Synthesis and Stereochemical Assignments of *cis*- and *trans*-1-Amino-4-ethylcyclohexa-2,5-diene as Models for Amiclenomycin

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In memoriam Sophie Carillon[†]

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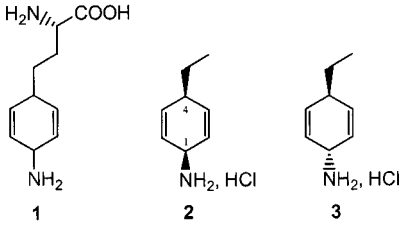
As an approach to the synthesis of amiclenomycin (**1**), we describe here the synthesis of a 1-aminocyclohexa-2,5-diene moiety. The *cis* isomer **2** was obtained by means of a Diels–Alder reaction between *trans*-1,2-bis(phenylsulfonyl)ethylene and *N*-(allyloxycarbonyl)hexa-1,3-diene (**13**), followed by reductive elimination of the phenylsulfinyl groups. To obtain the *trans* isomer **3**, *O*-(trimethylsilyl)hexa-1,3-diene (**16**) was used. This afforded the *cis*-hydroxylated Diels–Alder adducts **18**, which were transformed into the corresponding *trans*-amino derivative by a Mitsunobu reaction. The stereochemistry of several intermediates was confirmed by X-ray crystallography. Conformations calculated by molecular modelling were in excellent agreement with those observed in the X-ray structures. According to the NMR spectroscopic data, the cyclohexadiene final products are planar.

Introduction

Amiclenomycin (**1**; Scheme 1) was isolated from *Streptomyces lavendulae* by Okami and co-workers in 1974.[1] It was described as an inhibitor of diaminopelargonic acid (DAPA) synthase, a PLP-dependent enzyme involved in the biosynthetic pathway of biotin. As a consequence, amiclenomycin presents in vitro antibiotic properties, which were found to be specific for mycobacteria.[2]

In order to study the mechanism of inhibition of DAPA synthase further, and as the natural product was no longer available, we undertook the synthesis of amiclenomycin. In addition, the *trans* geometry originally assigned to the natural product[1] on the basis of the value of the long-range coupling constant (^5J) between the two allylic hydrogen atoms of this single isomer was questionable, and it was important to obtain both isomers to establish the stereochemistry rigorously.



Scheme 1

Because of the expected instability of the 1-amino-2,5-cyclohexadienyl ring, prone to conjugation and (or) aromatisation, we first examined the synthetic routes to this moiety on a simple model before the construction of the amino acid side chain. The synthesis of both isomers, **2** and **3**, together with the assignment of their stereochemistries, are described in this paper.

Results and Discussion

Synthetic Approaches to the Cyclohexadienyl Ring

We first examined whether the aminocyclohexadienyl ring could be obtained through Birch reduction of the appropriate aromatic compound. It is well established that the regiochemistry of this reduction is determined by the electron-donating or -accepting properties of the substituents.

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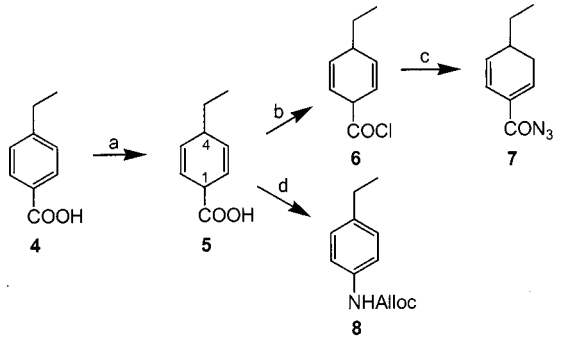
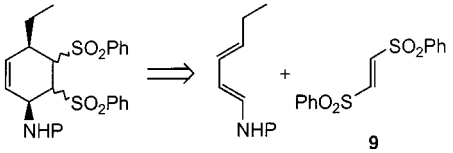
[†] S. C. died recently in a car accident. This paper is dedicated to her, as she performed a large part of this work.

To obtain a 1-substituted 2,5-cyclohexadiene, an electron-accepting substituent at C-1 is necessary, which rules out aniline derivatives as starting materials. A nitro group is also precluded, since it would be reduced more rapidly than the aromatic ring, but a carboxylic group could be a suitable choice. Indeed, when the acid **4** was reduced with Li/NH_3,[3] the expected 2,5-diene **5** was obtained, as a 1:2 mixture of isomers. The corresponding acid chloride **6** could also be prepared, but conjugation of the double bonds was always observed during its conversion into the acyl azide. The direct acid → acyl azide transformation with diphenylphosphoryl azide, followed by quenching with allyl alcohol,[4] was also attempted. In that case, only the aromatic compound **8** could be isolated (Scheme 2).

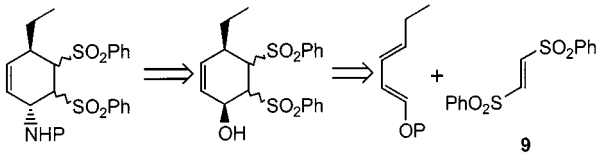


Scheme 2. Reagents and conditions: (a) (i) Li/NH_3, −78 °C, 15 min, (ii) EtOH, 96%; (b) $(COCl)_2$, CH_2Cl_2, room temp., 1 h, 88%; (c) NaN_3, H_2O/acetone, 0 °C, 1 h, 90%; (d) $(C_6H_5O)_2P(O)N_3$, NEt_3, allyl alcohol, reflux, 1 h, 15%

Thus, another route had to be explored, in the form of a Diels−Alder reaction between a 1,3-diene and an acetylene equivalent, since acetylene itself is not reactive enough. From the possible acetylene equivalents, we selected *trans*-1,2-bis(phenylsulfonyl)ethylene (**9**), developed by De Lucchi et al.,[5] because of its high reactivity (the *trans* isomer is much more reactive than the *cis* one) and the mild conditions used to regenerate the double bond. Reductive elimination of the phenylsulfinyl groups can indeed be achieved at room temperature with sodium amalgam in methanol buffered with potassium dihydrogenophosphate.[5] The Diels−Alder reaction between *trans*-1,2-bis(phenylsulfonyl)-ethylene and an *N*-protected (1*E*,3*E*)-diene should provide the *cis* compound (Scheme 3). The *trans* isomer could be obtainable from a Mitsunobu reaction on a *cis*-hydroxy compound formed in a Diels−Alder reaction with an *O*-protected (1*E*,3*E*)-diene (Scheme 4).



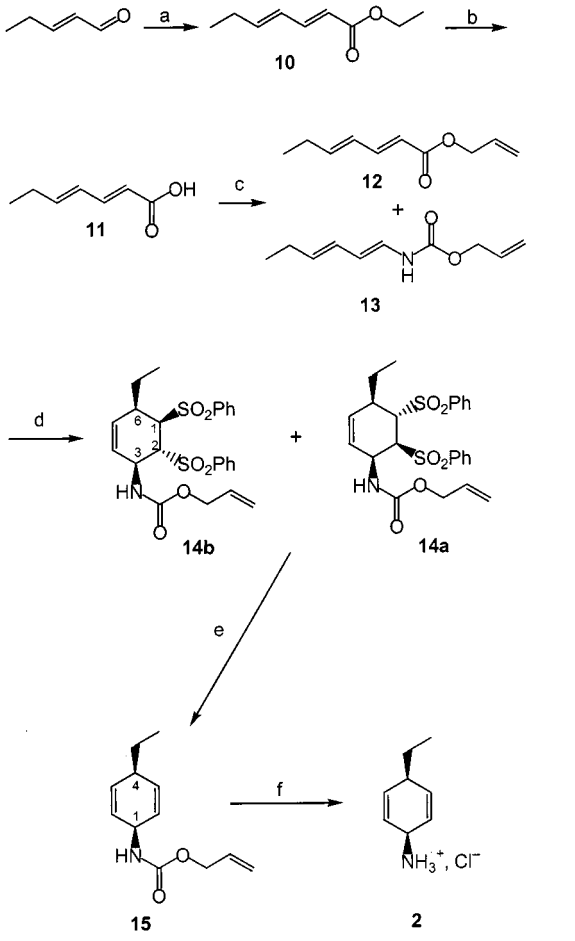
Scheme 3



Scheme 4

Synthesis of the *cis* Isomer 2

The synthesis of the *cis* isomer is depicted in Scheme 5. As a diene we chose compound **13**, in which the amino group is protected with an allyloxycarbonyl group, since this can be removed under mild, neutral conditions[6] compatible with the cyclohexadienyl structure. The starting material was *trans*-pent-2-enal, which was transformed into the *trans*-conjugated ester **10** through a Wittig−Horner reaction with triethyl phosphonoacetate. After saponification, the resulting acid **11** was submitted to a Curtius reaction, according to Shiori et al.,[4] with triethylamine and diphenylphosphoryl azide in refluxing allyl alcohol to give only the (1*E*,3*E*)-diene **13**. The poor yield of isolated carba-



