Electronic Supplementary Information

Fused Tetracycles with a Benzene or Cyclohexadiene Core: [2+2+2] Cycloadditions on Macrocyclic Systems

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Contents

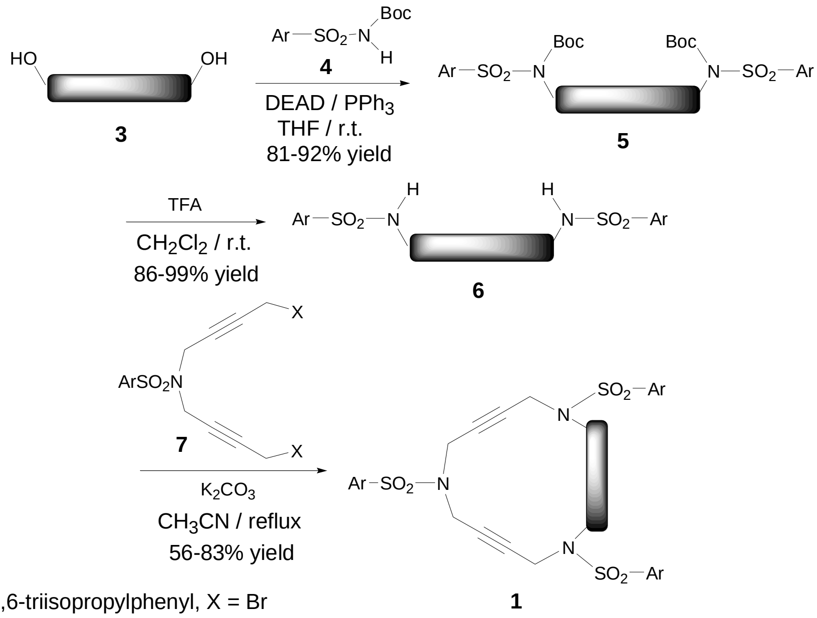
Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All reactions requiring anhydrous conditions were conducted in oven-dried glassware under a dry nitrogen atmosphere. The solvents acetonitrile, dichloromethane and tetrahydrofuran were degassed and dried under nitrogen by passing through solvent purification columns (MBraun, SPS-800). Toluene was distilled under nitrogen over sodium as the drying agent. Solvents were removed under reduced pressure with a rotary evaporator. When necessary, reaction mixtures were chromatographed on silica gel (230-400 mesh) using a gradient solvent system as the eluent.

^{1}H and ^{13}C NMR spectra were recorded on a 600, 500 or 200 MHz NMR spectrometer. Chemical shifts (δ) for ^{1}H and ^{13}C NMR were referenced to internal solvent resonances and reported relative to $SiMe_4$. Characterization of the cycloisomerized compounds were performed using typical gradient-enhanced 2D experiments, such as COSY, NOESY, HSQC, and HMBC, recorded under routine conditions.

2,4,6-Triisopropylphenylsulfonamide, 4-methylphenylsulfonamide, 1,4-dichlorobutyne, and 3-hexyne-1,6-diol, **3d**, are commercially available and used without further purification.

1,4-dibromobutyne,[1] *N-tert*-butyloxycarbonylarylsulfonamides, **4**,[2] 2-pentyne-1,5-diol, **3a,**[3] 2-pentene-1,5-diol, (**3b** + **3c**),[4] (*Z*)-2-phenyl-1,4-dibromo-2-butene[5], (*E*)-2-phenyl-1,4-dibromo-2-butene[6], and 1-methyl-2-butyne-1,5-diol, **3h**,[7] were prepared following the described procedures. 1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazaundeca-3,8-diyne, **8,**[8] (*E*)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3-ene-8,13-diyne, **1e**,[9] *trans*-2,5,8-tris[(4-methylphenyl)sulfonyl]3a,3b-dihydro-1*H*-2,5,8-triazatrindane, **2e**[9] were previously prepared by us.

S.1. Synthesis of macrocycles 1a, 1b, 1c, 1d, 1h



7a, Ar = 2,4,6-triisopropylphenyl, X = Br
7bBr, Ar = 4-methylphenyl, X = Br
7bCl, Ar = 4-methylphenyl, X = Cl

Scheme S1. General synthetic scheme for macrocycles **1a, 1b, 1c, 1d,** and **1h**.

