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15 and 30-Membered polyolefinic macrocycles. Periphery modification by aromatic nucleophilic substitution of fluorine

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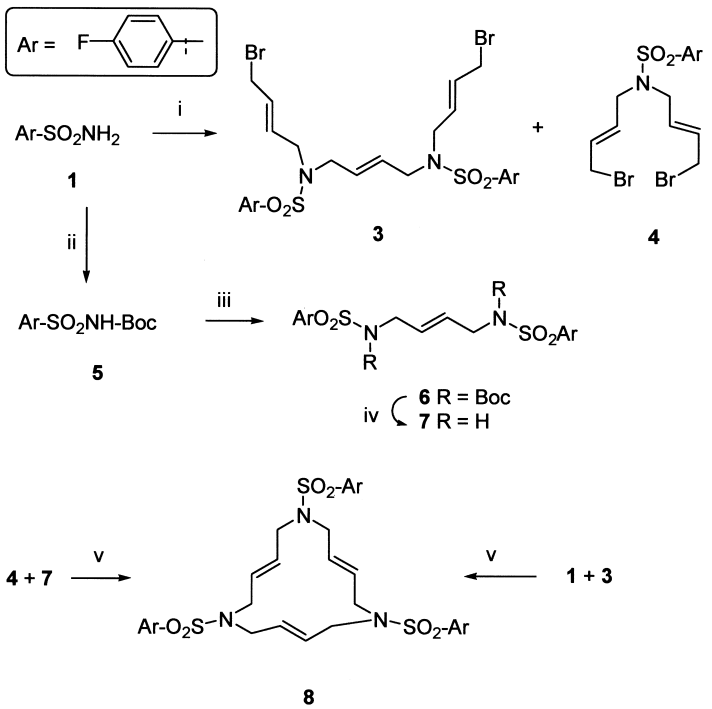
Abstract—Tris[(4-fluorophenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene is a pivotal 15-membered triolefinic macrocycle from which a vast array of different derivatives are prepared by substitution of fluorine atoms. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Nitrogen-containing 15-membered macrocycles are common.[1–3] However, nitrogen-containing, 15-membered macrocycles featuring internal olefinic double bonds are uncommon. Apart from the contribution of our group, the few examples described contain only one double bond, and the key step for their preparation is metathesis.[4,5] Thirty-membered macrocycles containing olefinic double bonds are still more scarce.[6,7]

Tris(arenesulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-trienes such as **8** (Scheme 1) are 15-membered triolefinic macrocycles containing three units ($-CH_2-CH{=}CH-CH_2-N(SO_2-Ar)-$). Members of this family of macrocycles are easily accessible with configurations *E*,*E*,*E*[8] and



Scheme 1. Preparation of **8**; *reagents and conditions*: (i) (*E*)-$BrCH_2CH{=}CHCH_2Br$ (**2**) (sixfold molar), K_2CO_3, CH_3CN; (ii) $(Boc)_2O$, Et_3N, DMAP, dichloromethane; (iii) **2** (0.5 fold molar), K_2CO_3, CH_3CN; (iv) TFAA, dichloromethane; vs K_2CO_3, CH_3CN.

Keywords: macrocycles; aromatic nucleophilic substitution; alkene; phosphane; palladium complex; nitrogen heterocycle; cyclization.

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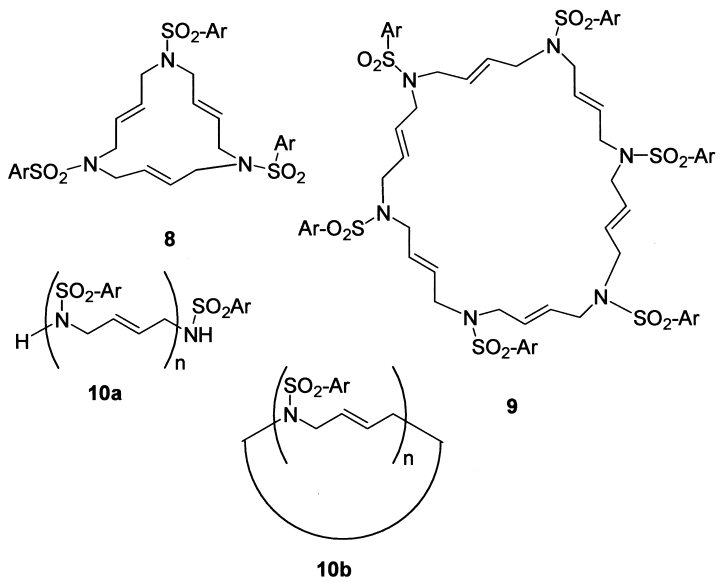


Figure 1. Products formed in the reactions between **4** and **7**.

