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Rhodium(I)-Catalyzed [2 + 2 + 2] Cycloaddition Reactions of Triacetylenic 15-Membered Aza Macrocycles: A Comparative Structural Study

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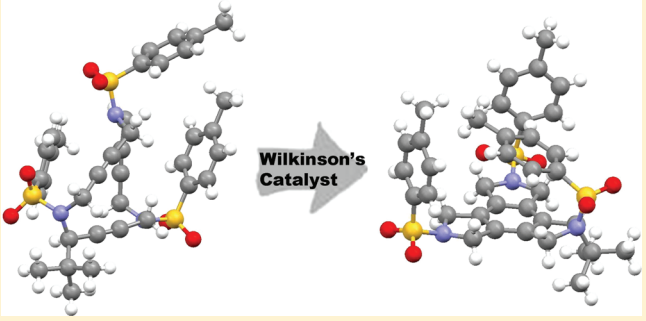
Supporting Information

ABSTRACT: A variety of new nitrogen-containing 15-membered triacetylenic macrocycles with one or two alkyl substituents in a propargylic position have been efficiently synthesized and completely characterized. These macrocyclic systems undergo [2 + 2 + 2] cycloaddition reactions, leading to the corresponding fused tetracycles with a benzene core on treatment with Wilkinson's catalyst, $[RhCl(PPh_3)_3]$. The effects of alkyl chains have been evaluated on both the efficiency of the reaction and the conformational and structural analysis of the reactants.



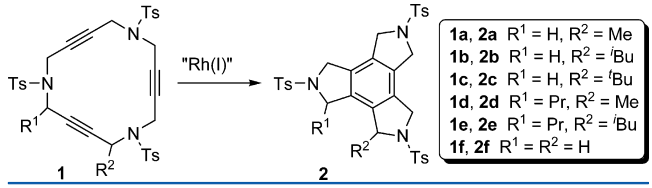
INTRODUCTION

A highly reliable and atom-economical method for the synthesis of polysubstituted benzene derivatives is the transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes.[1] Intramolecular reactions are especially interesting, as they provide multicyclic compounds in one synthetic operation. This attractive strategy has been widely applied in open-chain systems, but its application in macrocycles is an area that is relatively unexplored. A reason for this neglect can be found in the low reactivity shown by most macrocyclic triynes. 1,5,9-Cyclododecatriyne, prepared by Vollhardt in 1976, proved to be inert in the presence of light, high pressure and temperature, acidic conditions, and the $CpCo(CO)_2$ catalyst.[2] Similarly, tribenzocyclotriynes, which are known to interact with transition-metal complexes,[3] have never been found to undergo [2 + 2 + 2] cycloaddition reactions, and only a lithium-induced cyclization to a fulvalene dianion has been reported.[4] It should be noted that both macrocycles would have led to three 4-membered rings fused to the central benzene core after cyclization. Only with a larger macrocycle, such as the 15-membered silicon-tethered macrocycles reported by Sakurai et al., does the cycloisomerization reaction afford 5-membered rings fused to the benzene, as has been reported, although with low yields and in the presence of other π-electron systems.[5]

The incorporation of a nitrogen tether in 15-membered triacetylenic macrocycles has been shown by our group to give macrocycles which participate in the [2 + 2 + 2] cycloisomerization reaction, leading to tetrafused cyclic structures in a highly efficient reaction with good yields. Various aspects of this fascinating transformation have been evaluated: the efficiency of the catalyst used,[6] the reaction media,[7] the effect of the size of the different cycles on the fused structures formed during the cycloisomerization,[8,9] and the detailed mechanistic outcome.[9,10]

As part of this ongoing project, here we study the effect of introducing one or two substituents in propargylic positions of the 15-membered aza macrocycles and their effect on their cycloisomerization reactions (Scheme 1). By means of NMR and X-ray diffraction, the structural characteristics induced by these substituents will also be evaluated in the macrocycles and thus in their reactivity.

Scheme 1. [2 + 2 + 2] Cycloisomerization Reaction of Mono- and Disubstituted Macrocycles Catalyzed by Rh(I)



RESULTS AND DISCUSSION

Synthesis of Macrocycles. With the aim of obtaining a series of triyne macrocycles with various substituents at the

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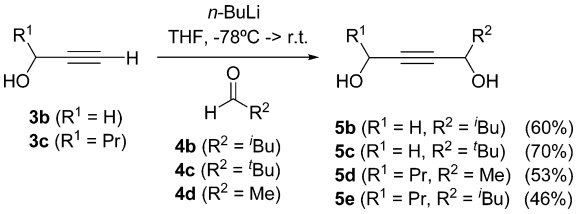
propargylic positions, the synthetic routes described by our group for unsubstituted triyne macrocycles[6b,8] were fine tuned to achieve the precise incorporation of the substituents at the appropriate positions. The substituents were introduced in all cases in the 2-alkyne-1,4-diols of type **5** (Scheme 2) used as

Scheme 2. Synthesis of Diols 5



starting materials for these macrocyclic syntheses. These diols were synthesized according to Scheme 2: i.e., treatment of the commercially available propargylic alcohol with 2 equiv of *n*-butyllithium, followed by the addition of the appropriate aldehyde to afford the corresponding diols with moderate to good yields.[11]

A monosubstituted macrocycle featuring the CH_3 substituent **1a** (Scheme 1) has already been described by our group,[8] and its synthesis was used as a model for the preparation of monosubstituted macrocycles with bulkier substituents such as ^{i}Bu and ^{t}Bu. The synthesis started with the Mitsunobu reaction of the corresponding 1,4-diol with 2 equiv of the N-BOC protected *p*-methylphenylsulfonamide **6** to give the bis-sulfonamidic intermediates **7**. After deprotection with trifluoroacetic acid, compounds of type **8** were obtained which could be macrocyclized with the dialkylated sulfonamide **9**[8] to the corresponding macrocycles **1**, as outlined in Scheme 3.

The macrocycles with two substituents were synthesized through an alternative synthetic pathway starting also with the 1,4-diols **5**, which were converted to the corresponding tosylates **10** and were directly used in the alkylation reaction of the trisulfonamide intermediate **11**,[6a] leading to the corresponding macrocycles (Scheme 4). It should be noted that both disubstituted diols and their corresponding ditosylates and macrocycles were obtained as an inseparable mixture of diastereoisomers.

All new products were fully characterized with NMR experiments and mass spectrometry. For the disubstituted macrocycles **1d,e**, the two possible diastereoisomers could be clearly differentiated in both the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum for macrocycle **1d** shows two signals of equal intensity for the CH_3 in the propargylic position, as well as the terminal CH_3 of the propyl chain, indicating an equimolar mixture of diastereoisomers. The hydrogens in geminal positions of the substituents could also be differentiated. Also, clear evidence of the diastereomeric mixture is found in the ^{13}C NMR spectrum, where two sets of six signals are observed for the acetylenic carbons and two sets of signals for the geminal carbons. Macrocycle **1e** shows a similar trend, although some signals are superimposed mainly due to the increased number of signals in the aliphatic region.

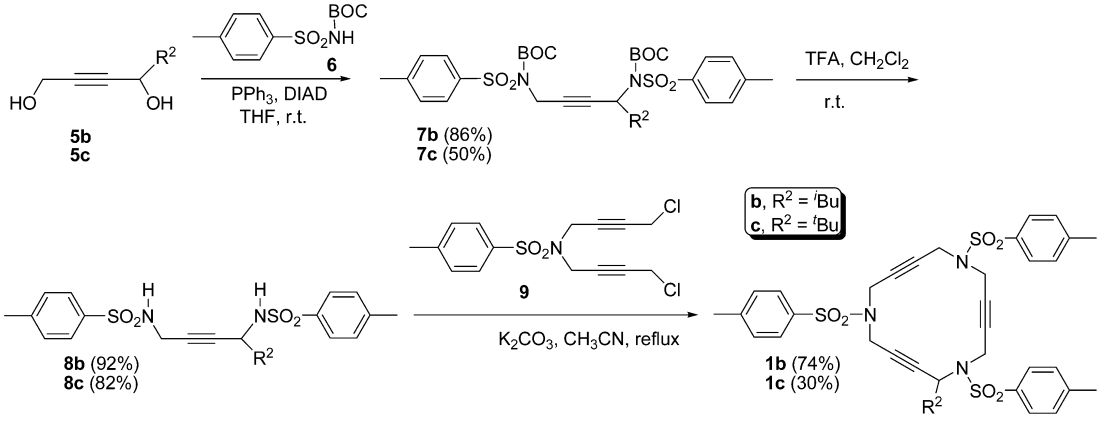
Crystals suitable for X-ray diffraction could be obtained for macrocycles **1a,c,e** (described below when discussing the reactivity).