***N,N'*-Bis(4-bromo-2-butinyl)-(2,4,6-triisopropylphenyl)sulfonamide 7a.** A mixture of 2,4,6-triisopropylphenylsulfonamide (0.43g, 1.51 mmols) and potassium carbonate (0.65g, 4.70 mmols) in acetonitrile (30 cm^3) was stirred at room temperature. 1,4-dibromobutyne (1.26g, 5.94 mmols) was added dropwise to this suspension and the resulting mixture was heated to reflux for 16h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The oily residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate (10/1) as the eluent to afford **7a** (0.36g, 55% yield) as a colourless solid (Found: C, 50.49 and 50.50; H, 5.93 and 6.01; N, 2.61 and 2.59; S, 5.56 and 5.57. $C_{23}H_{31}Br_2NO_2S$ requires C, 50.65; H, 5.73; N, 2.57; S, 5.88%); mp 87-89 ºC; ν_{max} (ATR)/cm^{-1} 2960, 2932, 1316 and 1150; δ_H(200 MHz; $CDCl_3$; Me_4Si) 1.23-1.28 (m, 18H), 2.91 (sept, J = 7.0 Hz, 1H), 3.88 (t, J = 2.0 Hz, 4H), 4.03 (sept, J = 6.8 Hz, 2H), 4.14 (t, J = 2.0 Hz, 4H) and 7.17 (s, 2H); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.6, 24.2, 25.4, 30.1, 34.9, 36.2, 80.9, 81.1, 124.8, 130.6, 152.6 and 154.4; *m*/*z* (ESI-MS) 546-548 [M+H]$^+$.

***N,N'*-Bis(4-bromo-2-butinyl)-(4-methylphenyl)sulfonamide (7bBr).** **7bBr** was prepared according to the method described above for **7a**. (26% yield) Colourless oil (Found: C, 41.52 and 42.10; H, 3.49 and 3.57; N, 3.13 and 3.14; S, 6.91 and 6.92. $C_{15}H_{15}Br_2NO_2S$ requires C, 41.59; H, 3.49; N, 3.23; S, 7.40%); ν_{max} (ATR)/cm^{-1} 2921, 1351 and 1163; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.44 (s, 3H), 3.74 (t, J = 2.0 Hz, 4H), 4.19 (t, J = 2.0 Hz, 4H), 7.33 (AA' part of the AA'BB' system, J = 8.4 Hz, 2H) and 7.72 (BB' part of the AA'BB' system, J = 8.4 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 14.3, 22.3, 37.6, 79.9, 81.5, 128.5, 130.3, 135.7 and 144.7; ESI-MS (*m*/*z*) 475-477 $[M+CH_3CN+H]^+$.

***N,N'*-Bis(4-chloro-2-butinyl)-(4-methylphenyl)sulfonamide (7bCl).** **7bCl** was prepared according to the method described above for **7a**. (32% yield) Yellowish oil; ν_{max} (ATR)/cm^{-1} 1349 and 1159; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.43 (s, 3H), 3.97 (s, 4H), 4.18 (s, 4H), 7.32 (AA' part of the AA'BB' system, J = 8.0 Hz, 2H) and 7.72 (BB' part of the AA'BB' system, J = 8.0 Hz, 2H); δ_C (50 MHz, $CDCl_3$, Me_4Si) 22.2, 30.6, 37.5, 79.7, 81.2, 128.5, 130.3, 135.7 and 144.8; *m*/*z* (ESI-MS) 346 $[M+H]^+$; HRMS calcd. for $[C_{15}H_{15}Cl_2NO_2S + Na]^+$: 366.0093. Found: 366.0067.