E,*E*,*Z*.[9] These macrocycles are excellent ligands for palladium(0), platinum(0), and silver(I) by coordination through the olefins.[9,10] The palladium(0)-macrocycle complexes are recoverable catalysts in Suzuki cross-couplings[11] and in the telomerization of butadiene.[12] In particular the polystyrene-anchored version can be recovered by simple filtration.[11] Recent developments include the preparation of 15-membered macrocycles featuring ferrocene units at the sulfonamide groups. These ferrocene-containing macrocycles coordinate palladium(0), and the corresponding complexes exhibit catalytic activity in Suzuki cross-couplings and in the Heck reaction.[13] Twenty-membered macrocycles featuring four ($-CH_2-CH{=}CH-CH_2-N(SO_2-Ar)-$) units have also been prepared.[14]

All 15 and 20-membered macrocycles can be synthesized stepwise from easily available arenesulfonamides and 1,4-dibromobutenes. Moreover, high dilution is a non-crucial factor in their preparation. However, a more profound study has revealed that under certain conditions 30-membered macrocycles containing six repeated units can be isolated. On the other hand, we required a versatile pivotal 15-membered macrocycle which by simple transformations, could be converted into more complicated architectures. In this paper, we present the studies of 4-fluorophenyl series, the analysis of the influence of concentration on the formation of macrocycles, and the aromatic nucleophilic substitution of fluorine with phosphorus, nitrogen, and sulfur nucleophiles.

Table 1. Effect of concentration in the formation of **8**–**10**

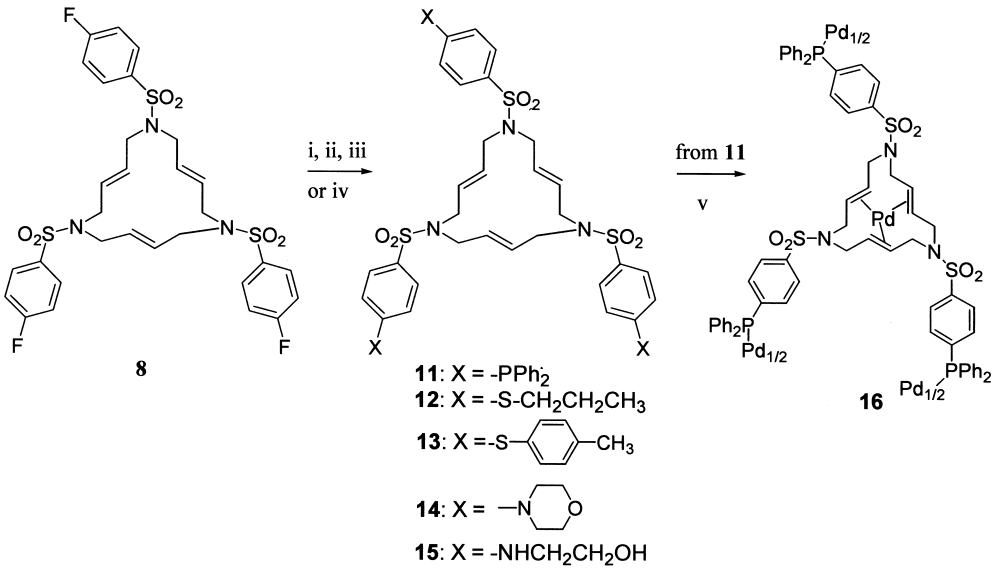
[**4**] and [**7**]/temperature (°C)[a]	**8**, % (crude[b]–pure[c])	**9**, % (crude[b]–pure)	**10**, %[d]
0.0065/70	72	20	–
0.0127/70	82–43	15	–
0.0248/70	63–41	20	16
0.0248/rt	50–34	30	12
0.0496/70	32–23	32–6[e]	29
0.0992/70	20	20	7.11 g[f]

[a] Conditions: anhydrous K_2CO_3 (10 equiv.) was added to a stirred solution of **7** in acetonitrile (80 mL). Then, **4** in acetonitrile (20 mL) was added and the mixture stirred for 12 h.
[b] Monitored by NMR.
[c] Recrystallization from ethyl acetate–hexane.
[d] The residue insoluble in acetonitrile was washed with water, filtered, and dried.
[e] Column chromatography through silica gel with $CHCl_3$–trifluoroacetic acid (95:5 (v/v)).
[f] With higher concentration of starting materials larger amounts of completely insoluble material were obtained.