[2 + 2 + 2] Cycloaddition Reactions. On the basis of the optimized conditions described by our group before,[8] the newly synthesized triacetylenic macrocycles **1b−e** were submitted to the [2 + 2 + 2] cycloaddition reaction using Wilkinson's complex as the catalyst. Toluene was used as the solvent in all the reactions, and the temperature and reaction time were adjusted for each experiment. Macrocycle **1a**,[8] featuring a CH_3 substituent in one of the propargylic positions, and the parent unsubstituted macrocycle **1f**[6a] were cycloisomerized under analogous conditions in order to have comparable data. The results obtained are summarized in Table 1.

Remarkably, the temperature and time needed to perform the cycloaddition is quite variable depending on the substituents. Whereas all macrocycles could be cycloisomerized at room temperature, monosubstituted macrocycle **1c**, which is the only one with a tertiary alkyl substituent and which had the greatest steric hindrance (*t*-Bu), needed 1 day at reflux to afford a 70% yield.[12] At first sight, this might be ascribed to the steric hindrance of the bulky *t*-Bu group. However, steric hindrance was not able to explain all the results obtained, since surprisingly the disubstituted macrocycles afforded the benzenic products much more quickly than did the monosubstituted macrocycles (compare entries 4 and 5 with entries 1 and 2).

The crystal structures of macrocycles **1a,c,e** were determined by performing single-crystal X-ray diffraction analysis (see Figure 1 for perspective views of the molecules and Table 2 for crystal data). Macrocycle **1e** was obtained as an inseparable mixture of diastereoisomers, and only one of these, namely the *SS*/*RR* pair of enantiomers (with the two substituents in a relative trans position, which we will now refer to as **1e-*trans***) was crystallized. The molecules show a folded structure with

Scheme 3. Synthesis of Monosubstituted Macrocycles 1b,c



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Scheme 4. Synthesis of Disubstituted Macrocycles 1d,e

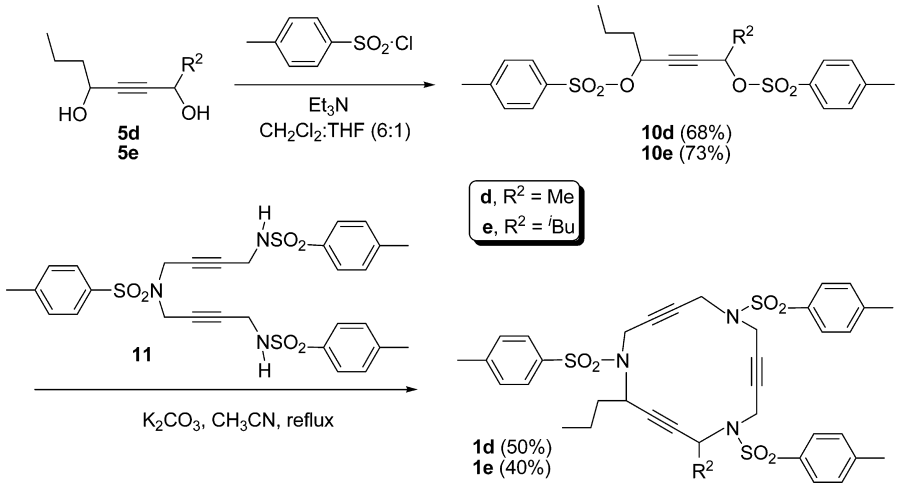
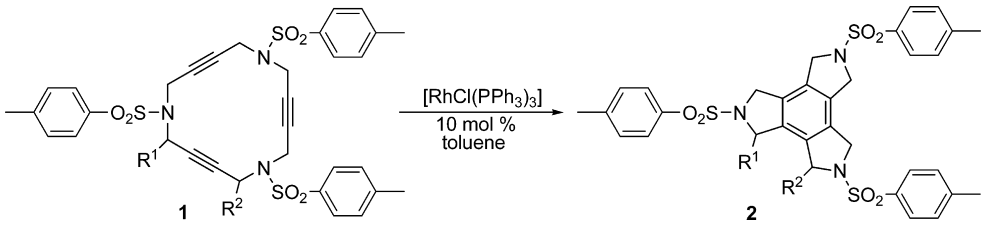


Table 1. Cycloisomerization Reactions of Mono- and Disubstituted Triyne Macrocycles 1a–f



entry	macrocycle (R^1/R^2)	temp	reacn time (h)	product (R^1/R^2)	yield (%)
1[a]	**1a** (H/Me)	room temp	26	**2a** (H/Me)	91
2	**1b** (H/^{i}Bu)	room temp	15.5	**2b** (H/^{i}Bu)	75
3	**1c** (H/^{t}Bu)	reflux	24	**2c** (H/^{t}Bu)	70
4	**1d** (Pr/Me)	room temp	2	**2d** (Pr/Me)	99
5	**1e** (Pr/^{i}Bu)	room temp	2	**2e** (Pr/^{i}Bu)	83
6[a]	**1f** (H/H)	room temp	1.5	**2f** (H/H)	84

[a]Cycloisomerizations of compounds **1a,f** were already described in refs 4 and 2, respectively, although under slightly different conditions.

the arylsulfonamide groups ordered in different planes and wrapping the macrocyclic cavity.

A more detailed analysis of the molecular structures obtained for macrocycles **1a,c** and **1e-*trans*** and that already published for macrocycle **1f**[6a] help to explain the different reactivities of the macrocycles. The C–C distances in each of the triple bonds in the X-ray structures of macrocycles **1a,c**, **1e-*trans***, and **1f** (see the Supporting Information) were collected and analyzed. No significant differences were found between them, and so inductive effects played by the substituents on the electronics of the triple bond were discarded. A more interesting aspect to be analyzed was the geometry adopted by the macrocycles depending on the substituents: although these data are extracted from the solid-state structure, it must follow the same trend in average in solution. Accurate analysis of the relative orientation of the linear triple bonds in each folded structure shows that two triple bonds are nearly on the same plane, whereas the third is almost perpendicular (Figure 1). The distances between consecutive triple bonds were measured (Figure 2) as well as the dihedral angle between the planes defined by each pair of consecutive triple bonds[13] (Table 3). Analysis of these data together with the generally accepted mechanism reveals certain interesting trends. The rhodium-catalyzed [2 + 2 + 2] cycloaddition is proposed to occur through a sequential coordination of two alkynes followed by an oxidative addition that generates a rhodacyclopentadiene. This step is considered to be the rate-determining step of the overall catalytic cycle. The third alkyne is then coordinated, generating a complex which may evolve either by alkyne insertion or a cycloaddition, and finally reductive elimination furnishes the benzene product and the catalyst is recovered. For the oxidative addition step to occur, the two triple bonds have to be close in space and, as far as possible, on the same plane. The pair of triple bonds in each structure located in almost a perpendicular relative conformation can be excluded as the ones reacting in the first step in the catalytic cycle (distances and angles in black in Figure 2 and in boldface in Table 3). Therefore, the differences should be analyzed between the other two pairs, that between the triple bonds linked by unsubstituted propargylic positions (in red in Figure 2 and in italics in Table 3) and that with one alkyl radical in one of the propargylic positions of the linker (in blue in Figure 2 and in boldface italics in Table 3).[14]