S.1.1. Synthesis of macrocycle 1a

***N,N'*-Bis(*tert*-butyloxycarbonyl)-*N,N'*-bis(2,4,6-triisopropylphenyl)sulfonyl-2-pentyne-1,5-diamine (5a).** A mixture of *N*-*tert*-butyloxycarbonyl-2,4,6-triisopropylphenylsulfonamide **4a** (1.00g, 2.61 mmols), 2-pentyne-1,5-diol **3a** (0.13g, 1.31 mmol), and triphenylphosphane (0.89g, 3.39 mmols) in anhydrous and degassed tetrahydrofuran (20 cm^3) was stirred and cooled to 0ºC in an ice-water bath. Diethyl azodicarboxylate (DEAD) (0.53 cm^3, 3.39 mmols) was added dropwise to this solution and the resulting mixture was stirred at room temperature for 22h (TLC monitoring). The solvent was removed and the oily residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate (20/1) as the eluent to afford **5a** (0.89g, 81% yield) as a colourless solid (Found: C, 64.94; H, 8.86; N, 3.46. $C_{45}H_{70}N_2O_8S_2$ requires C, 65.03; H, 8.49; N, 3.37%); mp 119-121 ºC; ν_{max} (ATR)/cm^{-1} 2965, 2163, 1726, 1336 and 1148; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.16-1.32 (m, 36H + 18H), 2.60-2.75 (m, 2H), 2.91 (sept, J = 6.9 Hz, 2H), 3.75-4.10 (m, 6H), 4.57 (br s, 2H), 7.13 (s, 2H) and 7.14

(s, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 20.5, 24.3, 25.1, 25.3, 28.4, 28.5, 30.0, 34.9, 35.3, 44.8, 77.4, 80.5, 84.5, 84.7, 124.1, 124.2, 134.2, 134.8, 150.8, 151.2, 151.4, 151.5, 153.9 and 154.0; *m*/*z* (ESI-MS) 853 $[M+Na]^+$ and 869 $[M+K]^+$.

***N,N'*-Bis(2,4,6-triisopropylphenyl)sulfonyl-2-pentyne-1,5-diamine (6a).** A mixture of **5a** (0.80g, 0.96 mmols), dichloromethane (6 cm^3) and trifluoroacetic acid (4 cm^3, 34.69 mmol) was stirred at room temperature for 1h (TLC monitoring). The solvent was removed and the oily residue was redissolved in ethyl acetate (10 cm^3), and washed with sodium bicarbonate (3x10 cm^3) and brine (10 cm^3). The organic layer was dried with anhydrous sodium sulfate and the solvent removed by vacuum distillation to afford **6a** (0.55g, 89% yield) as a colourless solid; mp 153-155 ºC; ν_{max} (ATR)/cm^{-1} 3267, 2960, 1323 and 1143; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.25 (d, *J* = 6.6 Hz, 24H), 1.27 (d, *J* = 6.6 Hz, 12H), 2.15-2.25 (m, 2H), 2.75-2.90 (m, 2H), 2.91 (sept, *J* = 6.6 Hz, 2H), 3.77 (d, *J* = 6.0 Hz, 2H), 4.11 (sept, *J* = 6.6 Hz, 4H), 4.53 (t, *J* = 6.0 Hz, 1H), 4.65 (t, *J* = 6.4 Hz, 1H), 7.15 (s, 2H) and 7.16 (s, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 20.7, 24.2, 25.5, 30.2, 30.3, 33.6, 34.8, 41.9, 77.6, 82.2, 124.5, 133.0, 150.9, 151.1, 153.5 and 153.6; *m*/*z* (ESI-MS) 631 $[M+H]^+$; HRMS calcd. for $[C_{35}H_{54}N_2O_4S_2 + H]^+$: 631.3598. Found: 631.3583.

1,6,11-Tris[(2,4,6-triisopropylphenyl)sulfonyl]-1,6,11-triazacyclohexadeca-3,8,13-triyne (1a). A mixture of **6a** (0.45g, 0.71 mmol) and potassium carbonate (0.49g, 3.55 mmols) in acetonitrile (50 cm^3) was stirred at room temperature. A solution of **7a** (0.45g, 0.82 mmols) in acetonitrile (5 cm^3) was added dropwise, and the resulting mixture was stirred at reflux for 25h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate (15/1) as the eluent to afford **1a** (0.59g, 82% yield) as a colourless solid (Found: C, 68.02 and 67.92; H, 8.19 and 8.36; N, 4.13 and 4.15; S, 9.04 and 9.15. $C_{58}H_{83}N_3O_6S_3{\cdot}CH_3OH$ requires C, 67.71; H, 8.38; N, 4.02; S, 9.19%); mp 195-197 ºC; ν_{max} (ATR)/cm^{-1} 2960, 1320 and 1152; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.24 (apparent t, *J* = 6 Hz, 54H), 2.52 (br abs, 2H), 2.90 (sept, *J* = 6.8 Hz, 3H), 3.57 (t, *J* = 6.8 Hz, 2H), 3.92-4.13 (m, 6H), 4.04 (br s, 10H) and 7.15 (s, 6H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 19.3, 24.2, 25.4, 30.0, 34.9, 36.2, 36.6, 37.1, 37.6, 44.9, 76.4, 79.0, 79.5, 80.6, 80.7, 84.1, 124.8, 130.3, 130.5, 130.8, 152.4, 152.5, 154.3, 154.4 and 154.5; *m*/*z* (ESI-MS) 1014 $[M+H]^+$.