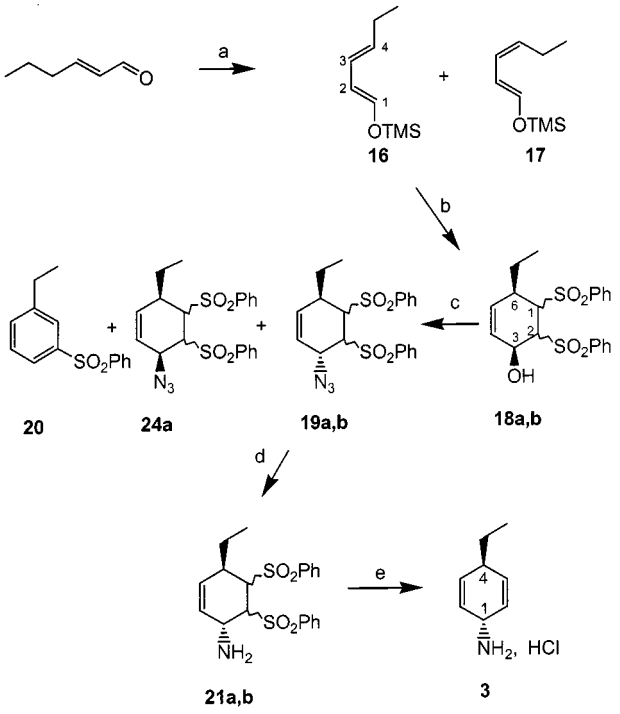
Scheme 5. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −20 °C, 30 min, 70%; (b) NaOH, MeOH/H_2O, 50 °C, 50 min, 92%; (c) $(PhO)_2P(O)N_3$, NEt_3, allyl alcohol, reflux, 3.5 h, **13**: 31%, **12**:20%; (d) **9**, *ortho*-xylene, 120 °C, 49%; (e) Na(Hg), KH_2PO_4, MeOH, room temp., 30 min, 87%; (f) (i) $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, room temp., 30 min; (ii) HCl/H_2O, 80%

mate **13** can be explained by the concomitant formation of the allyl ester **12** and probably also by polymerisation reactions.

Cycloaddition between diene **13** and disulfone **9** in *ortho*-xylene provided a mixture of diastereoisomers **14a** and **14b** in a 60:40 ratio. The structure of **14a** was established by X-ray crystallography (see below). Desulfonylation of the **14a/14b** mixture with sodium amalgam gave the cyclohexadiene **15**. After cleavage of the allyloxycarbonyl group by $Pd(PPh_3)_4$ in the presence of phenylsilane,[6] the target compound **2** was obtained.

Synthesis of the *trans* Isomer 3

The synthesis of **3**, shown in Scheme 6, requires an oxygenated diene. We chose a silylated derivative, easily obtainable by the Bozouin[7]−Danishefsky[8] method; *trans*-hex-2-enal, activated with $ZnCl_2$, was treated with bromotrimethylsilane in the presence of triethylamine to afford **16** and **17** in a 40:60 ratio. The two dienes could not be separated by distillation, but the mixture could be used in the Diels−Alder reaction, as only the required (1*E*,3*E*) isomer **16** is reactive under the conditions used. However, the proportion of **16** was only 35% and we tried to improve it by isomerisation of the mixture. Indeed, an 80:20 ratio of **16/17** was obtained after treatment with a catalytic amount of iodine in ether at room temperature. Removal of iodine was necessary for the Diels−Alder reaction to occur with an acceptable yield. This was achieved by treatment with a sodium thiosulfate solution adjusted to pH = 10.5.

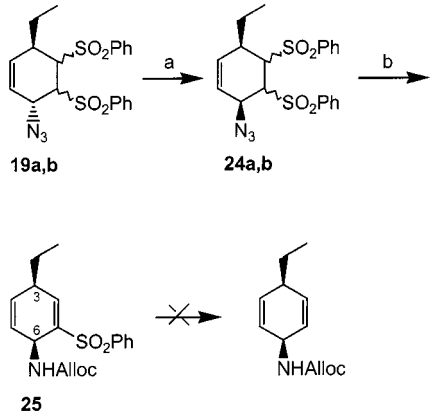


Scheme 6. Reagents and conditions: (a) TMSBr, NEt_3, $ZnCl_2$, toluene, 12 h, reflux, 81%; (b) (i) **9**, *ortho*-xylene, 120 °C, 24 h; (ii) MeOH, H^+, 30 min, 85%; (c) PPh_3, DIAD, $(PhO)_2P(O)N_3$, 0 °C, 3.5 h, **19a**,**b**: 50%, **20**: 30%; (d) H_2 5 bar, Pd (5%)/$CaCO_3$/Pb (3.5%), THF/*i*PrOH, room temp.; (e) (i) Na(Hg), MeOH, KH_2PO_4, room temp., 2 h; (ii) HCl, 41% from **19**

The temperature of the Diels−Alder reaction, performed in *ortho*-xylene, was optimised at 120 °C. The yields, calculated on the desilylated products **18a** and **18b** (based on the proportion of **16** in the mixture), were 85% and 54%, respectively, when the 40:60 mixture (isolated by distillation) or the 80:20 mixture (obtained after isomerisation and carefully dried) were used as starting material. Hence, the final yield was not improved by the isomerisation of the diene. The lower yield with the latter mixture may be due to remaining traces of water. The ratio of **18a/18b** was reproducibly 25:75.

To introduce the amino group with inversion of configuration, the obvious method was the Mitsunobu reaction. As nucleophiles, we first tried to use *N*-protected amines $HN(Alloc)_2$ [9] or HN(Ts)Alloc[10] under classical Mitsunobu conditions (DIAD, PPh_3, CH_2Cl_2), but the starting material was recovered unchanged. On the other hand, the alcohols **18** could be transformed into azides **19** with diphenylphosphoryl azide.[11] The aromatic compound **20** was also isolated, with a reproducible yield of 30%. The relative proportions of **19a/19b** were about 40:60, starting from a 25:75 mixture of alcohol **18a/18b**. We have no satisfactory explanation for this development, which cannot be accounted for by a selective aromatisation of **18a** and **18b**. Furthermore, during the Mitsunobu reaction we also observed the formation of another compound (5−10%), namely the azide **24a**, in which the azido group was epimerised (see below). A selective reduction of the azido group of **19** could be achieved with hydrogen in the presence of Lindlar catalyst.[12] The **19a/19b** mixture was transformed into **21a** and **21b**, which gave **3** after desulfonylation.

In dichloromethane or chloroform solution at room temperature, azides **19a** and **19b** were not stable and were transformed into azides **24a** and **24b** until a constant 33:66 ratio of **19/24** was reached (Scheme 7). Compounds **24a** and **24b**, according to their NMR spectra, had to possess the attributed structures. The reactivity of these isomers was quite different from that of **19a** and **19b**. Indeed, treatment of

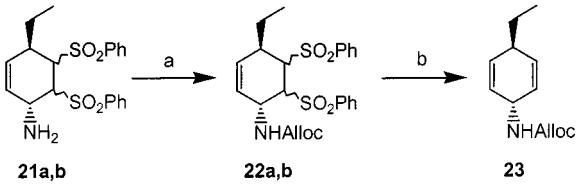


Scheme 7. Reagents and conditions: (a) CH_2Cl_2, room temp., 3 days, **19**: 33%, **24**: 66%; (b) (i) H_2 (5 bar), Lindlar catalyst [Pd (5%)/$CaCO_3$/Pb (3.5%)], 1:1 *i*PrOH/THF, room temp., 12 h; (ii) $ClCO_2All$, $NaHCO_3$, EtOH, room temp., 1.5 h, 28%

24a/24b under the conditions used to reduce azides **19** and then with allyl chloroformate gave a complex mixture from which only the vinyl sulfone **25** could be isolated. Attempts to cleave the sulfonyl group by reduction with sodium amalgam, lithium in diethylamine[13] or *n*BuMgCl in presence of $Ni(acac)_2$ [14] resulted only in degradation products.

The structure of **25** was deduced from its NMR spectrum. The Nuclear Overhauser Effect between 3-H and 6-H as well as the value of the long-range coupling constant proved the *cis* relationship between the ethyl and amino groups. It is also reasonable to postulate a *cis* relationship between the ethyl and azido groups in **24,** this confirming the epimerisation of the azido group.

The ^1H and ^{13}C NMR spectra of the *cis* and *trans* isomers **2** and **3**, however, were strikingly similar and no NOE was observed between the allylic hydrogen atoms either in **2** or in **3**. The **21a/21b** mixture was alternatively protected by an Alloc group. The resulting products **22a** and **22b** were desulfonylated to afford **23** (Scheme 8), which was compared to the *cis* isomer **15**. Again, the two compounds displayed similar spectra without NOEs between 1-H and 4-H.