Macrocycles **1e-*trans*** and **1f**, featuring two alkyl substituents and no substituents, respectively, are those which reacted fastest in the series (2 h and 1.5 h at room temperature for **1e-*trans*** and **1f**, respectively; see Table 1). For unsubstituted macrocycle **1f**, if we dismiss the pair of triple bonds folded in an almost perpendicular position (in black in Figure 2), the other two possible pairs of triple bonds are quite close spatially and

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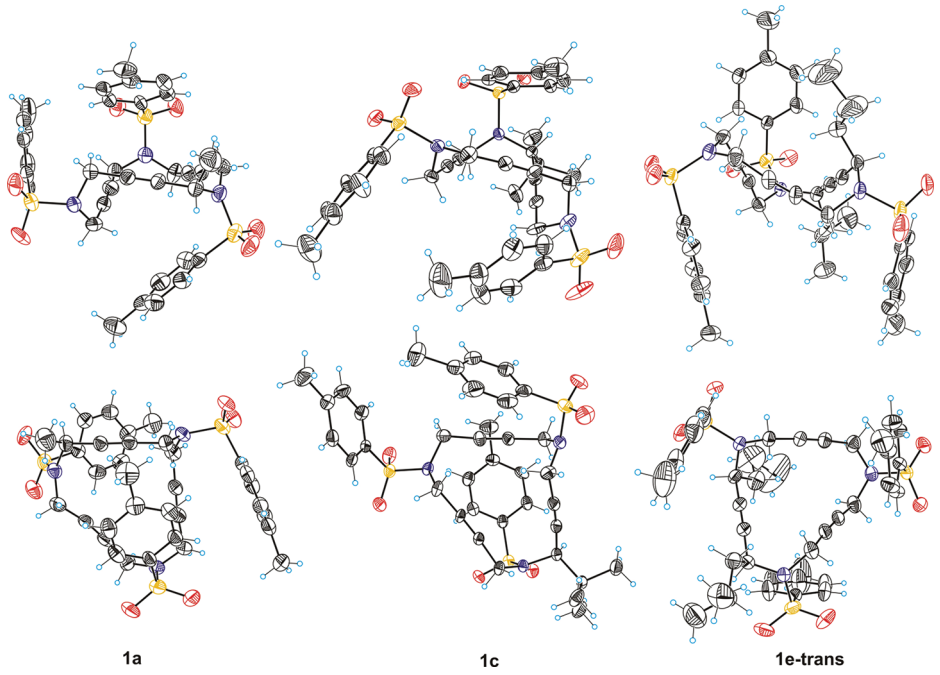

Figure 1. Ortep plots (30%) obtained from the X-ray crystallographic structural analyses of **1a,c** and **1e-*trans*** with two different views of each molecule.

Table 2. Crystallographic Data for Structures 1a,c and 1e-*trans*

	1a	1c	1e-*trans*
empirical formula	$C_{34}H_{35}N_3O_6S_3$	$C_{37}H_{41}N_3O_6S_3$	$C_{40}H_{47}N_3O_6S_3$
formula wt	677.83	719.91	761.99
temp, K	300(2)	300(2)	300(2)
wavelength, Å	0.710 73	0.710 73	0.710 73
cryst syst	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
a, Å	17.728(9)	28.676(14)	19.242(12)
b, Å	13.503(7)	14.915(7)	10.721(7)
c, Å	15.199(8)	18.614(9)	0.441(13)
β, deg	108.275(7)	93.087(10)	95.836(11)
V, Å^3	3455(3)	7950(7)	4195(5)
Z	4	8	4
ρ (g/cm^3)	1.303	1.203	1.207
R1[a] ($I > 2\sigma(I)$)	0.0867	0.0879	0.0579
wR_2[b]	0.2052	0.1873	0.1574

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum\{w(F_o^2 - F_c^2)^2\}/\sum\{w(F_o^2)^2\}]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0042P)^2]$ and $P = (F_o^2 + 2F_c^2)/3$.

have relatively small dihedral angles, making them well-positioned for the oxidative addition to occur. In the case of the trans diastereoisomer of macrocycle **1e**, the two triple bonds linked by the unsubstituted N linker have values that are comparable to those observed for **1f**. Thus it seems that the substituents exert an influence on the folding of the macrocyclic structure, resulting in two of the triple bonds becoming closer and thus facilitating the oxidative addition step of the [2 + 2 + 2] cycloaddition (generally accepted to be the rate-determining step and supported as such in the 15-membered macrocycles by DFT calculations[9]). This suitable positioning of two of the triple bonds may speed up the whole cycloaddition reaction in the disubstituted macrocycles.[15] Next in the series in terms of

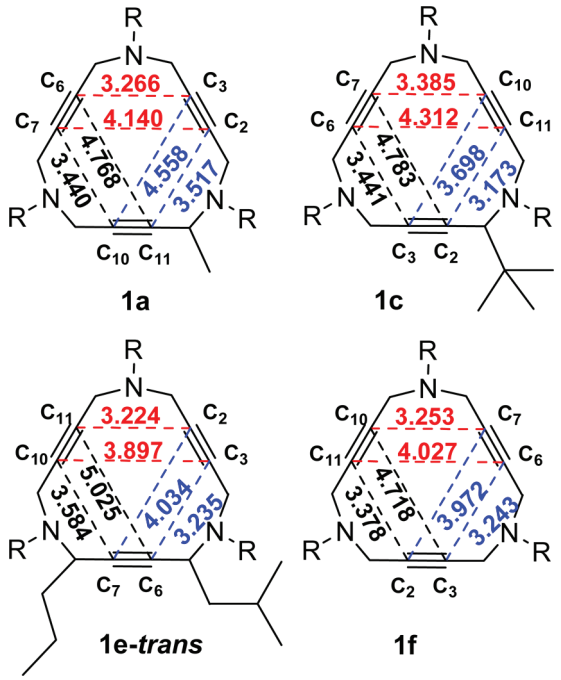

Figure 2. Distances (in Å) between triple bonds extracted from the X-ray structures.

ease of reaction is macrocycle **1a**, which has a methyl substituent (26 h at room temperature). The oxidative addition of macrocycle **1a** is presumably less favored, since neither of the pairs of triple bonds is particularly well positioned for the reaction to take place. On the one hand, the pair of triple bonds that is closest to being on the same plane (those in blue) are quite far apart and, furthermore, the methyl substituent in the linker may exert steric hindrance. On the other hand, the remaining pair of triple bonds (in red in Figure 2) is generally

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Table 3. Dihedral Angles between Acetylenes Extracted from the X-ray Structures[a]

entry	macrocycle (R^1/R^2)	atoms	Dihedral angle (°)
1	**1a** (H/Me)	$C_2-C_3-C_6-C_7$	*−27.4*
		$C_6-C_7-C_{10}-C_{11}$	**−77.8**
		$C_{10}-C_{11}-C_2-C_3$	***−15.4***
2	**1c** (H/^{t}Bu)	$C_2-C_3-C_6-C_7$	**81.5**
		$C_6-C_7-C_{10}-C_{11}$	*−33.0*
		$C_{10}-C_{11}-C_2-C_3$	***25.1***
3	**1e-*trans*** (Pr/^{i}Bu)	$C_2-C_3-C_6-C_7$	***25.8***
		$C_6-C_7-C_{10}-C_{11}$	**−71.5**
		$C_{10}-C_{11}-C_2-C_3$	*22.6*
4	**1f** (H/H)	$C_2-C_3-C_6-C_7$	***25.8***
		$C_6-C_7-C_{10}-C_{11}$	*22.1*
		$C_{10}-C_{11}-C_2-C_3$	**−79.0**

[a]Angles given in boldface correspond to those in black in Figure 2, those in italics to those in red, and those in boldface italics to those in blue.

not sufficiently well positioned as to be optimal for the cycloaddition to take place. Finally, there is the case of macrocycle **1c**, featuring a *tert*-butyl substituent, which has the two acetylenes in closer proximity of the series (in blue, 3.17/3.70 Å) but reacts in a much slower way. We explain this by the fact that two triple bonds which are better suited geometrically for the oxidative addition step are hindered by the *tert*-butyl group and thus might not be reactive, forcing the system to react by another pair of triple bonds (in red, 3.39/4.31 Å and 33.0°) which are less well-positioned for the oxidative addition to take place.