S.1.2. Synthesis of macrocycles 1b and 1c

(*E*)-*N*,*N*'-Bis(*tert*-butyloxycarbonyl)-*N*,*N*'-bis[(4-methylphenyl)sulfonyl]-2-pentene-1,5-diamine (5b) and (*Z*)-*N*,*N*'-Bis(*tert*-butyloxycarbonyl)-*N*,*N*'-bis[(4-methylphenyl)sulfonyl]-2-pentene-1,5-diamine (5c). The **5b** and **5c** 4.5:1 mixture was prepared according to the method described above for **5a**. (86% yield) Pale yellow oil (Found: C, 57.10; H, 7.04; N, 4.59; S, 10.16. $C_{29}H_{40}N_2O_8S_2$ requires C, 57.22; H, 6.62; N, 4.60; S, 10.53%); ν_{max} (ATR)/cm^{-1} 2979, 1724, 1351 and 1152; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.35 (s, 18H + 18H), 2.44 (s, 6H + 6H), 2.47-2.59 (m, 2H + 2H), 3.83-3.94 (m, 2H + 2H), 4.40 (d, *J* = 5 Hz, 2H, **5b**), 4.54 (d, *J* = 4.6 Hz, 2H, **5c**), 5.61-5.85 (m, 2H + 2H), 7.31 (AA' part of the AA'BB' system, *J* = 8.2 Hz, 4H + 4H) and 7.79 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 4H + 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) (mixture of **5b** and **5c**) 21.7, 28.0, 33.2, 46.4, 48.2, 84.3, 84.3, 127.9, 128.1, 129.3, 129.4, 130.7, 137.4, 137.5, 144.1, 144.2, 150.8 and 151.9; *m*/*z* (ESI-MS) 631 $[M+Na]^+$.

(*E*)-*N*,*N*'-bis[(4-methylphenyl)sulfonyl]-2-pentene-1,5-diamine (6b) and (*Z*)-*N*,*N*'-bis[(4-methylphenyl)sulfonyl]-2-pentene-1,5-diamine (6c). The **6b** and **6c** mixture was prepared according to the method described above for **6a**. (88% yield) Pale yellow oil; ν_{max} (ATR)/cm^{-1} 3277, 2925, 1320 and 1152; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.03-2.20 (m, 2H + 2H), 2.42 (s, 6H + 6H), 2.95 (apparent q, *J* = 6.4 Hz, 2H + 2H), 3.47 (t, *J* = 6 Hz, 2H, **6b**), 3.55 (t, *J* = 6.2 Hz, 2H, **6c**), 4.82 (br abs, 2H + 2H), 5.26-5.51 (m, 2H + 2H), 7.30 (AA' part of the AA'BB' system, *J* = 8.2 Hz, 4H + 4H) and 7.73 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 4H + 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) (mixture of **6b** and **6c**) 21.6, 29.7, 32.1, 40.0, 42.2, 42.4, 45.0, 127.1, 127.2, 128.4, 129.8, 136.9, 137.0 and 143.5; *m*/*z* (ESI-MS) 431 $[M+Na]^+$ and 447 $[M+K]^+$; HRMS calcd. for $[C_{19}H_{24}N_2O_4S_2 + Na]^+$: 431.1070. Found: 431.1070.