Scheme 8. Reagents and conditions: (a) $ClCO_2All$, EtOH, $NaHCO_3$, sonication, 1.5 h, room temp., 51%; (b) Na(Hg), MeOH, KH_2PO_4, room temp., 30 min, 80%

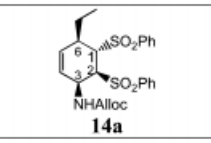
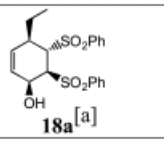
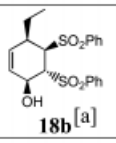
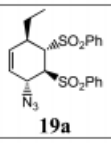
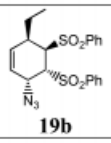
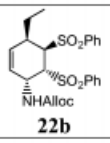
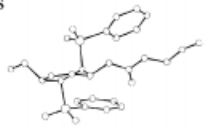
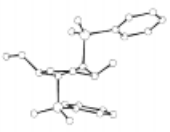
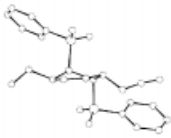
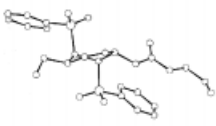
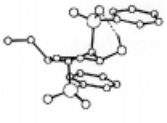
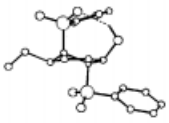
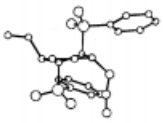
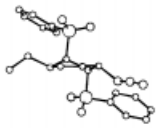
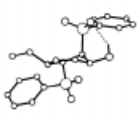
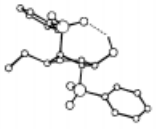
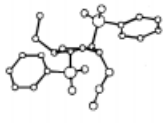
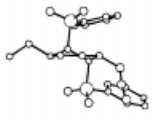
Confirmation of the Stereochemistry

To eliminate a possible epimerisation that could have occurred either during the Mitsunobu reaction or afterwards on the azido compound, and to make sure that **2** and **3** (as well as **15** and **23**) were the expected *cis* and *trans* isomers, we tried to obtain independent stereochemical proofs. Compounds **14a, 18a**, **19b** and **22b** could be crystallised, and their structures were established by X-ray crystallography (Table 1).

The *cis* relationships between the ethyl side chain and both the hydroxy group in **18a** and the amino group in **14a** shows that the Diels−Alder reaction had taken place with the expected stereochemistry. The structure of **19b** revealed that the Mitsunobu reaction had occurred with inversion, and the structure of **22b** that hydrogenation had not brought about any configurational change.

Indeed, a more thorough analysis of the ^1H NMR spectra showed that the ^5J coupling constants were different for the *cis* and *trans* isomers, 8.6 and 8.2 Hz for **15** and **2**, and 5.6 Hz for **23** and **3**, proving that we were dealing with dif-

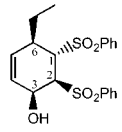
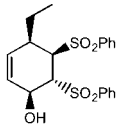
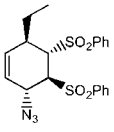
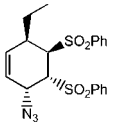
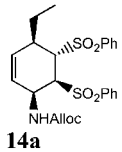
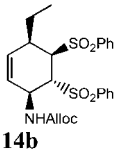
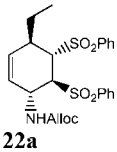
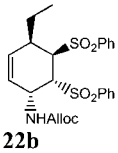
Table 1. X-ray structures of disulfones **14a**, **18a**, **19b** and **22b** and comparison with modelled structures calculated by AM1 semiempirical methods; two minimum-energy structures were calculated for each diastereoisomer **18a/18b** and **19a/19b**; the dihedral angle Φ was defined as the intersection of the (C-6, C-1, 1-S) and (C-1, 1-S, C(Ph)] planes

	 **14a**	 **18a**[a]	 **18b**[a]	 **19a**	 **19b**	 **22b**
X-ray structures						
ϕ	174.8°	170.8°			103.4°	80.6°
Modelled structures						
		18a	**18b**	**19a**	**19b**	
E (kcal/mol)		−107.40	−107.34	28.00	29.08	
ϕ		154°	173°	162°	98°	
Modelled structures						
		18a'	**18b'**	**19a'**	**19b'**	
E (kcal/mol)		−102.60	−106.44	28.69	30.82	
ϕ		68°	116°	64°	166°	

ferent compounds. By calculation, Marshall et al.[15] and then Grossel[16] described a conformational dependence of the homoallylic coupling constants in such systems. In cases of planar rings, *cis* and *trans* homoallylic constants were very close ($^5J = 6-8.5$ Hz), but with $^5J_{cis}$ higher than $^5J_{trans}$. A boat-puckering of the ring induced an increase in the *cis* value whereas the *trans* constant decreased. According to these literature data, the ^5J coupling values of **2** and **3** and of **15** and **23** suggested a planar geometry of the ring, which could explain why no NOE was observed. An NMR study of compound **25** allowed a ^5J coupling value of 9.2 Hz to be measured and an NOE was observed between the two allylic protons, compatible with a *cis* geometry and a boat-puckered ring.

A correlation could be established between the relative configurations of the sulfonyl groups and the chemical shifts of the 3-H and 6-H hydrogen atoms, as well as the C-3 and C-6 carbon atoms (Table 2). These chemical shift values depended on the *cis* or *trans* orientations of the substituents at C-3 and C-6 with respect to its vicinal sulfonyl group. They were always lower for a *trans* relationship than for a *cis* one.

Table 2. Representative NMR chemical shifts (ppm) of hydrogen and carbon atoms in Diels−Alder adducts and derivatives; spectra were recorded in $CDCl_3$ at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR

				
	18a	**18b**	**19a**	**19b**
1-H	4.15	4.16	4.14	4.67
2-H	4.37	3.96	4.21	4.46
3-H	4.88	4.55	4.42	4.88
6-H	2.58	2.86	2.70	3.02
C-3	65.15	61.73	50.91	54.99
C-6	33.60	37.04	33.78	37.07
CH_3	11.50	12.53	11.19	12.18
				
	14a	**14b**	**22a**	**22b**
1-H	4.20	4.42	4.18	4.39
2-H	4.06	4.02	4.06	4.15
3-H	4.63	4.76	4.63	5.04
6-H	2.80	2.94	2.46	2.96
C-3	45.75	42.86	41.78	46.44
C-6	32.69	36.60	33.65	37.28
CH_3	11.45	12.38	11.48	12.81

The three-dimensional structures of the four crystalline compounds **14a**, **18a**, **19b** and **22b** showed that they all adopted conformations with the phenylsulfonyl groups in axial orientations. We were interested in using molecular modelling to investigate how favoured these conformations were. Another question was to understand why only one diastereoisomer could be crystallised in each of the pairs **14a/14b**, **18a/18b**, **19a/19b** and **22a/22b**.

Molecular modelling was performed by semiempirical AM1 calculations for **18a** and **19b** and their stereoisomers **18b** and **19a**. For **18a** and **19b**, the most stable conformations were quite similar to those observed by X-ray crystallography (Table 2). The energy differences with the next best conformations **18a′** and **19b′** were rather high, at 4.8 kcal and 1.7 kcal·mol^{-1}, respectively. For the other noncrystalline stereoisomers **18b** and **19a**, on the other hand, the differences between the two best conformations were only 0.9 kcal·mol^{-1} (**18b′** vs. **18b**) and 0.7 kcal·mol^{-1} (**19a′** vs. **19a**), allowing the coexistence of several conformers to be inferred, which could explain why crystallisation could not be achieved.

The energy difference between axial and equatorial cyclohexyl phenyl sulfones was calculated by the same AM1 method. The equatorial conformation was found to be more stable by 2.3 kcal·mol^{-1}. The good agreement with the A value given for a cyclohexyl methyl sulfone (2.5 kcal·mol^{-1})[17] shows the reliability of the AM1 calculations.

For a 1-(phenylsulfonyl)cyclohex-3-ene, this value dropped to 1.8 kcal·mol^{-1}. For the *trans*-disubstituted cyclohexenes, the axial preference is thus due to repulsion between the two phenylsulfonyl groups in the diequatorial conformation.

For each compound, the two best conformations differed only in the rotation of the phenylsulfonyl group adjacent to the ethyl substituent. The conformation with the larger dihedral angle around the S−(C-1) bond (close to *anti*) was the most stable, except in the pair **19a/19a′**.

In the case of compounds **18a** and **18b**, the most stable conformations contained a hydrogen bond between OH and a sulfone oxygen atom. Other conformations of the OH group were less stable by ca. 7 kcal·mol^{-1}.

The H−O distances, 2.16 and 2.10 Å for **18a** and **18b**, respectively, were shorter than the calculated OH−X (X = Cl or O) distances in 2-chloro- or 2-hydroxycyclohexanols, 2.6−2.8 and 2.4−2.6 Å, respectively. Indeed, the calculated charges on the oxygen atoms of the sulfone were high (ca. −0.93 ua) compared to those on Cl (−0.14 ua) or OH (−0.33 ua).