2. Results

Preparation of tris[(4-fluorophenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene, **8** (Scheme 1) was performed either by reaction of 1,14-dibromo-5,10-diaza-5,10-bis[(4-fluorophenyl)sulfonyl]tetradeca-2,12-diene, **3**, with 4-fluorophenylsulfonamide, **1**, or by reaction of 1,9-dibromo-5-aza-5-[(4-fluorophenyl)sulfonyl]nona-2,7-diene, **4**, with *N*,*N*′-bis-[(4-fluorophenyl)sulfonyl]-2-butene-1,4-diamine, **7**. Thus, reaction of **1** with an excess **2** in the presence of potassium carbonate affords a mixture of **3** (17% yield) and **4** (49% yield), easily separable by column chromatography. Reaction of **3** with sulfonamide **1** afforded **8** in 50% yield. Alternatively, reaction of dibromide **4** with bissulfonamide **7** afforded **8** in yields around 40% in several different batches. The route **4**+**7** is preferred albeit longer due to the higher yield of **4** with respect to **3** in the condensation of arenesulfonamides with dibromobutene **2**. Both synthetic routes are ultimately based on simple or commercially available starting materials: *p*-fluorobenzenesulfonamide, **1**, and (*E*)-1,4-dibromo-2-butene, **2**.

No special precautions concerning high dilution have been adopted. However, we felt that higher concentration ought to favor the formation of higher rings and, eventually, of polymeric materials. Indeed, this is the case. Thus, increased concentrations afforded insoluble material **10**, probably polymeric in nature. Indeed, at intermediate concentrations (Fig. 1 and entry 5 in Table 1) the formation of the



Scheme 2. Nucleophilic aromatic substitutions in **8**; *reagents and conditions*: (i) Ph_2PH, NaOH, DMSO; (ii) 1-propanethiol or *p*-methylthiophenol, K_2CO_3, DMSO, rt; (iii) morpholine, 100°C; (iv) ethanolamine, 100°C; (v) $PdCl_2$, hydrazine hydrate, DMSO, 120°C.

30-membered macrocycle, hexakis[(4-fluorophenyl)sulfonyl]-1,6,11,16,21,26-hexaazacyclotriaconta-3,8,13,18,23,28-hexaene, **9**, gained importance. Mixtures were monitored by ^1H and ^{19}F NMR, compound **8** featuring in $CDCl_3$ a broad singlet and a singlet at δ 5.65 (^1H) and −105.37 (^{19}F), whereas **9** presents the signals at δ 5.56 and −105.33, respectively. A pure sample of **9** was isolated and characterized by MALDI-TOF mass spectrometry (*m*/*z*=1385.1 (M+Na) and 1401.0 (M+K)). Moreover, a third component showed broad peaks at 5.51 and −105.31. Table 1 contains the distribution of **8**, **9**, and higher products **10** depending on concentration. Material **10** was made of polymer **10a** and macrocycles **10b**. MALDI-TOF mass spectra of **10** showed two series of peaks corresponding to *n* values from 5 to 24, with *n*=6 predominating. The difference between consecutive peaks within one series corresponds to *m*/*z*=227 Da (fragment F–Ph–SO_2–N–CH_2–CH=CH–CH_2–), whereas the difference of corresponding peaks of different series is *m*/*z*=52 Da (CH_2–CH=CH–CH_2–2H).

Nucleophilic aromatic substitution with phosphorus,[15,16] nitrogen,[17–20] and sulfur[21,22] have been performed in *p*-fluorobenzenesulfonyl derivatives. Examples with sulfur nucleophiles are more scarce. This synthetic tool has proved very valuable for replacement of the three fluorine atoms of **8** (Scheme 2). Thus, treatment of **8** with the conjugate base of diphenylphosphane afforded **11** in 66% yield. Triple substitution was achieved with sulfur nucleophiles under potassium carbonate in DMSO. In this manner trisulfides **12** and **13** were isolated in 77 and 68% yields. Macrocycle **8** was simply heated in amines such as morpholine or monoethanolamine to afford compounds **14** and **15** in 85 and 77% yield, respectively.