(*E*)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclohexadeca-13-ene-3,8-diyne (1b) and (*Z*)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclohexadeca-13-ene-3,8-diyne (1c). The mixture of **6b** and **6c** (0.12g, 0.29 mmols) and potassium carbonate (0.20g, 1.48 mmols) in acetonitrile (30 cm^3) was stirred at room temperature. A solution of **7bBr** (0.15g, 0.34 mmols) in acetonitrile (4 cm^3) was added dropwise to this solution and the resulting mixture was stirred at reflux for 25h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate/dichloromethane of increasing polarity (9/1/0 to 7/1/3) as the eluent to afford separately **1b** (0.13g, 63% yield) as a colourless solid and **1c** (0.03g, 13% yield) as a colourless solid.

(*E*)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclohexadeca-13-ene-3,8-diyne (1b): mp 118-121 ºC (dec); ν_{max} (ATR)/cm^{-1} 2921, 1345, 1157 and 1090; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.25 (apparent q, *J* = 6.6 Hz, 2H), 2.44 (s, 9H), 3.11 (t, *J* = 7 Hz, 2H), 3.67 (d, *J* = 6.6 Hz, 2H), 3.70-3.90 (m, 8H), 5.28-5.46 (m, 1H), 5.52-5.70 (m, 1H), 7.27-7.35 (m, 6H) and 7.56-7.66 (m, 6H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.6, 30.6, 36.7, 36.8, 37.3, 37.9, 47.3, 50.7, 77.5, 78.5, 79.7, 80.4, 126.4, 127.5, 127.7, 127.9, 129.7, 129.9, 132.6, 134.8, 135.2, 135.9, 143.9, 144.1 and 144.4; HRMS calcd. for $[C_{34}H_{37}N_3O_6S_3 + Na]^+$: 702.1737. Found: 702.1707.

(*Z*)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclohexadeca-13-ene-3,8-diyne (1c): mp 176-179 ºC (dec); ν_{max} (ATR)/cm^{-1} 2921, 1351, 1164 and 1091; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.30-2.40 (m, 2H), 2.41 (s, 3H), 2.46 (s, 6H), 2.90-3.05 (m, 2H), 3.47 (s, 2H), 3.59 (s, 2H), 3.75 (d, *J* = 7.0 Hz, 2H), 3.82 (s, 2H), 3.98 (s, 2H), 5.25-5.39 (m, 1H), 5.50-5.64 (m, 1H), 7.22-7.36 (m, 6H) and 7.55-7.70 (m, 6H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.7, 27.4, 35.5, 36.1, 36.3, 37.8, 42.7, 47.3, 77.5, 77.9, 79.0, 80.1, 126.4, 127.4, 127.9, 129.8, 129.9, 130.9, 134.5, 135.6, 135.7, 144.1, 144.4 and 144.6; HRMS calcd. for $[C_{34}H_{37}N_3O_6S_3 + Na]^+$: 702.1737. Found: 702.1707.

S.1.3. Synthesis of macrocycle 1d

(*E*)-*N,N'*-Bis(*tert*-butyloxycarbonyl)-*N,N'*-bis[(4-methylphenyl)sulfonyl]-3-hexene-1,6-diamine (5d). 5d was prepared according to the method described above for **5a**. (92% yield) Colourless solid (Found: C, 57.57; H, 7.28; N, 4.67. $C_{30}H_{42}N_2O_8S_2$ required C, 57.86; H, 6.80; N, 4.50%);.mp 137-138 ºC; ν_{max} (ATR)/cm^{-1} 2974, 1726, 1340 and 1151; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.35 (s, 18H), 2.44 (s, 6H), 2.35-2.54 (m, 4H), 3.84 (t, *J* = 7.5 Hz, 4H), 5.52 (br abs, 2H), 7.30 (AA' part of the AA'BB' system, *J* = 8.0 Hz, 4H) and 7.79 (BB' part of the AA'BB' system, *J* = 8.0 Hz, 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.3, 28.6, 34.1, 47.3, 84.7, 128.5, 129.6, 129.9, 138.2, 144.7 and 151.6; *m*/*z* (ESI-MS) 645 $[M+Na]^+$ and 661 $[M+K]^+$.