Conclusion

We have described the synthesis of the 1-aminocyclohexa-2,5-diene moiety. NMR analysis of both isomers **2** and **3** revealed coupling constants that, according to literature data, were consistent with a planar cyclohexadienyl ring. This explains the absence of NOEs in the *cis* compound. Based on the methodology described in this paper, the synthesis of amiclenomyan was achieved.[19]

Experimental Section

General Procedures: Solvents were dried by distillation under Ar from CaH_2 (CH_2Cl_2, toluene, *ortho*-xylene, NEt_3), Mg (MeOH) or Na/benzophenone (THF, Et_2O). All other commercially available reagents were used without further purification. Column chromatography was performed with flash silica (Merck 230,

0.040−0.063 mm). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a Bruker ARX 400 at room temperature in $CDCl_3$ solution, unless otherwise stated (some spectra were recorded with a Bruker AC 200). All chemical shifts are reported as δ values (ppm) relative to $CDCl_3$ (or CD_3OD): δ = 7.28 (δ = 3.34) and δ = 77.16 (δ = 49.86) for ^{1}H NMR and ^{13}C NMR spectra, respectively. Irradiation experiments and Nuclear Overhauser Effect measurements were carried out at 400 MHz. IR spectra were recorded with a Perkin−Elmer 1420 instrument. CI mass spectra were obtained with a NERMAG R30−10 apparatus. High-resolution mass spectra were recorded with a JEOL MS700 BE (CH_4). Melting points were measured with a Kofler bank and are uncorrected. Elemental analyses were performed by the Service Régional de Microanalyse (SIAR-Jussieu).

Determination of the ^5J Coupling Constant Values: The ^5J coupling constants between 1′-H and 4′-H in compounds **2**, **3**, **15** and **23** were measured from the 4′-H signal after irradiation of 3′-H. The experiments were carried out with a Bruker ARX 400 apparatus in CD_3OD. For **2** and **15**, the ^5J values were 8.2 and 8.6 Hz, respectively, and for **3** and **23** 5.6 Hz.

Molecular Modelling: Semiempirical AM1 calculations[18] were performed with the AMPAC Version 2.14 package. The energies of the various conformations of sulfones **18** and **19** were determined in this way, starting with the half-chair conformation for the cyclohexene ring and calculating all the staggered conformations for the different substituents. The geometries were optimised by using the Davidson−Fletcher−Powell algorithm (FLEPO procedure), minimising the energy with respect to all internal coordinates. Further refinement by minimising the energy gradient (NLLSQ) gave only poor improvements in energy and insignificant differences in geometrical parameters. Representation of these structures was performed with the MOLPLT graphic program implemented in the GAMESS package (information about GAMESS is available at http://www.msg.amelab.gov/GAMES/GAMESS.html).

Crystallographic Data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-162257 (**19b**), -162258 (**22b**), -162259 (**14a**) and -162260 (**18a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

4-Ethylcyclohexa-2,5-dienecarboxylic Acid (5): Lithium (330 mg, 48 mmol) was added at −78 °C over 6 min to a stirred solution of acid **4** (1.81 g, 12 mmol) in freshly distilled ether (12 mL) and ammonia (35 mL). Stirring was maintained for 12 min, and freshly distilled ethanol (3 mL) was then added over 5 min. After 5 min, powdered ammonium chloride (2.54 g, 48 mmol) was added carefully. After evaporation of the ammonia, the residue was acidified at 0 °C with a 12 N aqueous hydrochloric acid solution and extracted with ether. The organic layer was dried with $MgSO_4$ and concentrated to give a yellow oil (1.76 g, 96%) as a mixture of two diastereoisomers, **5a** and **5b**, in a 1:2 ratio. ^{1}H NMR: **5a:** δ = 0.87 (t, J = 7.5 Hz, 3 H, CH_3), 1.44−1.52 (m, 2 H, CH_2), 2.67−2.74 (m, 1 H, 4-H), 3.71−3.76 (m, 1 H, 1-H), 5.80−5.87 (m, 4 H, 2-H, 3-H, 5-H, 6-H); **5b:** δ = 0.88 (t, J = 7.4 Hz, 3 H, CH_3), 1.44−1.52 (m, 2 H, CH_2), 2.67−2.74 (m, 1 H, 4-H), 3.71−3.76 (m, 1 H, 1-H), 5.80−5.87 (m, 4 H, 2-H, 3-H, 5-H, 6-H). ^{13}C NMR (50 MHz): **5a:** δ = 10.30 (CH_3), 28.19 (CH_2), 36.20 (C-4), 41.93 (C-1), 121.37−131.56 (C-2, C-3, C-5, C-6), 179.21 (C=O); **5b:** δ = 10.57 (CH_3), 28.31 (CH_2), 36.53 (C-4), 42.16 (C-1), 121.37−131.56 (C-2, C-3, C5, C-6), 179.21 (C=O). MS: m/z = 170 $[MNH_4]^+$.

4-Ethylcyclohexa-2,5-dienecarbonyl Chloride (6): A solution of acid **5** (152 mg, 1 mmol) and oxalyl chloride (225 μL, 2.6 mmol) in anhydrous dichloromethane (2 mL) was stirred for 1 h under argon at room temp. After evaporation of the solvents, the desired acyl chloride was obtained as a mixture of the two diastereoisomers (a yellow oil) **6a** and **6b** in a 1:2 ratio (150 mg, 88%). ^{1}H NMR (200 MHz): **6a** and **6b:** δ = 0.87 (t, J = 7.4 Hz, 3 H, CH_3), 1.43−1.59 (m, 2 H, CH_2), 2.73−2.75 (m, 1 H, 4-H), 4.06−4.13 (m, 1 H, 1-H), 5.82−5.96 (m, 4 H, 2-H, 3-H, 5-H, 6-H). ^{13}C NMR: **6a:** δ = 10.25 (CH_3), 27.86 (CH_2), 36.41 (C-4), 53.30 (C-1), 119.97−133.35 (C-2, C-3, C-5, C-6), 173.46 (C=O); **6b:** δ = 10.53 (CH_3), 27.80 (CH_2), 36.25 (C-4), 53.54 (C-1), 119.97, 133.42 (C-2, C-3, C-5, C-6), 173.52 (C=O).

4-Ethylcyclohexa-1,5-dienecarbonyl Azide (7): Sodium azide (350 mg, 5.4 mmol), dissolved in water (2 mL), was added to a solution of acyl chloride **6** (250 mg, 1.5 mmol) in acetone (3 mL). The mixture was stirred at 0 °C for 1 h, diluted with water and extracted with cyclohexane. The organic layer, dried with $MgSO_4$ and concentrated, afforded the azide **7** (yellow oil, 235 mg, 90%). ^{1}H NMR: δ = 0.91 (t, J = 7.4 Hz, 3 H, CH_3), 1.33−1.51 (m, 2 H, CH_2), 2.13−2.28 (m, 2 H, 3-H, 4-H), 2.44−2.51 (m, 1 H, 3-H), 5.86 (dd, J = 9.9, 3.2 Hz, 1 H, 5-H), 6.34 (ddd, J = 9.9, 1.7, 1.7 Hz, 1 H, 6-H), 7.00 (dt, J = 4.8, 1.5 Hz, 1 H, 2-H). ^{13}C NMR: δ = 11.18 (CH_3), 27.24 (CH_2), 29.06 (C-3), 33.50 (C-4), 120.05 (C-6), 129.74 (C-1), 132.97 (C-5), 139.67 (C-2), 170.94 (C=O). IR: $\tilde{\nu}$ = 1685 cm^{-1} (C=O), 2120 cm^{-1} (N_3).

Allyl (4-Ethylphenyl)carbamate (8): Diphenylphosphoryl azide (1.3 mL, 6 mmol) and triethylamine (850 μL, 6 mmol) were added to a solution of acid **5** (750 mg, 5 mmol) in allyl alcohol (5 mL). After refluxing for 1 h, the mixture was concentrated and chromatographed (cyclohexane/ethyl acetate, 95:5) to give carbamate **8** (15%). ^{1}H NMR: δ = 1.21 (t, J = 7.6 Hz, 3 H, CH_3), 2.60 (q, J = 7.6 Hz, 2 H, CH_2), 4.66 (dt, J = 5.6, 1.3 Hz, 2 H, OCH_2), 5.25 (tdd, J = 10.4, 1.2, 1.2 Hz, 1 H, =CH_2), 5.35 (tdd, J = 17.2, 1.5, 1.5 Hz, 1 H, =CH_2), 5.96 (ddt, J = 17.2, 10.4, 5.6 Hz, 1 H, CH=CH_2), 6.76 (m, 1 H, NH), 7.12 (d, J = 8.4 Hz, 2 H, 2-H, 6-H), 7.30 (d, J = 8.3 Hz, 2 H, 3-H, 5-H). ^{13}C NMR: δ = 15.73 (CH_3), 28.25 (CH_2), 65.82 (OCH_2), 118.16 (=CH_2), 119.09, 128.40, 135.46, 139.60 (C-1-C-6), 132.60 (CH=CH_2), 153.48 (C=O). $C_{12}H_{15}O_2N$ (205.262): calcd. C 70.27, H 7.31 N, 6.83; found C 70.16, H 7.43, N 6.79.