To sum up, the reactivity of the substituted macrocycles is conditioned by (a) the geometry adopted by the macrocycle, which determines the relative position of the acetylenes, and (b) the steric hindrance introduced by the substituents.

All new cycloisomerized products have been characterized by NMR experiments. The unique substituent of the tetrafused benzene derivatives **2b**,**c** breaks the symmetry of these compounds, which could be observed as a single set of resonances in the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of the two compounds show overlapping multiplets between 4.20 and 4.60 ppm corresponding to the 10H of the CH_2 units of the five-membered rings and the CH appears at a lower field. In addition, two of the three methyl groups in the *p*-toluensulfonyl units resonate at the same δ value, while that attached to the N next to the substituent appears at a different δ value. This is in good agreement with the structural differences found in the X-ray structures (see below). The NMR spectra of the disubstituted cycloisomerized compounds **2d**,**e** show two sets of signals with a high degree of signal overlapping, confirming the presence of two diastereoisomers as a 1:1 mixture.

Single-crystal X-ray structures have been obtained for the cycloisomerized compounds **2c**,**d**,**f** (see Figure 3 for perspective views of the molecules and Table 4 for crystal data). Cycloadduct **2d** is obtained as an inseparable mixture of diastereoisomers, and only one of these, namely the *SR*/*RS* pair of enantiomers, has been crystallized. If we compare the X-ray structure for the unsubstituted cycloisomerized structure **2f** (Figure 3) with the compounds having substituents (compound **2c** with one ^{t}Bu substituent and compound **2d** having a methyl and propyl substituents), clear differences can be observed in the orientation of the arylsulfonamide groups. The unsubstituted structure has the three arylsulfonamide units located almost perpendicular to the plane defined by the central tetracyclic fused core, in a structure that resembles a three-legged table. In contrast, in the other two compounds having substituents, one of the arylsulfonamide units is folded toward the center of the structure in an almost parallel position above the central benzene ring formed in the [2 + 2 + 2] cycloaddition reaction. The folded arylsulfonamide rest is always located next to the bulkiest alkane substituent, indicating that steric effects are forcing the folding.

As a singular feature of the structure for cycloisomerized compound **2f**, it can be seen that a dichloromethane molecule[16] is trapped inside the cavity formed by the triazatriindane structure and the three *p*-tolyl units ("below the three-legged table"). The molecule was found disordered in three orientations ($^1/_3$:$^1/_3$:$^1/_3$), was also observed in the ^{1}H NMR spectra, and could not be removed by heating the sample at 40 °C for 1 h, proving the quite strong interactions which exist in this supramolecular structure.

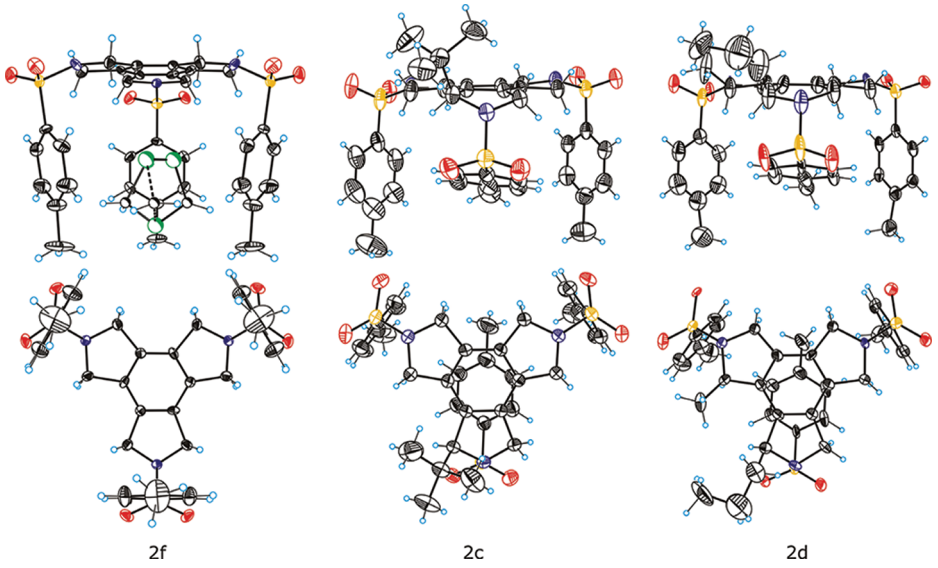

Figure 3. Ortep plots (**2f**, 50% ellipsoids; **2c**,**d**, 30% ellipsoids) of the structure of **2f**,**c**,**d** with two different views of the molecule (side and front views). For **2f** the delocalized dichloromethane molecule is included in the first side view.

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Table 4. Crystallographic Data for Structures 2f,c,d

	2f	2c	2d
empirical formula	$C_{34}H_{35}Cl_2N_3O_6S_3$	$C_{41}H_{49}N_3\ O_7S_3$	$C_{37.25}H_{41.50}Cl_{0.50}N_3O_6S_3$
formula wt	748.73	792.01	741.14
temp, K	153(2)	300(2)	100(2)
wavelength, Å	0.710 73	0.710 73	0.710 73
cryst syst	rhombohedral	monoclinic	monoclinic
space group	*R*3*m*	*C*2/*c*	*Cc*
a, Å	17.866(3)	29.726(8)	23.107(2)
b, Å	17.866(3)	11.085(3)	10.9792(7)
c, Å	9.887(3)	24.760(7)	29.489(2)
β, deg		96.319(5)	96.160(6)
V, Å^3	2733.1(10)	8109(4)	7438.1(10)
Z	3	8	8
ρ(g/cm^3)	1.365	1.297	1.324
Flack param (std)	0.1(2)		0.55(14)
R1[a] ($I > 2\sigma(I)$)	0.0655	0.0703	0.0713
wR2[b]	0.1386	0.1710	0.1710

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum\{w(F_o^2 - F_c^2)^2\}/\sum\{w(F_o^2)^2\}]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0042P)^2]$ and $P = (F_o^2 + 2F_c^2)/3$.

CONCLUSIONS

In conclusion, we have synthesized an array of differently substituted triaza macrocycles and demonstrated that their rhodium-catalyzed [2 + 2 + 2] cycloaddition can be effectively accomplished. A complete structural analysis by means of NMR and X-ray analysis of the macrocycles has allowed us to discuss the effects of the substituents on the conformation of the reactants and thus their reactivity.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Compounds **9**[8] and **11**[6a] were prepared as described by us. 5,5-Dimethyl-2-hexyne-1,4-diol (**5c**)[17] and 3-octyne-2,5-diol (**5d**)[18] were prepared by following the method described previously in the literature.

NMR spectra were recorded on 500, 400, and 200 MHz NMR spectrometers. Chemical shift assignments were performed by a concerted use of 2D COSY, NOESY, HSQC, and HMBC experiments recorded under routine conditions. Chemical shifts (δ) for ^{1}H and ^{13}C NMR were referenced to internal solvent resonances and reported relative to $SiMe_4$. ESI-MS analyses were recorded on an Esquire 6000 Ion Trap Mass Spectrometer (Bruker) equipped with an electrospray ion source.