The macrocyclic triphosphane **11** (Scheme 2) was loaded with palladium(0) to afford oligomeric material **16**, featuring two different types of palladium(0) in two different environments. We thought that **16** could be an insoluble and easily recoverable catalyst. The ^{31}P NMR spectrum of **16** presents two singlets at 29.07 (2P) and 29.43 (1P) ppm, showing the typical behavior of palladium(0) complexes of 15-membered macrocycles **8**.[10] Further evidence of the existence of a palladium atom coordinated with the three olefins derives from the chemical shift of olefinic protons which give signals at high field δ<5. Moreover, the ^{31}P NMR chemical shifts indicate coordination of phosphorus atoms with palladium atom (see above). Elemental analysis is compatible with structure **16** where external palladium is coordinated by two phosphanes, defining a sort of PdL_2 complex. This requires 2.5 overall palladium atoms per macrocycle. MALDI-TOF mass spectrum of **16** exhibits a cluster of peaks at *m*/*z* 1288–1291 ($C_{66}H_{60}N_3O_6P_3PdS_3$+H) corresponding to the monomeric complex with a centrally coordinated palladium atom but decoordinated phosphorus atoms. Since this rather insoluble material showed little catalytic activity in Suzuki and Tsuji–Trost reactions, further studies on its structure were not performed.

3. Conclusion

In summary, we have prepared a 15-membered macrocycle featuring three olefins and three *p*-fluorophenylsulfonyl moieties. The fluorine atoms can be replaced by nucleophilic aromatic substitution affording more complicated architectures. Under certain concentration conditions 30-membered macrocycles featuring six olefinic double bonds are accessible.

4. Experimental

4.1. General

^{19}F (223 MHz), ^{31}P (101 MHz), ^1H (250 MHz), and ^{13}C (62.5 MHz) NMR chemical shifts are expressed relative to trifluoroacetic acid, to phosphoric acid, to chloroform (δ 7.26 (^1H) and 77.00 (^{13}C)), and tetramethylsilane, respectively. MALDI-TOF spectra were recorded on a system

equipped with a pulsed nitrogen laser (337 nm), operating in positive-ion reflector mode, and using 19 kV acceleration voltage. Matrices (α-cyanocinnamic acid) were prepared at 5 mg/mL in THF. Analytes were dissolved at concentration between 0.1 and 5 mg/mL in THF or chloroform.

4.1.1. *N*-(*tert*-Butyloxycarbonyl)-4-fluorobenzenesulfonamide, 5. It was prepared in 96% yield by treating **1** with $(Boc)_2O$, triethylamine, and dimethylaminopyridine in dichloromethane according to a general method.[23] It presented mp 112–114°C; IR (KBr) 3270, 1743, 1591, 1346, 1153, 546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 7.22–7.29 (m, 2H), 8.05–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.8, 84.3, 116.1 (d, J=22.9 Hz), 131.1 (d, J=9.5 Hz), 134.8 (br), 149.2, 165.6 (d, J=254.6 Hz); ^{19}F NMR ($CDCl_3$) δ −103.72. Anal. calcd for $C_{11}H_{14}FNO_4S$: C, 47.98; H, 5.12; N, 5.08; S, 11.64; found: C, 47.82; H, 5.11; N, 5.09; S, 11.56.

4.1.2. (*E*)-*N*,*N*′-Bis(*tert*-butyloxycarbonyl)-*N*,*N*′-bis[(4-fluorophenyl)sulfonyl]-2-butene-1,4-diamine, 6. Anhydrous K_2CO_3 (7.60 g, 55.0 mmol) was added under stirring at 65°C to a solution of **5** (3.70 g, 13.4 mmol) in CH_3CN (70 mL). After 30 min, **2** (1.43 g, 6.7 mmol) in CH_3CN (10 mL) was added and the suspension was stirred for 15 h at 65°C. The mixture was filtered and evaporated to afford **6** (3.67 g, 91%), mp 138–140°C; IR (KBr) 1732, 1591, 1494, 1350, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 18H), 4.51 (m, 4H), 5.95 (m, 2H), 7.17–7.23 (m, 4H), 7.94–8.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 27.8, 47.5, 84.7, 115.9 (d, J=23.0 Hz), 129.0, 131.0 (d, J=9.6 Hz), 135.9, 150.4, 165.3 (d, J=256.2 Hz); ^{19}F NMR ($CDCl_3$) δ −104.45. Anal. calcd for $C_{26}H_{32}F_2N_2O_8S_2$: C, 51.82; H, 5.35; N, 4.65; S, 10.64; found: C, 51.67; H, 5.39; N, 4.71; S, 10.47.