Ethyl Hepta-2,4-dienoate (10): Triethyl phosphonoacetate (35 mL, 175 mmol) was added dropwise with vigorous stirring to a 60% dispersion of NaH in mineral oil (7.0 g) in dry THF (100 mL), cooled at −20 °C. After the mixture had been stirred for 30 min at this temperature, *trans*-pentenal (8.4 g, 100 mmol) was added and the mixture was kept for 20 min at −20 °C and then for 30 min at room temp. The solution was diluted with 200 mL of diethyl ether and the mixture was washed with a saturated NH_4Cl solution. The organic layer was washed with a saturated Na_2CO_3 solution (2 × 100 mL) followed by brine (2 × 100 mL) and dried with $MgSO_4$. After concentration and flash chromatography (cyclohexane/ethyl acetate, 97:3), **10** was obtained as a yellow oil (10.5 g, 70%). ^{1}H NMR: δ = 1.13 (t, J = 7.6 Hz, 3 H, 7-H), 1.37 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.28 (m, 2 H, 6-H), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 5.87 (d, J = 15.3 Hz, 1 H, 2-H), 6.24−6.28 (m, 2 H, 4-H, 5-H), 7.32−7.38 (m, 1 H, 3-H). ^{13}C NMR: δ = 13.19 (C-7), 14.62 (OCH_2CH_3), 26.35 (C-6), 60.42 (OCH_2), 119.56 (C-2), 127.75,

146.19 (C-4, C-5), 145.40 (C-3), 167.55 (C-1). HRMS: *m*/*z* calcd. for $C_9H_{14}O_2$ $[MH]^+$ 155.1072, found 155.1075.

Hepta-2,4-dienoic Acid (11): Sodium hydroxide solution (2 M, 150 mL) was added to a solution of ester **10** (10.1 g, 65.4 mmol) in methanol (115 mL). The mixture was stirred at 50 °C for 50 min and acidified to pH = 2 with 12 N hydrochloric acid. Evaporation of the solvents gave a white solid, which was dissolveded in water (30 mL). After extraction with dichloromethane (3 × 100 mL) and concentration of the organic layer to dryness, the pure acid **11** was obtained as a white crystalline solid (7.68 g, 92%), m.p. 41 °C. ^{1}H NMR: δ = 1.03 (t, *J* = 7.4 Hz, 3 H, 7-H), 2.18 (m, 2 H, 6-H), 5.78 (d, *J* = 15.6 Hz, 1 H, 5-H), 6.18−6.21 (m, 2 H, 4-H, 3-H), 7.32 (dd, *J* = 15.6, 9.6 Hz, 1 H, 2-H), 12.43 (s, 1 H, OH). ^{13}C NMR: δ = 12.80 (C-7), 26.16 (C-6), 118.49 (C-2), 127.37, 147.56, 147.66 (C-3, C-4, C-5), 173.24 (C-1). $C_7H_{10}O_2$ (126.157): calcd. C 66.65, H 7.99 found C 66.59, H 8.10.

Allyl Hexa-1,3-dienylcarbamate (13): Diphenylphosphoryl azide (1.2 mL, 5.6 mmol) and triethylamine (800 μL, 5.6 mmol) were added to a solution of acid **11** (500 mg, 4 mmol) in allyl alcohol (10 mL). The mixture was stirred under reflux for 3.5 h and the solvents were evaporated under vacuum. The resulting oil was purified by flash chromatography (cyclohexane/ethyl acetate, 99:1−95:5) to afford the desired diene **13** (295 mg, 31%) as a yellow oil. ^{1}H NMR: δ = 0.99 (t, *J* = 7.4 Hz, 3 H, 6-H), 2.04−2.13 (m, 2 H, 5-H), 4.61 (d, *J* = 5.0 Hz, 2 H, OCH_2), 5.23 (d, *J* = 10.1 Hz, 1 H, =CH_2), 5.32 (d, *J* = 17.2 Hz, 1 H, =CH_2), 5.52−5.58 (m, 1 H, 4-H), 5.64−5.70 (m, 1 H, 2-H), 5.89−5.98 (m, 2 H, 4-H, *CH*=CH_2), 6.62 (m, 1 H, 1-H), 6.71 (d, *J* = 8.5 Hz, 1 H, NH). ^{13}C NMR: δ = 14.09 (C-6), 26.08 (C-5), 66.41 (OCH_2), 118.57 (=CH_2), 133.31 (C-4), 112.35 (C-2), 126.75−133.21 (C-3, *C*H=CH_2), 124.89 (C-1), 153.80 (C=O). HRMS: *m*/*z* calcd. for $C_{10}H_{15}O_2N$ $[MH]^+$ 182.1181, found 182.1180. A second product, namely the allyl ester **12**, was also isolated by chromatography (132 mg, 20%). ^{1}H NMR: δ = 0.97 (t, *J* = 7.4 Hz, 3 H, 7-H), 2.08−2.15 (m, 2 H, 6-H), 4.57 (dd, *J* = 5.6, 1.5 Hz, 2 H, OCH_2), 5.15 (d, *J* = 10.4 Hz, 1 H, =CH_2), 5.25 (d, *J* = 17.2 Hz, 1 H, =CH_2), 5.74 (d, *J* = 15.4 Hz, 1 H, 2-H), 5.83−5.92 (m, 1 H, *CH*=CH_2), 6.09−6.11 (m, 2 H, 4-H, 5-H), 7.18−7.22 (m, 1 H, 3-H). ^{13}C NMR: δ = 12.89 (C-7), 26.08 (C-6), 64.90 (OCH_2), 117.98 (=CH_2), 118.83 (C-2), 132.48 (*C*H=CH_2), 127.43, 146.31 (C-4, C-5), 145.63 (C-3), 166.90 (C-1). HRMS: *m*/*z* calcd. for $C_{10}H_{14}O_2$ $[MH]^+$ 167.1072, found 167.1071.

Allyl *t*-3-[*t*-6-Ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-enyl]carbamate (14a) and Allyl *c*-3-[*c*-6-Ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-enyl]carbamate (14b): *trans*-1,2-Bis(phenylsulfonyl)ethylene (**9**, 1.5 g, 4.9 mmol) was added to a solution of diene **13** (890 mg, 4.9 mmol) in anhydrous *ortho*-xylene (5 mL). The reaction was allowed to proceed at 120 °C until complete disappearance of sulfone **9** (40 h). After evaporation of the solvent under high vacuum, the residual oil was purified by flash chromatography (cyclohexane/ethyl acetate, 9:1−7:3) to give a 6:4 mixture of two diastereoisomers (800 mg, 49%). Recrystallisation from ethyl acetate afforded the major isomer **14a** as colourless crystals, m.p. 187 °C. ^{1}H NMR: δ = 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.65−1.72 (m, 2 H, CH_2), 2.80 (m, 1 H, 6-H), 3.87 (dd, *J* = 13.1, 5.4 Hz, 1 H, OCH_2), 4.20 (m, 2 H, OCH_2, 1-H), 4.38 (d, *J* = 5.9 Hz, 1 H, 2-H), 4.96 (m, 1 H, 3-H), 5.13 (d, *J* = 10.7 Hz, 1 H, =CH_2), 5.17 (d, *J* = 18.0 Hz, 1 H, =CH_2), 5.38 (d, *J* = 8.0 Hz, 1 H, NH), 5.64 (d, *J* = 10.2 Hz, 1 H, 5-H), 5.65−5.81 (m, 1 H, *CH*=CH_2), 5.81 (d, *J* = 10.2 Hz, 1 H, 4-H), 7.36−8.01 (m, 10 H, Ph). ^{13}C NMR: δ = 11.45 (CH_3), 27.84 (CH_2), 32.69 (C-6), 45.75 (C-3), 58.51 (C-2), 60.55 (C-1), 65.46 (OCH_2), 117.71 (=CH_2), 124.78 (C-5), 127.24−141.37 (Ph), 130.10 (C-4), 132.23 (*C*H=CH_2), 154.55 (C=O). $C_{24}H_{27}O_6NS_2$ (489.612): calcd. C 58.88, H 5.56, N 2.86; found C 58.79, H 5.73, N 2.79. Crystal data: $C_{24}H_{27}O_6NS_2$, space group $P2_1/a$ with *a* = 8.255(2), *b* = 11.967(2), *c* = 24.365(4) Å, *V* = 2407(1) Å^3, final *R* value 0.044 for 1835 reflections. The mother liquors contained mainly the noncrystalline minor isomer **14b**, characterised by its NMR spectra. ^{1}H NMR: δ = 0.89 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.63−1.70 (m, 2 H, CH_2), 2.94 (m, 1 H, 6-H), 4.02 (m, 1 H, 2-H), 4.42 (m, 3 H, 1-H, OCH_2), 4.76 (m, 1 H, 3-H), 5.16 (d, *J* = 10.3 Hz, 1 H, =CH_2), 5.23 (d, *J* = 17.2 Hz, 1 H, =CH_2), 5.62 (d, *J* = 9.3 Hz, 1 H, NH), 5.73 (d, *J* = 10.2 Hz, 1 H, 5-H), 5.77−5.85 (m, 1 H, *CH*=CH_2), 5.95 (d, *J* = 10.2 Hz, 1 H, 4-H), 7.54−7.85 (m, 10 H, Ph). ^{13}C NMR: 12.38 (CH_3), 25.11 (CH_2), 36.60 (C-6), 42.86 (C-3), 58.28 (C-1), 64.10 (C-2), 65.74 (OCH_2), 117.72 (=CH_2), 124.26 (C-5), 128.10−140.35 (Ph), 130.21 (C-4), 132.72 (*C*H=CH_2), 154.65 (C=O).