X-ray Diffraction Studies. Crystals of compounds **1a**,**c**, **1e**-*trans*, and **2c** were used for room-temperature (300(2) K) X-ray structure determinations. The measurements were carried out on a Bruker SMART APEX CCD diffractometer using graphite-monochromated Mo Kα radiation from an X-ray tube. Full-sphere data collection was carried out with ω and φ scans. Programs used: data collection, Smart version 5.631 (Bruker AXS 1997-02); data reduction, SAINT;[19] absorption correction, SADABS.[20] Structure solution and refinement was done using SHELXTL.[21] For compounds **1a**,**c** only extremely weakly diffracting crystals were available and a long exposure time was needed to collect suitable data sets. Due to the small size of the crystals, high R_{int} values and low ratios of observed to unique reflections were obtained. In spite of these bad values, it was considered that these structures were of enough quality to be reported. Since for compound **1c** solvent molecules could not be properly modeled, the program SQUEEZE (Platon) was used.[22] The disordered solvent molecules were treated as a diffuse contribution to the overall scattering without specific atom positions.

Crystals of **2d** were twinned and of low quality. After several attempts a suitable data set could be collected using a crystal fragment of small dimensions (0.04 × 0.03 × 0.01 mm^3). The measured crystal was prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation. Measurements were made on a Bruker-Nonius diffractometer equipped with a APEX 2 4K CCD area detector, a FR591 rotating anode with Mo Kα radiation, Montel mirrors as a monochromator, and a Kryoflex low-temperature device (T = −100(2) °C). Full-sphere data collection was used with ω and φ scans. For data collection Apex2 V2009.1-0 (Bruker-Nonius 2004) and for data reduction[19] and absorption correction SADABS[20] programs were used. For structure solution and refinement SHELXTL[21] was used. A structure solution could be obtained in the space groups *C*2/*c* and *Cc*. Using the centrosymmetrical space group *C*2/*c* the best R1 value refined to 10.5%. Using the space group *Cc* and refining the structure as a racemic twin, the R1 value could be lowered to 7.13%. In the asymmetric unit two independent molecules were refined, which were both disordered in two shifted positions. The ratio of the shifted positions is 50:50 for the first molecule and 61:39 for the second molecule. The disordered shifted positions of the independent molecules are respectively equivalent to a mixture of the *RS* and *SR* enantiomers. In addition to the main molecule, also dichloromethane could be localized in the unit cell. The dichloromethane is localized in two disordered positions with a total occupation ratio of $^1/_4$ molecule of dichloromethane for each organic molecule. The basf parameter related to the twinning of the crystal gave a ratio of 55:45.

A small crystal needle of **2f** was prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation (dimensions 0.28 × 0.14 × 0.04 mm^3). Measurements were made on a Bruker SMART 1000 CCD diffractometer equipped with a MACScience M18X-HF rotating anode with Mo Kα radiation, a graphite monochromator, and a Kryoflex low-temperature device (T = −120(2) °C). Full-sphere data collection was used with ω and φ scans. For data collection SMART (Bruker 2002), for data reduction SAINT,[19] and for absorption correction SADABS[20] programs were used. For structure solution and refinement SHELXTL[21] was used. The measured compound crystallized in the trigonal chiral space group *R*3*m* with $^1/_6$ of the molecule in the asymmetric unit (C_{3v} symmetry). Additionally to the main molecule the unit cell contains a dichloromethane molecule which is disordered in three positions around the *C*3 axes. The structure was refined and solved in the space groups *R*3 and *R*3*m*. Although in the space group *R*3 the disordered dichloromethane molecule can be better refined and a lower R1 value was obtained (R1 = 6.24%), the space group *R*3*m* was selected, due to the higher symmetry (R1 = 6.55%).

All the structures were solved by direct methods and refined by full-matrix least-squares methods on F^2. The non-hydrogen atoms were refined anisotropically. The H atoms were placed in geometrically optimized positions and forced to ride on the atom to which they are attached.

1,4-Alkynediol Synthesis. *6-Methyl-2-heptyne-1,4-diol (**5b**):* prepared according to the method reported in the literature for similar compounds[18] (1.51 g, 60% yield) as a colorless oil; IR (ATR) ν_{max} 3321, 2922, 1466, 1019 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 0.94 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.46−1.73 (m, 2H), 1.85 (m, 1H), 2.40 (br abs, 2H), 4.31 (br abs, 2H), 4.46 (t, $^3J_{H,H}$ = 7.2 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 22.7, 24.8, 46.8, 51.1, 61.1, 83.1, 87.2 ppm; ESI-HRMS calcd *m*/*z* for $[C_8H_{14}O_2 + Na]^+$ 165.0886, found 165.0894.

*2-Methyl-5-decyne-4,7-diol (**5e**):* prepared according to the method reported in the literature for similar compounds[18] (0.86 g, 53% yield) as a mixture of diastereoisomers as a yellowish oil; IR (ATR) ν_{max} 3298, 2933, 1468, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 0.90−0.98 (m, 9H + 9H), 1.40−1.60 (m, 3H + 3H), 1.59−1.76 (m, 3H + 3H), 1.83 (sept, $^3J_{H,H}$ = 6.8 Hz, 1H + 1H), 2.79 (br abs, 2H + 2H), 4.36−4.48 (m, 2H + 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 13.8, 18.5, 18.6, 22.5, 22.6, 24.8, 39.8, 39.9, 46.8, 46.9, 60.9, 62.2, 85.9, 86.0, 86.2, 86.3 ppm; ESI-MS (*m*/*z*) 207.0 $[M + Na]^+$. Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.00; H, 11.17.

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Synthesis of Monosubstituted Macrocycles. *N,N′-Bis(tert-butyloxycarbonyl)-N,N′-bis[(4-methylphenyl)sulfonyl]-1-isobutyl-2-butyne-1,4-diamine (**7b**).* A mixture of *N*-*tert*-butyloxycarbonyl-4-methylphenylsulfonamide (**6**; 3.82 g, 14.07 mmol), 6-methyl-2-heptyn-1,4-diol (**5b**; 1.00 g, 7.04 mmol), and triphenylphosphane (4.80 g, 18.31 mmol) in anhydrous and degassed tetrahydrofuran (70 mL) was stirred and cooled to 0 °C in an ice−water bath. Diisopropyl azodicarboxylate (DIAD; 3.5 mL, 18.05 mmol) was added dropwise to this solution, and the resulting mixture was stirred at room temperature for 5 h 30 min (TLC monitoring). The solvent was removed, and the oily residue was purified by column chromatography on silica gel using hexane/ethyl acetate/dichloromethane mixtures (11/0.5/2) as the eluent to afford **7b** (3.94 g, 86% yield) as a colorless solid: mp 137−139 °C; IR (ATR) ν_{max} 2954, 1728, 1348, 1165, 1087 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, $^3J_{H,H}$ = 6.4 Hz, 6H), 1.31 (s, 18H), 1.76 (m, 1H), 1.86−2.12 (m, 2H), 2.39 (s, 6H), 4.70 (s, 2H), 5.43 (t, $^3J_{H,H}$ = 7.6 Hz, 1H), 7.29 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 4H), 7.87 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.94 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 22.2, 22.6, 25.5, 27.9, 28.0, 36.0, 43.9, 48.5, 79.3, 82.0, 84.8, 84.9, 128.0, 128.3, 129.5, 136.9, 137.5, 144.1, 144.4, 150.2, 150.3 ppm; ESI-HRMS calcd *m*/*z* for $[C_{32}H_{44}N_2O_8S_2 + Na]^+$ 671.2431, found 671.2418. Anal. Calcd for $C_{32}H_{44}N_2O_8S_2$: C, 59.24; H, 6.84; N, 4.32; S, 9.88. Found: C, 58.91; H, 6.93; N, 4.19; S, 9.58.