4.1.3. (*E*)-*N*,*N*′-Bis[(4-fluorophenyl)sulfonyl]-2-butene-1,4-diamine, 7. A solution of **6** (3.25 g, 5.4 mmol) in TFA/CH_2Cl_2 (20 mL, 1:1) was stirred at rt for 4 h. Then, the solution was evaporated and the residue recrystallized from EtOH to afford **7** (1.90 g, 88%), mp 174–177°C; IR (KBr) 3278, 1596, 1497, 1430, 1328, 1165 cm^{-1}; ^1H NMR ([D_6] DMSO) δ 3.31 (br, 4H), 5.53 (br, 2H), 7.42 (m, 4H), 7.83 (m, 6H); ^{13}C NMR ([D_6] DMSO) δ 43.9, 116.4 (d, J=23.0 Hz), 128.0, 129.7 (d, J=9.6 Hz), 137.2, 164.3 (d, J=250.5 Hz); ^{19}F NMR ([D_6] DMSO) δ −106.71 (br). Anal. calcd for $C_{16}H_{16}F_2N_2O_4S_2$: C, 47.75; H, 4.01; N, 6.96; S, 15.94; found: C, 47.79; H, 3.87; N, 6.92; S, 15.82.

4.1.4. *N*,*N*-Bis[(*E*)-4-bromo-2-butenyl]-(4-fluorophenyl)-sulfonamide, 4, and (*E*,*E*,*E*)-1,14-dibromo-*N*,*N*′-bis[(4-fluorophenyl)sulfonyl]-5,10-diazatetradeca-2,7,12-triene, 3. Anhydrous K_2CO_3 (15.00 g, 110 mmol) was added to a solution of **1** (3.00 g, 17.1 mmol) in CH_3CN (100 mL). The mixture was stirred at 65°C for 30 min. Then, **2** (21.00 g, 102.0 mmol) in CH_3CN (50 mL) was added and the suspension was stirred overnight at 65°C. After filtration and evaporation, the resulting residue was chromatographed with mixtures of hexane/ethyl acetate of increasing polarity. First, **2** (12.20 g) was recovered, then **4** followed by **3** were eluted.

Product **4** (3.8 g, 49%) presented mp 48–55°C (normally obtained as oil); IR (film) 1592, 1493, 1339, 1154, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (d, J=6.4 Hz, 4H), 3.92 (dd, J=6.7, 0.7 Hz, 4H), 5.60 (m, 2H), 5.84 (m, 2H), 7.23 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.1, 48.2, 116.4 (d, J=23.0 Hz), 129.2, 129.8 (d, J=8.6 Hz), 130.9, 136.0 (br), 165.0 (d, J=252.7 Hz); ^{19}F NMR ($CDCl_3$) δ −105.35. Anal. calcd for $C_{14}H_{16}Br_2FNO_2S$: C, 38.12; H, 3.56; N, 3.17; S, 7.27; found: C, 38.35; H, 3.55; N, 3.15; S, 7.19.

Product **3** (0.9 g, 15%) presented mp 93–95°C; IR (KBr) 1593, 1492, 1338, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75–3.82 (m, 8H), 3.90 (m, 4H), 5.51–5.76 (m, 4H), 5.82 (m, 2H), 7.19–7.28 (m, 4H), 7.80–7.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 31.2, 48.2, 48.4, 116.4 (d, J=22.1 Hz), 129.1, 129.7 (d, J=9.6 Hz), 130.7, 135.9 (d, J=3.8 Hz), 165.0 (d, J=255.3 Hz); ^{19}F NMR ($CDCl_3$) δ −105.30. Anal. calcd for $C_{24}H_{26}Br_2F_2N_2O_4S_2$: C, 43.13; H, 3.92; N, 4.19; S, 9.59; found: C, 43.33; H, 3.85; N, 4.13; S, 9.45.

4.1.5. Tris[(4-fluorophenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene, 8. From **1** and **3**. A mixture of **1** (0.27 g, 1.54 mmol) in CH_3CN (40 mL) and anhydrous K_2CO_3 (0.85 g, 6.2 mmol) was stirred at 65°C for 30 min. Then, **3** (1.03 g, 1.54 mmol) in CH_3CN (10 mL) was added and the suspension was stirred overnight at 65°C. After filtration and evaporation the residue was recrystallized from ethyl acetate/hexane to afford **8** (0.52 g, 50%).