3.5% Sodium Amalgam:[19] Clean sodium (27 g) was placed in a 500-mL round-bottomed flange flask, fitted with a dropping funnel containing mercury (750 g) in its central socket. The air was displaced by dry nitrogen between two side sockets. Mercury (about 10 mL) was added slowly enough to control the temperature of the exothermic reaction. After addition of all mercury and cooling to room temp., a solid was obtained and powdered.

Allyl *r*-1-(*c*-4-Ethylcyclohexa-2,5-dienyl)carbamate (15): A solution of disulfone **14** (190 mg, 0.38 mmol) in dry methanol (8 mL), buffered with KH_2PO_4 (1.5 g, 1 mmol), was vigorously stirred with 3.5% sodium amalgam (2.15 g, 3.04 mmol) under argon for 30 min at room temp. Salts and mercury were then removed by filtration, the mixture was washed with dichloromethane (10 mL), and the filtrate was concentrated and flash-chromatographed (cyclohexane/ethyl acetate, 95:5−9:1). Compound **15** (70 mg) was obtained as a colourless oil (87%). ^{1}H NMR: δ = 0.88 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.46−1.54 (m, 2 H, CH_2), 2.65−2.68 (m, 1 H, 4-H), 4.58 (d, *J* = 5.6 Hz, 2 H, OCH_2), 4.71 (m, 1 H, 1-H), 4.73 (d, *J* = 7.8 Hz, 1 H, NH), 5.22 (dd, *J* = 10.3, 1.1 Hz, 1 H, =CH_2), 5.32 (dd, *J* = 17.2, 1.1 Hz, 1 H, =CH_2), 5.73−5.76 (m, 2 H, 2-H, 6-H), 5.76−5.93 (m, 2 H, 3-H, 5-H), 5.90−6.00 (m, 1 H, *CH*=CH_2). ^{13}C NMR: δ = 10.55 (CH_3), 27.41 (CH_2), 36.33 (C-4), 45.07 (C-1), 65.87 (OCH_2), 117.72 (=CH_2), 125.70 (C-2, C-6), 131.72 (C-3, C-5), 133.01 (*C*H=CH_2), 155.65 (C=O). HRMS: *m*/*z* calcd. for $C_{12}H_{17}O_2N$ $[MH]^+$ 208.1338, found 208.1337.

***r*-1-(*c*-4-Ethylcyclohexa-2,5-dienyl)amine Hydrochloride (2):** Phenylsilane (185 μL, 1.74 mmol) and a solution of $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in 25 mL of dry CH_2Cl_2 were added under argon to a solution of protected amine **15** (180 mg, 0.87 mmol) in dry CH_2Cl_2 (2.5 mL). The mixture was stirred for 30 min and concentrated. The crude product was chromatographed (CH_2Cl_2/ethanol, 1:0−8:2) and the combined fractions were acidified with 3 N aqueous HCl and partially concentrated. Amine hydrochloride **2** was extracted with water (4 × 50 mL) and the aqueous layer was lyophilised to furnish a white powder (112 mg, 80%). ^{1}H NMR (CD_3OD): δ = 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.60−1.65 (m, 2 H, CH_2), 2.75 (m, 1 H, 4-H), 4.36 (m, 1 H, 1-H), 5.90 (dd, *J* = 10.2, 1.5 Hz, 2 H, 2-H, 6-H), 6.15 (dd, *J* = 10.2, 1.5 Hz, 2 H, 3-H, 5-H). ^{13}C NMR (CD_3OD): δ = 12.27 (CH_3), 29.27 (CH_2), 38.94 (C-4), 47.19 (C-1), 122.62 (C-2, C-6), 137.50 (C-3, C-5). HRMS: *m*/*z* calcd. for $C_8H_{13}N$ $[MH]^+$ 124.1126, found 124.1119.

(1*E*,3*E*)-1-Trimethylsilyloxyhexa-1,3-diene (16) and (1*E*,3*Z*)-1-Trimethylsilyloxyhexa-1,3-diene (17): *trans*-Hexenal (5.8 mL, 50 mmol) and toluene (70 mL) were added to a stirred suspension of $ZnCl_2$ (200 mg) in triethylamine (23 mL). Trimethylsilyl bromide (14.5 mL, 110 mmol) was then added dropwise whilst stirring and

the mixture was refluxed overnight. After cooling to room temp., the solution was filtered through a Celite pad, concentrated, diluted with cyclohexane (400 mL) and cooled for 1 h at 4 °C. Further filtration through a Celite pad and concentration afforded a crude oil, which was distilled under high vacuum to give 6.9 g of a colourless oil (81%) as a 40:60 mixture of (1*E*,3*E*)/(1*E*,3*Z*) isomers, b.p. 110 °C, 0.5 mbar. **16:** ^{1}H NMR: δ = 0.18 [s, 9 H, $Si(CH_3)_3$], 0.97 (t, *J* = 7.4 Hz, 3 H, 6-H), 2.09 (ddq, *J* = 7.5, 7.5, 1.5 Hz, 2 H, 5-H), 5.49 (dt, *J* = 15.1, 6.5 Hz, 1 H, 4-H), 5.66 (dd, *J* = 11.3, 11.3 Hz, 1 H, 2-H), 5.78−5.92 (m, 1 H, 3-H), 6.43 (d, *J* = 11.5 Hz, 1 H, 1-H). ^{13}C NMR: δ = −0.45 [$Si(CH_3)_3$], 14.35 (C-6), 25.84 (C-5), 114.00 (C-2), 124.92 (C-3), 131.29 (C-4), 143.83 (C-1); **17:** ^{1}H NMR: δ = 0.20 [s, 9 H, $Si(CH_3)_3$], 0.96 (t, *J* = 7.4 Hz, 3 H, 6-H), 2.09 (ddq, *J* = 7.5, 7.5, 1.5 Hz, 2 H, 5-H), 5.19 (dt, *J* = 10.6, 7.4 Hz, 1 H, 4-H), 5.78−5.92 (m, 1 H, 3-H), 5.94 (ddd, *J* = 11.6, 11.6, 0.9 Hz, 1 H, 2-H), 6.49 (d, *J* = 11.6 Hz, 1 H, 1-H). ^{13}C NMR: δ = −0.45 [$Si(CH_3)_3$], 13.85 (C-6), 21.03 (C-5), 109.62 (C-2), 123.63 (C-3), 129.31 (C-4), 142.15 (C-1). HRMS: *m*/*z* calcd. for $C_9H_{18}OSi$ $[MH]^+$ 170.1127, found 170.1128.

***t*-6-Ethyl-*t*-3-hydroxy-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (18a) and *c*-6-Ethyl-*c*-3-hydroxy-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (18b):** *trans*-1,2-Bis(phenylsulfonyl)ethylene (**9**; 4.86 g, 15.8 mmol) was added to a mixture of dienes (6.9 g) **16** and **17** in a 4:6 ratio in anhydrous *ortho*-xylene (15 mL). The mixture was stirred at 120 °C until complete disappearance of the sulfone (24 h). After concentration under high vacuum, the crude product was solubilised in methanol (7 mL) with a drop of 12 N hydrochloric acid and stirred for 30 min. Concentration, followed by purification of the resulting oil by flash chromatography (cyclohexane/ethyl acetate, 95:5−1:1), afforded 6.3 g of a white foam (85%) as a mixture of two diastereoisomers in a 75:25 ratio. Recrystallisation from ethyl acetate gave the minor compound **18a** as colourless crystals, m.p. 129 °C. ^{1}H NMR: δ = 0.72 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.58−1.63 (m, 2 H, CH_2), 2.58 (m, 1 H, 6-H), 3.00 (m, 1 H, OH), 4.15 (s, 1 H, 1-H), 4.37 (s, 1 H, 2-H), 4.88 (m, 1 H, 3-H), 5.75 (ddd, *J* = 10.4, 2.8, 2.8 Hz, 1 H, 4-H), 5.88−5.94 (m, 1 H, 5-H), 7.45−7.91 (m, 10 H, Ph). ^{13}C NMR: δ = 11.50 (CH_3), 27.84 (CH_2), 33.60 (C-6), 61.59 (C-1, C-2), 65.15 (C-3), 127.87−141.94 (Ph), 128.76 (C-4), 129.75 (C-5). $C_{20}H_{18}O_5S_2$ (406.520): calcd. C 59.09, H 5.45; found C 59.04, H 5.54. Crystal data: space group $P\bar{1}$ with *a* = 8.749(3), *b* = 10.658(4), *c* = 11.513(4) Å, *V* = 975(1) Å^3, final *R* value 0.081for 2214 reflections. The mother liquors contained mainly the noncrystalline major isomer **18b**, characterised by its NMR spectra: ^{1}H NMR: δ = 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.71−1.89 (m, 2 H, CH_2), 2.86 (m, 1 H, 6-H), 3.44 (s, 1 H, OH), 3.96 (s, 1 H, 2-H), 4.16 (s, 1 H, 1-H), 4.55 (s, 1 H, 3-H), 5.90−5.94 (m, 1 H, 4-H, 5-H), 7.52−7.76 (m, 10 H, Ph). ^{13}C NMR: δ = 12.53 (CH_3), 25.13 (CH_2), 37.04 (C-6), 58.94 (C-1), 61.73 (C-3), 66.34 (C-2), 127.44, 129.75 (C-4, C-5), 127.87−139.27 (Ph).