*N,N′-Bis(tert-butyloxycarbonyl)-N,N′-bis[(4-methylphenyl)-sulfonyl]-1-tert-butyl-2-butyne-1,4-diamine (**7c**).* **7c** was prepared according to the method described above for **7b** (50% yield): colorless solid; mp 107−109 °C; IR (ATR) ν_{max} 2984, 1734, 1351, 1148, 1088 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.26 (s, 9H), 1.31 (s, 9H), 2.39 (s, 6H), 4.74 (br s, 2H), 5.30 (br s, 1H), 7.25−7.31 (m, 4H), 7.81 (m, 2H), 7.95 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 27.8, 27.9, 28.2, 36.2, 37.5, 59.0, 80.1, 81.1, 84.8, 128.3, 129.5, 137.0, 138.0, 143.9, 144.4, 150.3 ppm; ESI-HRMS. calcd *m*/*z* for $[C_{32}H_{44}N_2O_8S_2 + Na]^+$ 671.2431, found 671.2433. Anal. Calcd for $C_{32}H_{44}N_2O_8S_2$: C, 59.24; H, 6.84; N, 4.32. Found: C, 58.81; H, 6.87; N, 4.27.

*N,N′-Bis[(4-methylphenyl)sulfonyl]-1-isobutyl-2-butyne-1,4-diamine (**8b**).* A mixture of **7b** (1.80 g, 2.78 mmol), dichloromethane (8 mL), and trifluoroacetic acid (7.9 mL, 102.54 mmol) was stirred at room temperature for 9 h 30 min (TLC monitoring). The solvent was removed, and the oily residue was redissolved in ethyl acetate (75 mL) and washed with sodium bicarbonate (3 × 75 mL) and brine (75 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent removed by vacuum distillation to afford **8b** (1.14 g, 92% yield) as a colorless solid;mp 109−111 °C; IR (ATR) ν_{max} 3268, 2958, 1327, 1151, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, $^3J_{H,H}$ = 6.6 Hz, 3H), 0.83 (d, $^3J_{H,H}$ = 6.6 Hz, 3H), 1.11−1.42 (m, 2H), 1.62 (m, 1H), 2.45 (s, 6H), 3.50 (m, 2H), 3.87 (m, 1H), 4.26 (t, $^3J_{H,H}$ = 6.0 Hz, 1H), 4.38 (d, $^3J_{H,H}$ = 9.4 Hz, 1H), 7.32 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4H), 7.69 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.73 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 22.1, 24.6, 32.9, 44.1, 45.2, 78.6, 83.3, 127.6, 127.8, 129.6, 129.8, 136.9, 137.6, 144.0, 144.1 ppm; ESI-HRMS calcd *m*/*z* for $[C_{22}H_{28}N_2O_4S_2 + Na]^+$ 471.1383, found 471.1363. Anal. Calcd for $C_{22}H_{28}N_2O_4S_2$: C, 58.90; H, 6.29; N, 6.24. Found: C, 58.26; H, 6.38; N, 5.88.

*N,N′-Bis[(4-methylphenyl)sulfonyl]-1-tert-butyl-2-butyne-1,4-diamine (**8c**).* **8c** was prepared according to the method described above for **8b** (82% yield): colorless solid; mp 105−107 °C; IR (ATR) ν_{max} 3272, 2961, 1325, 1157, 1093 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 9H), 2.45 (s, 3H), 2.46 (s, 3H), 3.47−3.60 (m, 3H), 4.17 (t, $^3J_{H,H}$ = 5.4 Hz, 1H), 4.33 (d, $^3J_{H,H}$ = 10.0 Hz, 1H), 7.31 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.35 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.67 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.72 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 25.9, 32.8, 35.4, 55.5, 79.7, 82.0, 127.5, 127.8, 129.6, 129.9, 136.8, 137.4, 144.0, 144.1 ppm; ESI-HRMS calcd *m*/*z* for $[C_{22}H_{28}N_2O_4S_2 + Na]^+$ 471.1383, found 471.1381. Anal. Calcd for $C_{22}H_{28}N_2O_4S_2 + H_2O$: C, 56.63; H, 6.48; N, 6.00. Found: C, 56.61; H, 6.06; N, 5.63.

*2-Isobutyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triyne (**1b**).* A mixture of **8b** (0.90 g, 2.01 mmol) and potassium carbonate (1.39 g, 10.07 mmol) in acetonitrile (100 mL) was stirred at reflux. The dichloro derivative **9** (0.80 g, 2.32 mmol) in acetonitrile (100 mL) was added dropwise to this solution through a compensating pressure addition funnel, and the resulting mixture was stirred at reflux for 25 h (TLC monitoring). The mixture was cooled to room temperature, the salts were filtered off, and the solvent was removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using hexane/dichloromethane/ethyl acetate mixtures (7/2/1) as the eluent to afford **8b** (1.07 g, 74% yield) as a colorless solid: mp 106−108 °C; IR (ATR) ν_{max} 2922, 1347, 1156, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 0.90 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.34−1.45 (m, 2H), 1.55 (m, 1H), 2.41 (s, 3H), 2.43 (s, 3H), 2.44 (s, 3H), 3.55−3.96 (m, 9H), 4.25 (d, $^2J_{H,H}$ = 18.4 Hz, 1H), 4.47 (t, $^3J_{H,H}$ = 8.0 Hz, 1H), 7.23 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.28 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.30 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.60 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.62 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 22.1, 22.2, 24.4, 33.1, 36.7, 36.8, 37.7, 37.8, 43.4, 47.1, 77.7, 78.0, 78.2, 79.1, 80.0, 83.1, 127.6, 127.7, 127.8, 129.2, 129.5, 129.6, 134.4, 135.1, 137.2, 143.5, 144.1, 144.3 ppm; ESI-HRMS calcd *m*/*z* for $[C_{37}H_{41}N_3O_6S_3 + H]^+$ 720.2230, found 720.2209. Anal. Calcd for $C_{37}H_{41}N_3O_6S_3$: C, 61.73; H, 5.74; N, 5.84. Found: C, 62.06; H, 6.15; N, 5.43.

*2-tert-Butyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triyne (**1c**).* **1c** was prepared according to the method described above for **1b** (30% yield): colorless solid; mp 115−117 °C; IR (ATR) ν_{max} 2922, 1346, 1157, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.39 (s, 3H), 2.43 (s, 3H), 2.44 (s, 3H), 3.40−4.10 (m, 10H), 4.28 (s, 1H), 7.20 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.25 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.31 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.55 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.62 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 21.7, 27.6, 29.8, 36.2, 37.4, 38.3, 38.4, 59.0, 78.4, 79.0, 79.5, 79.7, 79.8, 81.5, 127.8, 127.9, 128.1, 129.1, 129.6, 129.9, 134.7, 135.9, 138.1, 143.5, 143.9, 144.1, 144.5 ppm; ESI-HRMS calcd *m*/*z* for $[C_{37}H_{41}N_3O_6S_3 + H]^+$ 720.2230, found 720.2248. Suitable crystals of **1c** (colorless needles) were grown by slow diffusion of diethyl ether into a CH_2Cl_2 solution.