***N,N'*-Bis(4-methylphenyl)sulfony-3-hexene-1,6-diamine (6d). 6d** was prepared according to the method described above for **6a**. (99% yield) Colourless; solid mp 139-141 ºC; ν_{max} (ATR)/cm^{-1} 3258, 2846, 1314, 1156 cm^{-1}; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.08-2.20 (m, 4H), 2.42 (s, 6H), 2.96 (apparent q, *J* = 6.4 Hz, 4H), 4.80 (t, *J* = 6.1 Hz, 2H), 5.25-5.33 (m, 2H), 7.29 (AA' part of the AA'BB' system, *J* = 8.0 Hz, 4H) and 7.74 (BB' part of the AA'BB' system, *J* = 8.0 Hz, 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.2, 33.2, 43.1, 127.7, 130.1, 130.4, 137.7 and 144.0; *m*/*z* (ESI-MS) 423 $[M+H]^+$, 445 $[M+Na]^+$ and 461 $[M+K]^+$; HRMS calcd. for $[C_{20}H_{26}N_2O_4S_2 + H]^+$: 423.1407. Found: 423.1397.

(*E*)-1,6,11-Tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacycloheptadeca-14-ene-3,8-diyne (1d). 1d was prepared according to the method described above for **1b/1c**. (83% yield) Colourless solid (Found: C, 60.33 and 60.23; H, 5.78 and 5.89; N, 6.04 and 6.04; S, 13.68 and 13.59. $C_{35}H_{39}N_3O_6S_3$ requires C, 60.58; H, 5.67; N, 6.06; S, 13.86%); mp 214-216 ºC (dec.); ν_{max} (ATR)/cm^{-1} 2957, 1353, 1328, 1161 and 1091; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.14-2.26 (m, 4H), 2.45 (s, 9H), 3.10 (t, *J* = 6.6 Hz, 4H), 3.82 (s, 4H), 3.84 (s, 4H), 5.44 (br abs, 2H), 7.31 (AA' part of the AA'BB' system, *J* = 7.9 Hz, 6H) and 7.62 (BB' part of the AA'BB' system, *J* = 7.9 Hz, 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.21, 22.25, 31.8, 37.0, 38.5, 48.5, 78.3, 80.5, 128.1, 128.6, 129.8, 130.3, 130.4, 135.4, 136.0, 144.5 and 144.9; *m*/*z* (ESI-MS) 694 $[M+H]^+$, 716 $[M+Na]^+$ and 732 $[M+K]^+$; HRMS calcd. for $[C_{35}H_{39}N_3O_6S_3 + Na]^+$: 716.1893. Found: 716.1891.