***c*-3-Azido-*t*-6-ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (19a), *t*-3-Azido-*c*-6-ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (19b):** A mixture of alcohol **18** (863 mg, 1.97 mmol) and triphenylphosphane (750 mg, 2.75 mmol) in anhydrous dichloromethane (6 mL) was stirred at 0 °C. After 10 min, diisopropyl azodicarboxylate (541 μL, 2.75 mmol) and diphenylphosphoryl azide (599 μL, 2.75 mmol) were added. The solution was kept at 0 °C for 3.5 h and concentrated. Purification of the crude product by flash chromatography (cyclohexane/ethyl acetate, 9:1−8:2) afforded the desired azide (56%) as a yellow oil as a 3:1 mixture of two diastereoisomers. Recrystallisation from ethyl acetate/cyclohexane (8:2) afforded the major isomer **19b** as colourless crystals, m.p. 138 °C. ^{1}H NMR: δ = 0.81 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.43−1.50 (m, *J* = 7.4 Hz, 1 H, CH_2), 1.64−1.71 (m, 1 H, CH_2), 2.99−3.04 (m, 1 H, 6-H), 4.46 (dd, *J* = 6.6, 2.0 Hz, 1 H, 2-H), 4.67 (dd, *J* = 5.1, 2.0 Hz, 1 H, 1-H), 4.88 (m, 1 H, 3-H), 5.82 (d, *J* = 10.2, Hz, 1 H, 5-H), 6.01 (d, *J* = 10.2 Hz, 1 H, 4-H), 7.58−7.97 (m, 10 H, Ph). ^{13}C NMR: δ = 12.18 (CH_3), 24.73 (CH_2), 37.07 (C-6), 54.99 (C-3), 60.39 (C-2), 62.40 (C-1), 122.06 (C-5), 128.21−141.49 (Ph), 131.58 (C-4). $C_{20}H_{21}N_3O_4S_2$ (431.540): calcd. C 55.67, H 4.90, N 9.74; found C 55.70, H 5.01, N 9.63. Crystal data: space group $P\bar{1}$ with *a* = 8.461(4), *b* = 11.607(7), *c* = 12.076(6) Å, *V* = 1001(1) Å^3, final *R* value 0.076 for 1634 reflections. The mother liquors contained mainly the minor isomer **19a**, characterised by its NMR spectra. ^{1}H NMR: δ = 0.71 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.50−1.63 (m, 2 H, CH_2), 2.68−2.73 (m, 1 H, 6-H), 4.14 (s, 1 H, 1-H), 4.21 (m, 1 H, 2-H), 4.42 (m, 1 H, 3-H), 5.85 (dd, *J* = 10.4, 4.1 Hz, 1 H, 4-H), 6.15 (dd, *J* = 10.4, 5.1 Hz, 1 H, 5-H), 7.33−7.92 (m, 10 H, Ph). ^{13}C NMR: δ = 11.19 (CH_3), 27.03 (CH_2), 33.78 (C-6), 50.91 (C-3), 57.89 (C-1), 61.10 (C-2), 120.53 (C-4), 127.87−141.26 (Ph), 133.35 (C-5). IR: $\tilde{\nu}$ = 2100 cm^{-1} (N_3). 3-Ethyl-1-(phenylsulfonyl)-benzene (**20**) was also isolated by chromatography with a yield of 30% as white crystals, m.p. 79 °C. ^{1}H NMR: δ = 1.23 (t, *J* = 7.6 Hz, 3 H, CH_3), 2.69 (q, *J* = 7.6 Hz, 2 H, CH_2), 7.41 (m, 1 H, 4-H), 7.40−7.42 (m, 1 H, 5-H), 7.74 (dt, *J* = 6.6, 2.2 Hz, 1 H, 6-H), 7.81 (m, 1 H, 2-H), 7.96−7.99 (m, 2 H, 2′-H), 7.48−7.58 (m, 3 H, 3′-H, 4′-H); δ = ^{13}C NMR: 15.59 (CH_3), 29.04 (CH_2), 146.20 (C-3), 132.71 (C-4), 129.13 (C-5), 124.92 (C-6), 141.28 (C-1), 126.60 (C-2), 141.58 (C-1′), 127.43 (C-2′), 129.13 (C-3′), 133.01 (C-4′). $C_{14}H_{14}O_2S$ (246.331): calcd. C 68.27; H,5.72; found C 68.09, H 5.71.

Allyl *c*-3-[*t*-6-Ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-enyl]carbamate (22a) and Allyl *t*-3-[*c*-6-Ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-enyl]carbamate (22b): Azides **19** (517 mg, 1.20 mmol), solubilised in a THF/isopropyl alcohol (1:1) solution (20 mL), were introduced into a reactor with Lindlar catalyst (300 mg). After the mixture had been stirred for 14 h under 5 bar hydrogen pressure, the catalyst was removed by centrifugation and washed with dichloromethane (4 × 20 mL). After concentration of the combined layers, a yellow oil containing two diastereoisomers, **21a** and **21b**, was obtained. This crude product was directly used in the following steps without purification. To this mixture in absolute ethanol (20 mL), buffered with $NaHCO_3$ (1 g, 12 mmol), allyl chloroformate (190 μL, 1.8 mmol) was added. The solution was sonicated for 1.5 h at room temp. and then concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate, 9:1−6:4) afforded two diastereoisomers (51%, calculated from **19**) in a 1:1 ratio. Recrystallisation from ethyl acetate/cyclohexane (1:1) afforded the isomer **22b** as colourless crystals, m.p. 156 °C. ^{1}H NMR: δ = 0.92 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.67−1.75 (m, 1 H, CH_2), 1.81−1.91 (m, 1 H, CH_2), 2.96 (m, 1 H, 6-H), 3.76 (dd, *J* = 13.2, 5.6 Hz, 1 H, OCH_2), 4.10−4.17 (m, 1 H, OCH_2), 4.13−4.17 (m, 1 H, 2-H), 4.39 (d, *J* = 5.1 Hz, 1 H, 1-H), 5.04−5.16 (m, 4 H, 3-H, $=CH_2$, NH), 5.53 (d, *J* = 10.7 Hz, 1 H, 4-H), 5.56−5.67 (m, 1 H, $CH{=}CH_2$), 5.84 (d, *J* = 10.2 Hz, 1 H, 5-H), 7.37−8.00 (m, 10 H, Ph). ^{13}C NMR: 12.81 (CH_3), 25.39 (CH_2), 37.25 (C-6), 46.44 (C-3), 60.51 (C-2), 62.02 (C-1), 65.95 (OCH_2), 118.21 ($=CH_2$), 124.96 (C-4), 127.70−134.58 (Ph), 130.71 (C-5), 132.63 ($CH{=}CH_2$), 154.96 (C=O). $C_{24}H_{27}O_6NS_2$ (489.614): calcd. C 58.88, H 5.56, N 2.86; found C 58.99, H 5.56, N 2.84. Crystal data: space group $P2_1/a$ with *a* = 9.020(3), *b* = 20.568(6), *c* = 12.727(3) Å, V = 2332(1) Å^3, final *R* value 0.050 for 2382 reflections. The mother liquors contained mainly the isomer **22a**, characterised by its NMR spectra. ^{1}H NMR: δ = 0.52 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.45−1.58 (m, 2 H, CH_2), 2.46 (m, 1 H, 6-H), 4.06 (s, 1 H, 2-H), 4.02 (s, 1 H, 1-H), 4.29−4.35 (m, 2 H, OCH_2), 4.61−4.65 (m, 1 H, 3-H), 5.06 (d, *J* = 10.2 Hz, 1 H, $=CH_2$), 5.14

(d, J = 17.3 Hz, 1 H, =CH_2), 5.64 (d, J = 10.2 Hz, 1 H, NH), 5.68−5.78 (m, 1 H, CH=CH_2), 5.74 (d, J = 10.2 Hz, 1 H, 4-H), 5.87 (dd, J = 10.2, 4.1 Hz, 1 H, 5-H), 7.56−7.93 (m, 10 H, Ph). ^{13}C NMR: δ = 11.48 (CH_3), 27.19 (CH_2), 33.65 (C-6), 41.78 (C-3), 57.71 (C-1), 60.67 (C-2), 65.99 (OCH_2), 117.92 (=CH_2), 122.75 (C-4), 129.15−138.00 (Ph), 130.75 (C-5), 132.98 (CH=CH_2), 155.12 (C=O).