Synthesis of Disubstituted Macrocycles. *2,5-Bis(p-toluenesulfonyloxy)-3-octyne (**10d**).* 3-Octyn-2,5-diol (**5d**; 0.30 g, 2.11 mmol) was dissolved in a dichloromethane/tetrahydrofuran (6/1, v/v) mixture (6 mL) and cooled to −20 °C. *p*-Toluenesulfonyl chloride (1.00 g, 5.25 mmol) and triethylamine (0.7 mL, 5.02 mmol) were slowly added, and the mixture was stirred at −20 °C for 3 h. Then the mixture was warmed to room temperature while the reaction was monitored by TLC (24 h). The mixture was washed with water (3 × 15 mL) and dried with anhydrous magnesium sulfate and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate mixtures of increasing polarity (9/1 to 8/2) as the eluent to afford **10d** (0.64 g, 68% yield, mixture of diastereoisomers) as a colorless solid: IR (ATR) ν_{max} 2920, 1361, 1170, 1096 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (mixture of diastereoisomers) δ 0.79 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 0.80 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 1.09−1.21 (m, 2H + 2H), 1.22 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.24 (d, $^3J_{H,H}$ = 6.8 Hz, 3H), 1.38−1.59 (m, 2H + 2H), 2.41 (s, 6H), 2.42 (s, 6H), 4.96 (dt, $^3J_{H,H}$ = 6.8 Hz and $^5J_{H,H}$ = 0.8 Hz, 1H), 5.03 (dt, $^3J_{H,H}$ = 7.2 Hz and $^5J_{H,H}$ = 1.6 Hz, 1H), 5.10 (dq, $^3J_{H,H}$ = 6.4 Hz and $^5J_{H,H}$ = 0.8 Hz, 1H), 5.16 (dq, $^3J_{H,H}$ = 6.8 Hz and $^5J_{H,H}$ = 1.6 Hz, 1H), 7.47 (AA′ part of a AA′BB′ system, $^3J_{H,H}$ = 7.6 Hz, 4H + 4H), 7.71−7.79 (m, 4H + 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) (mixture of diastereoisomers) δ 13.0, 13.1, 17.2, 17.3, 21.0, 21.1, 21.7, 21.8, 36.5, 36.6, 67.4, 67.5, 70.6, 70.7, 82.4, 82.5, 84.0, 84.1, 127.5, 127.6, 127.7, 127.8, 129.9, 130.0, 130.1, 132.9, 133.0, 133.1, 145.0, 145.05, 145.1, 145.15 ppm; ESI-HRMS calcd *m*/*z* for $[C_{22}H_{26}O_6S_2 + Na]^+$ 473.1063, found 473.1069. Anal. Calcd for $C_{22}H_{26}O_6S_2$: C, 58.64; H, 5.82; S, 14.23. Found: C, 58.92; H, 5.90; S, 14.46.

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*2-Methyl-4,7-bis(p-toluenesulfonyloxy)-5-decyne (**10e**).* **10e** was prepared according to the method described above for **10d** (73% yield): colorless solid; IR (ATR) ν_{max} 2956, 1367, 1175, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 0.82−0.88 (m, 9H + 9H), 1.23−1.37 (m, 3H + 3H), 1.44−1.70 (m, 4H + 4H), 2.44 (s, 3H + 3H), 2.45 (s, 3H + 3H), 4.82−4.95 (m, 2H + 2H), 7.30−7.35 (m, 4H + 4H), 7.71−7.77 (m, 4H + 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 13.4, 17.9, 18.0, 21.6, 21.7, 21.8, 21.9, 22.4, 22.5, 24.2, 24.3, 37.3, 37.5, 44.2, 44.3, 69.7, 69.8, 70.8, 83.3, 83.5, 83.6, 83.8, 127.9, 128.0, 128.1, 128.15, 128.2, 129.7, 129.8, 129.9, 130.0, 134.0, 134.1, 144.8, 144.9, 145.0, 145.1 ppm; ESI-HRMS calcd m/z for $[C_{25}H_{32}O_6S_2 + Na]^+$ 515.1533, found 515.1517. Anal. Calcd for $C_{25}H_{32}O_6S_2$: C, 60.95; H, 6.55; S, 13.02. Found: C, 61.26; H, 6.69; S, 13.29.

*5-Methyl-2-propyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triyne (**1d**).* A mixture of 1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazaundeca-3,8-diyne (**11**; 0.20 g, 0.33 mmol) and potassium carbonate (0.24 g, 1.75 mmol) in acetonitrile (12 mL) was stirred and heated to reflux. 2,5-Bis(*p*-toluenesulfonyloxy)-3-octyne (**10d**; 0.17 g, 0.38 mmol) in acetonitrile (20 mL) was added dropwise to this solution, and the resulting mixture was stirred at reflux for 19 h (TLC monitoring). The mixture was cooled to room temperature, the salts were filtered off, and the solvent was removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate mixtures (7/3) as the eluent to afford **1d** (0.12 g, 50% yield, mixture of diastereisomers) as a colorless solid: IR (ATR) ν_{max} 2922, 1332, 1156, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.86 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 0.91 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 1.18 (d, $^3J_{H,H}$ = 7.2 Hz, 3H), 1.26−1.33 (m, 2H + 2H), 1.36 (d, $^3J_{H,H}$ = 7.2 Hz, 3H), 1.45−1.68 (m, 2H + 2H), 2.41 (s, 3H), 2.42 (s, 3H), 2.43 (s, 9H), 2.44 (s, 3H), 3.61−3.89 (m, 6H + 6H), 3.97−4.09 (m, 2H + 2H), 4.51 (t, $^3J_{H,H}$ = 7.6 Hz, 1H), 4.57 (dt, $^3J_{H,H}$ = 7.6 Hz and $^5J_{H,H}$ = 2.8 Hz, 1H), 4.67 (q, $^3J_{H,H}$ = 7.2 Hz, 1H), 4.72 (dq, $^3J_{H,H}$ = 7.2 Hz and $^5J_{H,H}$ = 2.8 Hz, 1H), 7.23−7.32 (m, 6H + 6H), 7.50−7.71 (m, 6H + 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 13.5, 19.3, 19.5, 21.5, 21.6, 21.7, 33.8, 33.9, 34.0, 36.8, 36.9, 37.4, 37.5, 37.6, 44.8, 44.9, 49.0, 49.2, 77.5, 77.7, 77.8, 77.9, 80.5, 80.6, 80.7, 80.8, 82.1, 82.3, 83.3, 83.6, 127.4, 127.6, 127.7, 127.8, 127.9, 129.4, 129.5, 129.6, 129.7, 129.8, 134.6, 134.8, 136.7, 136.8, 137.0, 137.1, 143.7, 143.8, 143.9, 144.2, 144.3 ppm; ESI-HRMS calcd m/z for $[C_{37}H_{41}N_3O_6S_3 + Na]^+$ 742.2050, found 742.2061.

*2-Isobutyl-5-propyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triyne (**1e**).* **1e** was prepared according to the method described above for **1d** (40% yield): colorless solid; IR (ATR) ν_{max} 2957, 1333, 1156, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.86−0.94 (m, 9H + 9H), 1.15−1.68 (m, 7H + 7H), 2.42 (s, 12H), 2.44 (s, 6H), 3.67−4.05 (m, 8H + 8H), 4.51 (t, $^3J_{H,H}$ = 7.6 Hz, 1H), 4.57 (dt, $^3J_{H,H}$ = 7.6 Hz and $^5J_{H,H}$ = 2.4 Hz, 1H), 4.64 (t, $^3J_{H,H}$ = 7.6 Hz, 1H), 4.66 (dt, $^3J_{H,H}$ = 7.6 Hz and $^5J_{H,H}$ = 2.4 Hz, 1H), 7.23−7.33 (m, 6H + 6H), 7.58−7.69 (m, 6H + 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 13.5, 13.6, 19.3, 19.5, 21.6, 21.7, 22.0, 22.2, 22.3, 22.5, 24.6, 24.9, 33.9, 34.0, 34.1, 37.1, 37.2, 37.6, 37.7, 37.8, 43.5, 43.8, 47.7, 47.8, 49.2, 49.3, 77.3, 77.6, 77.7, 77.8, 77.9, 80.6, 80.7, 80.8, 82.6, 82.7, 82.8, 83.1, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 129.5, 129.6, 129.61, 129.62, 129.64, 129.8, 134.6, 134.9, 136.8, 136.9, 137.0, 137.1, 143.6, 143.7, 143.8, 144.2, 144.3 ppm; ESI-HRMS calcd m/z for $[C_{40}H_{47}N_3O_6S_3 + Na]^+$ 784.2519, found 784.2513. Suitable crystals of **1e-*trans*** (colorless plates) were grown by slow diffusion of pentane into a CH_2Cl_2 solution.