From **4** and **7**. To a solution of **7** (see Table 1 for concentration) in CH_3CN (80 mL) anhydrous K_2CO_3 (10 equiv.) was added at the temperature indicated in the table and stirred for 30 min. Then, **4** in acetonitrile (20 mL) was added. The mixture was stirred at rt for 12 h. The reaction mixture was filtered and the filtrate was evaporated. Column chromatography through silica gel (ethyl acetate/hexane) failed to separate of **8** and **9**. Therefore, the residue from acetonitrile evaporation was digested in ethyl acetate. The portion soluble in ethyl acetate was 80% pure **8** (monitored by NMR), and recrystallization from ethyl acetate/hexane gave pure **8**. The ethyl acetate insoluble part was ca. 70% pure **9** (monitored by NMR), from which a pure sample of **9** was obtained by column chromatography using silica gel with $CHCl_3$/TFA (95:5). The initial acetonitrile insoluble solid residue directly from the reaction mixture, also containing inorganic salts, was washed with water, filtered and dried. It was **10** in ca. 80% purity (monitored by NMR). Higher concentrations of starting materials produced larger amounts of completely insoluble **10**.

Macrocycle **8** had mp 146–148°C; IR (KBr) 1591, 1493, 1340, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (br, 12H), 5.62 (br, 6H), 7.23 (m, 6H), 7.82 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 50.6, 116.4 (d, J=23.0 Hz), 129.7 (d, J=9.6 Hz), 129.4, 135.2 (d, J=3.8 Hz), 165.1 (d, J=255.3 Hz); ^{19}F NMR ($CDCl_3$) δ −105.37; MALDI-TOF MS m/z: 705.2 $[M+Na]^+$, 721.2 $[M+K]^+$. Anal. calcd for $C_{30}H_{30}F_3N_3O_6S_3$: C, 52.85; H, 4.44; N, 6.16; S, 14.11; found: C, 52.74; H, 4.70; N, 6.07; S, 14.02.

4.1.6. (*E*,*E*,*E*,*E*,*E*)-1,6,11,16,21,26-Hexakis[(4-fluorophenyl)sulfonyl]-1,6,11,16,21,26-hexaazacyclotriaconta-3,8,13,18,23,28-hexaene, 9. Presented mp 198–208°C; IR (KBr) 1593, 1494, 1341, 1157 cm^{-1}; ^1H NMR

($CDCl_3$/TFA) δ 3.74 (br, 24H), 5.59 (br, 12H), 7.26 (m, 12H), 7.83 (m, 12H); ^{13}C NMR ($CDCl_3$/TFA) δ 49.3, 117.0 (d, J=22.9 Hz), 129.4, 130.1 (d, J=9.5 Hz), 133.9 (br), 164.0 (d, J=255.6 Hz); ^{19}F NMR ($CDCl_3$) δ −105.33; MALDI-TOF MS m/z: 1385.1 $[M+Na]^+$, 1401.0 $[M+K]^+$. Anal. calcd for $C_{60}H_{60}F_6N_6O_{12}S_6$: C, 52.85; H, 4.44; N, 6.16; S, 14.11; found: C, 52.82; H, 4.26; N, 5.91; S, 14.17.

Material **10** presented mp 155–165°C; IR (KBr) 1593, 1494, 1341, 1155 cm^{-1}; ^1H NMR ($CDCl_3$/TFA) δ 3.71 (br, 4H), 5.48 (br, 2H), 7.23 (m, 2H), 7.81 (m, 2H); ^{13}C NMR ($CDCl_3$/TFA) δ 48.6, 116.7 (d, J=21.9 Hz), 128.9, 129.8 (d, J=8.6 Hz), 134.6, 165.4 (d, J=255.6 Hz); ^{19}F NMR ($CDCl_3$) δ −105.31; MALDI-TOF MS m/z for **10b**+K: 1174.2, 1401.2, 1628.2, 1855.3, 2082.3, 2309.4, 2536.5, 2763.6, 2992.7, 3218.7; for **10a**+K and **10b**+K at lower resolution: 3400.8 and 3453.2, 3626.9 and 3679.7, 3854.0 and 3906.3, 4076.6 and 4133.6, 4360.7, 4536.9 and 4588.6, 4761.1 and 4815.1, 4988.7 and 5041.0, 5271.5, 5496.8.