Allyl 1-*r*-(4-*t*-Ethylcyclohexa-2,5-dienyl)carbamate (23): A solution of disulfones **22a** and **22b** (165 mg, 0.33 mmol) in dry methanol (8 mL), buffered with KH_2PO_4 (1.5 g, 1 mmol), was vigorously stirred with 3.5% sodium amalgam (2.15 g, 3.04 mmol) under argon for 30 min at room temp. The salts and mercury were then removed by filtration and washed with dichloromethane (10 mL), and the filtrate was concentrated and flash-chromatographed (cyclohexane/ethyl acetate, 95:5−9:1). After recrystallisation from ether, **23** (56 mg, 80%) was obtained as white crystals, m.p. 67 °C. ^{1}H NMR: δ = 0.88 (t, J = 7.4 Hz, 3 H, CH_3), 1.44−1.51 (m, 2 H, CH_2), 2.63−2.68 (m, 1 H, 4-H), 4.60 (d, J = 5.5 Hz, 2 H, OCH_2), 4.72 (m, 1 H, 1-H), 5.22 (m, 1 H, NH), 5.23 (d, J = 10.4 Hz, 1 H, =CH_2), 5.33 (d, J = 17.2 Hz, 1 H, =CH_2), 5.75−5.79 (m, 2 H, 2-H, 6-H), 5.82−5.86 (m, 2 H, 3-H, 5-H), 5.90−6.00 (m, 1 H, CH=CH_2). ^{13}C NMR: δ = 10.20 (CH_3), 28.20 (CH_2), 36.51 (C-4), 44.80 (C-1), 65.69 (OCH_2), 117.84 (=CH_2), 125.83 (C-2, C-6), 131.55 (C-3, C-5), 132.69 (CH=CH_2), 155.65 (C=O). HRMS: *m*/*z* calcd. for $C_{12}H_{17}O_2N$ $[MH]^+$ 208.1338, found 208.1337.

1-*r*-(4-*t*-Ethylcyclohexa-2,5-dienyl)amine Hydrochloride (3): Sodium amalgam (4.4 g, 6.7 mmol) and KH_2PO_4 (4 g, 29 mmol) were added to a mixture of amines **21** (364 mg of hydrogenated azide) in 25 mL of anhydrous methanol. After the mixture had been stirred for 2 h at room temp., dichloromethane (50 mL) was added. The solution was filtered, concentrated and purified by chromatography (CH_2Cl_2/ethanol, 10:0−5:5) to furnish (after acidification with HCl) the hydrochloride **3** as a yellow oil (55 mg, 41% calculated from azide). ^{1}H NMR (CD_3OD): δ = 0.91 (t, J = 7.4 Hz, 3 H, CH_3), 1.57 (dq, J = 7.4, 6.1 Hz, 2 H, CH_2), 2.82−2.86 (m, 1 H, 4-H), 4.28 (m, 1 H, 1-H), 5.86 (ddd, J = 10.2, 3.3, 2.3 Hz, 2 H, 2-H, 6-H), 6.18 (ddd, J = 10.2, 3.1, 1.6 Hz, 2 H, 3-H, 5-H). ^{13}C NMR (CD_3OD): δ = 11.21 (CH_3), 29.37 (CH_2), 38.86 (C-4), 46.74 (C-1), 122.88 (C-2, C-6), 137.88 (C-3, C-5). HRMS: *m*/*z* calcd. for $C_8H_{13}N$ $[MH]^+$ 124.1126, found 124.1119.

***t*-3-Azido-*t*-6-ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (24a) and *c*-3-Azido-*c*-6-ethyl-*r*-1,*t*-2-bis(phenylsulfonyl)cyclohex-4-ene (24b):** A solution of the mixture of azides **19a** and **19b** in dry dichloromethane was stirred at room temp. for 3 d. After concentration and purification by flash chromatography (cyclohexane/ethyl acetate, 9:1−8:2), a 7:3 mixture of azides **24a** and **24b** was obtained as a yellow oil (66%). **24a:** ^{1}H NMR: δ = 0.75 (t, J = 7.4 Hz, 3 H, CH_3), 1.80−1.85 (m, 1 H, CH_2), 1.88−1.91 (m, 1 H, CH_2), 2.16−2.21 (m, 1 H, 6-H), 4.08 (d, J = 4.6 Hz, 1 H, 2-H), 4.26−4.28 (m, 2 H, 1-H, 3-H), 5.89 (dd, J = 10.2, 3.8 Hz, 1 H, 4-H), 6.27 (d, J = 10.2 Hz, 1 H, 5-H), 7.50−7.72 (m, 10 H, Ph). ^{13}C NMR: δ = 11.04 (CH_3), 26.95 (CH_2), 40.44 (C-6), 58.67 (C-2), 59.10 (C-1), 60.27 (C-3), 118.37 (C-4), 128.30−135.85 (Ph), 136.57 (C-5); **24b:** ^{1}H NMR: δ = 0.92 (t, J = 7.4 Hz, 3 H, CH_3), 1.71−1.76 (m, 1 H, CH_2), 1.90−2.00 (m, 1 H, CH_2), 2.32−2.35 (m, 1 H, 6-H), 3.91 (d, J = 5.6 Hz, 1 H, 2-H), 4.10 (m, 1 H, 1-H), 4.37 (d, J = 6.1 Hz, 1 H, 3-H), 5.60−5.65 (ddd, J = 10.6, 7.6, 3.1 Hz, 1 H, 4-H), 6.26 (d, J = 10.2 Hz, 1 H, 5-H), 7.50−7.72 (m, 10 H, Ph). ^{13}C NMR: δ = 9.92 (CH_3), 26.10 (CH_2), 39.38 (C-6), 58.07 (C-1), 59.32 (C-2), 59.50 (C-3), 119.22 (C-4), 128.30−135.85 (Ph), 137.16 (C-5). HRMS: *m*/*z* calcd. for $C_{20}H_{21}O_4N_3S_2$ $[MH]^+$ 432.1052, found 432.1051. IR: 2100 cm^{-1} (N_3).

Allyl 6-*r*-[*c*-3-Ethyl-1-(phenylsulfonyl)cyclohexa-1,4-dienyl]carbamate (25): The mixture of azides **24a** and **24b** (595 mg, 1.37 mmol) was reduced and protected as described for azides **19a** and **19b** and afforded, after chromatography (cyclohexane/ethyl acetate, 9:1−7:3), the vinyl sulfone **25** as a yellow oil (134 mg, 28%). ^{1}H NMR: δ = 0.92 (t, J = 7.4 Hz, 3 H, CH_3), 1.40−1.49 (m, 2 H, CH_2), 2.52 (m, 1 H, 3-H), 4.19 (m, 1 H, 6-H), 4.46 (d, J = 5.6 Hz, 2 H, OCH2), 4.76 (d, J = 9.2 Hz, 1 H, NH), 5.14 (d, J = 10.7 Hz, 1 H, =CH2), 5.21 (d, J = 16.8 Hz, 1 H, =CH2), 5.76−5.86 (m, 1 H, CH=CH2), 5.81 (dd, J = 10.2, 4.8 Hz, 1 H, 5-H), 6.10 (d, J = 10.2 Hz, 1 H, 4-H), 6.93 (d, J = 5.1 Hz, 1 H, 2-H), 7.48 (t, J = 7.6 Hz, 2 H, 2′-H), 7.56 (t, J = 7.4 Hz, 1 H, 4′-H), 7.80 (d, J = 8.1 Hz, 2 H, 3′-H). ^{13}C NMR: δ = 11.29 (CH_3), 24.45 (CH_2), 42.46 (C-3), 47.80 (C-6), 65.83 (OCH2), 118.08 (=CH2), 119.68 (C-4), 127.87 (C-2′), 128.92 (C-5), 129.47 (C-3′), 132.58 (CH=CH2), 133.68 (C-4′), 137.32, 139.46 (C-1, C-1′), 138.36 (C-2), 155.38 (C=O). HRMS: *m*/*z* calcd. for $C_{18}H_{21}O_4NS$ $[MH]^+$ 348.1270, found 348.1275.

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