General Procedure for the [2 + 2 + 2] Cycloaddition Reaction. A degassed mixture of triynic macrocycle **1b** (0.062 g, 0.087 mmol) and chlorotris(triphenylphosphane)rhodium(I) (Wilkinson's catalyst; 0.008 g, 0.008 mmol) in anhydrous and degassed toluene (10 mL) was stirred under a nitrogen atmosphere until completion (TLC monitoring; for temperatures and reaction times for all macrocycles see Table 1). The solvent was removed, and the residue was purified by column chromatography on silica gel using dichloromethane/ethyl acetate mixtures of increasing polarity (1/0 to 40/1) as the eluent to afford **2b** (0.046 g, 75% yield) as a colorless solid.

*1-Isobutyl-2,5,8-tris[(4-methylphenyl)sulfonyl]-1H-2,5,8-triazatrindane (**2b**):* colorless solid (75% yield); mp 162−165 °C; IR (ATR) ν_{max} 2921, 1342, 1162, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 0.88 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.46 (m, 1H), 1.54−1.63 (m, 2H), 2.24 (s, 3H), 2.35 (s, 6H), 4.24−4.42 (m, 10H), 4.88 (m, 1H), 7.05 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.26 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.27 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.52 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.66 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.67 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 21.5, 22.5, 23.8, 24.3, 43.1, 51.7, 51.8, 51.9, 52.0, 63.9, 127.2, 127.5, 127.6, 129.7, 129.9, 130.1, 130.2, 130.5, 130.6, 130.7, 130.8, 133.4, 133.5, 134.5, 136.1, 143.8, 144.1, 144.2 ppm; ESI-HRMS calcd m/z for $[C_{37}H_{41}N_3O_6S_3 + H]^+$ 720.2230, found 720.2191.

*1-tert-Butyl-2,5,8-tris[(4-methylphenyl)sulfonyl]-1H-2,5,8-triazatrindane (**2c**):* colorless solid (70% yield); mp 143−145 °C; IR (ATR) ν_{max} 2923, 1344, 1161, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 2.07 (s, 3H), 2.43 (s, 6H), 4.19−4.69 (m, 10H), 4.49 (s, 1H), 6.65 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.31 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.37 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4H), 7.76 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.77 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.7, 27.2, 39.4, 51.8, 52.0, 52.1, 53.2, 53.6, 74.7, 126.9, 127.8, 128.9, 130.2, 130.4, 130.5, 130.6, 132.1, 133.3, 133.5, 133.7, 134.4, 135.4, 143.7, 144.3, 144.4 ppm; ESI-HRMS calcd m/z for $[C_{37}H_{41}N_3O_6S_3 + H]^+$ 720.2230, found 720.2191. Suitable crystals of **2c** (colorless needles) were grown by slow diffusion of pentane into a THF solution.

*2-Methyl-1-propyl-3,6,9-tris[(4-methylphenyl)sulfonyl]-1H,2H-3,6,9-triazatrindane (**2d**):* colorless solid (99% yield); IR (ATR) ν_{max} 2922, 1342, 1160, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 0.55 (m, 1H), 0.76 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 0.85 (t, $^3J_{H,H}$ = 7.2 Hz, 3H), 1.15 (m, 2H), 1.37 (m, 1H), 1.45 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.51 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.62 (m, 1H), 1.69 (m, 1H), 1.94 (m, 1H), 2.03 (m, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.36 (s, 6H), 2.42 (s, 3H), 2.43 (s, 3H), 4.21−4.48 (m, 8H + 8H), 4.89−5.01 (m, 3H), 5.09 (m, 1H), 6.92 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.14 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.23 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.25 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.33 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.36 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.50 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.64 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.65 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.67 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.73 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.75 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 13.7, 14.0, 16.6, 17.9, 21.4, 21.5, 21.6, 21.7, 22.1, 23.1, 36.0, 37.6, 50.7, 51.3 51.7, 52.0, 52.3, 60.6, 60.9, 64.4, 65.3, 127.1 127.25, 127.27, 127.3, 127.6, 127.7, 129.5, 129.8, 129.9, 130.0, 130.07, 130.1, 130.3, 130.4, 130.5, 130.7, 130.75, 130.77, 131.3, 131.8, 133.5, 133.7, 134.3, 134.7, 134.8, 135.2, 135.7, 135.9, 136.7, 143.7, 143.8, 143.9, 144.0, 144.1, 144.2 ppm; ESI-HRMS calcd m/z for $[C_{37}H_{41}N_3O_6S_3 + Na]^+$ 742.2050, found 742.2014. Suitable crystals of **2d** (colorless needles) were grown by slow diffusion of diethyl ether into a CH_2Cl_2 solution.

*1-Isobutyl-2-propyl-3,6,9-tris[(4-methylphenyl)sulfonyl]-1H,2H-3,6,9-triazatrindane (**2e**):* colorless solid (83% yield); IR (ATR) ν_{max} 2956, 1343, 1159, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 0.46 (m, 1H), 0.65 (d, $^3J_{H,H}$ = 6.8 Hz, 3H), 0.74−0.88 (m, 3H + 3H), 0.91 (m, 1H), 0.90 (d, $^3J_{H,H}$ = 6.8 Hz, 3H), 0.97 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.04 (m, 1H), 1.09 (d, $^3J_{H,H}$ = 6.4 Hz, 3H), 1.15 (m, 1H), 1.31−1.55 (m, 2H + 2H), 1.61−1.75 (m, 3H), 1.94−2.05 (m, 2H), 2.06 (s, 3H), 2.18 (m, 1H), 2.32 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.43 (s, 6H), 3.68−4.55 (m, 8H + 8H), 4.91−5.03 (m, 2H + 2H), 6.56 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H),

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7.17 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.23 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.26 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.31 (BB′ part of an AA′BB′ system $^3J_{H,H}$ = 8.4 Hz, 2H), 7.34 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.38 (AA′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.58 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.65 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.72 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H), 7.75 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.76 (BB′ part of an AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (diastereoisomeric mixture) δ 13.5, 14.0, 16.3, 16.4, 21.1, 21.3, 21.5, 21.6, 22.4, 22.7, 23.7, 23.8, 24.1, 25.3, 36.2, 37.1, 43.1, 43.6, 50.1, 51.8, 51.9, 52.1, 52.4, 63.4, 63.7, 64.5, 65.2, 126.8, 127.1, 127.2, 127.3, 127.6, 127.7, 128.9, 129.8, 129.9, 130.0, 130.1, 130.4, 130.5, 130.6, 131.0, 131.1, 132.3, 133.4, 133.7, 134.0, 134.6, 134.8, 135.2, 135.6, 137.6, 143.5, 143.83, 143.87, 143.9, 144.1, 144.2 ppm; ESI-HRMS calcd m/z for $[C_{40}H_{47}N_3O_6S_3 + Na]^+$ 784.2519, found 784.2481.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, figures, and CIF files giving experimental details, NMR spectra for all new compounds and X-ray crystal structure data for compounds **1a**,**c**, **1e-*trans***, and **2c**,**d**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org. The crystallographic data as well as details of the structure solution and refinement procedures are reported in Tables 2 and 4. CCDC 836317 (**1a**), 836318 (**1c**), 836319 (**1e-*trans***), 836320 (**2c**), 836321 (**2f**), and 836322 (**2d**) also contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.: fax, +44 1223 336033; e-mail, deposit@ccdc.cam.ac.uk.

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(11) Yields were not optimized.

(12) The reaction did not proceed at all when carried out at room temperature.

(13) As an example of how the dihedral angles have been calculated, for structure **1a** (Figure 2), the C2−C3−C6−C7 dihedral angle (entry 1, Table 3) has been calculated as the angle between the planes defined by the C2−C3−C6 atoms and C3−C6−C7 atoms. We call this a dihedral angle and not a torsion angle because of the nonconsecutive nature of the atoms involved.

(14) Except for macrocycle **1f**, having all triple bonds linked by unsubstituted positions.

(15) Although the folding of the **1e-*cis*** diastereoisomer is not known (it has not been possible to obtain suitable crystals for its X-ray analysis), this might be quite favorable for the cycloaddition reaction to occur (the reaction time for the mixture of both diastereoisomers is comparable to that for the unsubstituted macrocycle **1f**).

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