4.1.7. (*E*,*E*,*E*)-1,6,11-Tris{[4-(diphenylphosphino)-phenyl]sulfonyl}-1,6,11-triazacyclopentadeca-3,8,13-triene, 11. Diphenylphosphane (0.12 mL, 0.66 mmol) was added to a solution of **8** (0.10 g, 0.15 mmol) in DMSO (1 mL) maintained under argon atmosphere. Then, a suspension of NaOH in DMSO was added dropwise at rt until the reaction mixture showed a stable yellow-orange color for 10 min. 5% Sulphuric acid was added dropwise until the color disappeared. The solution was stirred vigorously with hexane (2×20 mL) to extract the excess of diphenylphosphine. The DMSO phase was diluted with 5% H_2SO_4 (20 mL) and stirred again vigorously. The precipitate was filtered, washed with water (2×5 mL) and pressed on porous plate. The powder obtained was recrystallized from EtOH/THF (ca. 15 mL/7 mL), the crystals were filtered off and dried under high vacuo to afford **11** (0.12 g, 66%), mp 152–155°C; IR (KBr) 1581, 1435, 1342, 1162, 697, 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (br, 12H), 5.60 (br, 6H), 7.37–7.87 (m, 42H); ^{13}C NMR ($CDCl_3$) δ 50.5, 126.6 (d, J=5.8 Hz), 128.7 (d, J=6.7 Hz), 129.3, 133.5 (d, J=16.3 Hz), 133.9 (d, J=19.2 Hz), 135.4 (d, J=10.6 Hz), 138.9, 144.5 (d, J=16.3 Hz); ^{31}P NMR ($CDCl_3$) δ −3.78; ESIMS MS m/z: 1178.5 $[M-H]^+$, 1179.5 $[M]^+$, 1180.3 $[M+H]^+$, 1196.2 $[M+NH_4]^+$, 1213.3 $[M+Na]^+$. Anal. calcd for $C_{66}H_{60}N_3P_3S_3+1H_2O$: C, 66.15; H, 5.21; N, 3.51; S, 8.03; found: C, 65.91; H, 5.10; N, 3.51; S, 7.92.

4.1.8. (*E*,*E*,*E*)-1,6,11-Tris{[4-(propylthio)phenyl]sulfonyl}-1,6,11-triazacyclopentadeca-3,8,13-triene, 12. Macrocycle **8** (0.10 g, 0.15 mmol) in DMSO (1 mL) was stirred under argon with anhydrous K_2CO_3 (0.20 g). Then propanethiol (0.07 mL, 1.1 mmol) was added and the mixture was stirred for 12 h at rt. The excess of thiol was extracted with hexane (5 mL) from the DMSO phase. Upon addition of 5% H_2SO_4 (20 mL) product **12** precipitated; it was recrystallized from MeOH to afford pure **12** (0.10 g, 77%), mp 125–128°C; IR (KBr) 1580, 1342, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, J=7.3 Hz, 9H), 1.76 (m, 6H), 3.00 (t, J=7.2 Hz, 6H), 3.69 (s, 12H), 5.61 (s, 6H), 7.36 (d, 6H, J=8.8 Hz), 7.66 (d, 6H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 22.0, 34.0, 50.6, 126.8, 127.4, 129.4, 135.1, 144.8; MALDI-TOF MS m/z: 872.2 $[M+Na]^+$, 888.1 $[M+K]^+$. Anal. calcd for $C_{39}H_{51}N_3O_6S_6$: C, 55.09; H, 6.05; N, 4.94; S, 22.63; found: C, 54.79; H, 6.09; N, 4.78; S, 22.41.

4.1.9. (*E*,*E*,*E*)-1,6,11-Tris{[4-(*p*-tolylthio)phenyl]sulfonyl}-1,6,11-triazacyclopentadeca-3,8,13-triene, 13. A solution of **8** (0.10 g, 0.15 mmol) in DMSO (1 mL) was stirred under argon with anhydrous K_2CO_3 (0.20 g). Then *p*-methylthiophenol (0.07 g, 0.59 mmol) was added and the mixture was stirred for 12 h at rt. The excess of thiol was extracted with hexane (5 mL) from the DMSO phase. Upon addition of 5% H_2SO_4 (20 mL) product **13** precipitated. It was recrystallized from $CHCl_3$/hexane to afford pure **13** (0.10 g, 68%), mp 76–80°C; IR (KBr) 1580, 1338, 1161 cm^{-1}; ^1H NMR ([D_6] DMSO) δ 2.36 (s, 9H), 3.61 (s, 12H), 5.40 (s, 6H), 7.21 (d, J=8.4 Hz, 6H), 7.31 (d, J=7.9 Hz, 6H), 7.43 (d, J=7.9 Hz, 6H), 7.64 (d, J=8.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 21.2, 50.6, 126.8, 127.0, 127.5, 129.4, 130.6, 134.8, 135.6, 139.8, 146.1; MALDI-TOF MS m/z: 994.0 $[M+H]^+$, 1016.0 $[M+Na]^+$, 1032.0 $[M+K]^+$. Anal. calcd for $C_{51}H_{51}N_3O_6S_6$+1 $CHCl_3$): C, 56.10; H, 4.70; N, 3.77; found: C, 55.12; H, 4.59; N, 3.69.

