und Photochemie organischer Moleküle*; Verlag Chemie: Weinheim. 1989.
33. Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. *J. Am. Chem. Soc.* **1964**, *86*, 3197-3217.
34. Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6403-6405.
35. Naruse, N.; Konishi, M.; Oki, T.; Inouye, Y.; Kakisawa, H. *J. Antibiot.* **1991**, *44*, 756-761.

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