4.1.10. (*E*,*E*,*E*)-1,6,11-Tris[(4-morpholinophenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene, 14. Macrocycle **8** (0.10 g, 0.15 mmol) was stirred in morpholine (2.0 mL) for 12 h at 100°C. The formed precipitate was filtered off and recrystallized from $CHCl_3$/THF to afford **14** (0.11 g, 85%), mp 239–242°C; IR (KBr) 1593, 1332, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (t, J=4.9 Hz, 12H), 3.67 (s, 12H), 3.89 (t, J=4.9 Hz, 12H), 5.59 (s, 6H), 6.93 (d, J=9.1 Hz, 6H), 7.66 (d, J=8.9 Hz, 6H); MALDI-TOF MS m/z: 883.5 $[M+H]^+$, 905.5 $[M+Na]^+$, 920.4 $[M+K]^+$. Anal. calcd for $C_{42}H_{54}N_6O_9S_3$+1 $CHCl_3$: C, 51.52; H, 5.43; N, 8.38; found: C, 51.17; H, 5.58; N, 8.23.

4.1.11. (*E*,*E*,*E*)-1,6,11-Tris{[4-(2-hydroxyethylamino)-phenyl]sulfonyl}-1,6,11-triazacyclopentadeca-3,8,13-triene, 15. Macrocycle **8** (0.10 g, 0.15 mmol) was stirred in monoethanolamine (3.0 mL) for 18 h at 100°C. 1 M HCl (75 mL) was added to the solution cooled at rt and the formed precipitate was pressed on a porous plate to afford **15** (0.93 g, 77%), mp 91–93°C (THF/pyridine); IR (KBr) 3382, 1599, 1340, 1319, 1159 cm^{-1}; ^1H NMR ([D_6] DMSO) δ 3.13 (m, 6H), 3.54 (m, 18H), 4.76 (br, 3H), 5.45 (br, 6H), 6.57 (t, J=5.5 Hz, 3H), 6.65 (d, J=8.9 Hz, 6H), 7.42 (d, J=8.9 Hz, 6H); MALDI-TOF MS m/z: 827.3 $[M+Na]^+$, 843.3 $[M+K]^+$. Anal. calcd for $C_{36}H_{48}N_6O_9S_3+1H_2O$: C, 52.54; H, 6.12; N, 10.21; S, 11.69; found: C, 52.35; H, 6.05; N, 10.25; S, 11.30.

4.1.12. Palladium(0) complex of (*E*,*E*,*E*)-1,6,11-tris{((4-diphenylphosphino)phenyl(sulfonyl}-1,6,11-triazacyclopentadeca-3,8,13-trienepalladium(0), 16. $PdCl_2$ (0.03 g, 0.17 mmol) was added under argon in a solution of **11** (0.10 g, 0.085 mmol) in DMSO (2 mL) maintained at 120°C. Hydrazine hydrate (0.1 mL) was added in one portion to the red solution. The dark reaction mixture was quickly cooled down to rt and stirred for 12 h. The precipitate was filtered off, washed with EtOH (2×10 mL) and dried to afford material **16** (0.10 g, 41%), mp 198–204°C; IR (KBr) 1437, 1341, 1162, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.84 (m, 2H), 3.10 (m, 2H), 3.72 (m, 2H), 3.95 (m, 2H), 4.64 (m, 4H), 4.78 (m, 2H), 7.30–8.00

(m, 60H); ^{31}P NMR ($CDCl_3$) δ 29.07 (s, 2P), 29.43 (s, 1P); MALDI-TOF MS *m/z*: 1288.3 $[C_{66}H_{60}N_3O_6P_3PdS_3+H]^+$. Anal. calcd for $C_{66}H_{60}N_3O_6P_3Pd_{2.5}S_3$: C, 50.45; H, 4.18; N, 2.91; found: C, 49.33 and 49.18; H, 4.02 and 3.90; N, 2.63 and 2.63.

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