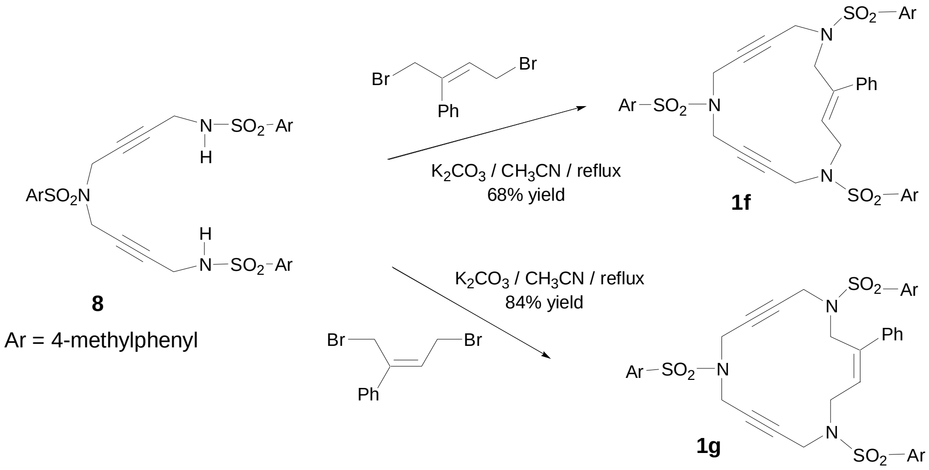
S.1.4. Synthesis of macrocycle 1h

***N,N'*-Bis(*tert*-butyloxycarbonyl)-*N,N'*-bis[(4-methylphenyl)sulfonyl]-1-methyl-2-butyn-1,4-diamine (5h).** **5h** was prepared according to the method described above for **5a**. (89% yield) Colourless solid (Found: C, 56.52 and 56.88; H, 6.85 and 6.87; N, 4.42 and 4.44. $C_{29}H_{38}N_2O_8S_2$ requires C, 57.41; H, 6.31; N, 4.62.); mp 148-151 ºC; ν_{max} (ATR)/cm^{-1} 2983, 1723, 1346 and 1150; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.31 (s, 9H), 1.32 (s, 9H), 1.76 (d, *J* = 7 Hz, 3H), 2.39 (s, 3H), 2.40 (s, 3H), 4.70 (d, *J* = 1.6 Hz, 2H), 5.54 (qt, *J* = 7.0 Hz and *J* = 1.6 Hz, 1H), 7.28 (AA' part of the AA'BB' system, *J* = 8.4 Hz, 4H), 7.86 (BB' part of the AA'BB' system, *J* = 8.4 Hz, 2H) and 7.92 (BB' part of the AA'BB' system, *J* = 8.4 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.7, 22.0, 27.9, 28.0, 35.9, 45.4, 78.6, 82.7, 84.8, 84.9, 127.9, 128.3, 129.4, 129.5, 136.9, 137.5, 144.2, 144.4, 150.2 and 150.3; HRMS calcd. for $[C_{29}H_{38}N_2O_8S_2 + Na]^+$: 629.1962. Found: 629.1970.

***N,N'*-bis[(4-methylphenyl)sulfonyl]-1-methyl-2-butyn-1,4-diamine (6h).** **6h** was prepared according to the method described above for **6a**. (86% yield) Colourless solid (Found: C, 56.01 and 56.03; H, 5.82 and 5.85; N, 6.64 and 6.65; S, 15.31 and 15.30. $C_{19}H_{22}N_2O_4S_2$ requires C, 56.14; H, 5.45; N, 6.89; S, 15.78%); mp 175-177 ºC; ν_{max} (ATR)/cm^{-1} 3260, 2924, 1329, 1152 and 1090; δ_H(200 MHz, DMSO-d_6, Me_4Si) 1.04 (d, *J* = 7.0 Hz, 3H), 2.39 (s, 3H), 2.40(s, 3H), 3.40 (d, *J* = 3.8 Hz, 2H), 3.75-3.95 (m, 1H), 7.38 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.40 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.67 (BB' part of the AA'BB' system, *J* = 8 Hz, 4H) and 7.87-7.96 (m, 2H); δ_C(50 MHz, DMSO-d_6, Me_4Si) 20.9, 21.9, 31.8, 40.2, 78.0, 83.1, 126.6, 129.2, 129.4, 137.6, 138.2, 142.5 and 142.6; HRMS calcd. for $[C_{19}H_{22}N_2O_4S_2 + Na]^+$: 429.0913. Found: 429.0929.

2-Methyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triyne (1h). A mixture of **6h** (1.00g, 2.46 mmols) and potassium carbonate (1.70g, 12.32 mmols) in acetonitrile (100 cm^3) was stirred at room temperature. **7bCl** (0.98g, 2.86 mmols) in acetonitrile (10 cm^3) was added dropwise to this solution and the resulting mixture was stirred at reflux for 18h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using mixtures of hexane/dichloromethane/ethyl acetate (7/2/2) as the eluent to afford **1h** (0.93g, 56% yield) as a colourless solid; mp 156-159 ºC (dec); ν_{max} (ATR)/cm^{-1} 2921, 1337, 1156 and 1089; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.24 (d, *J* = 7 Hz, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 2.45 (s, 3H), 3.60-4.32 (m, 10H), 4.56 (apparent q, *J* = 7 Hz, 1H), 7.20-7.35 (m, 6H) and 7.55-7.70 (m, 6H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.4, 21.7, 33.2, 36.8, 37.0, 37.9, 38.0, 44.6, 77.6, 78.1, 78.2, 79.5, 80.3, 83.7, 127.6, 127.8, 128.0, 129.5, 129.7, 134.6, 135.5, 137.2, 143.8, 144.2 and 144.4; *m*/*z* (ESI-MS) 678 $[M+H]^+$ and 700 $[M+Na]^+$ and 716 $[M+K]^+$; HRMS calcd. for $[C_{34}H_{35}N_3O_6S_3 + Na]^+$: 700.1580. Found: 700.1557.

S.2. Synthesis of macrocycles 1f and 1g



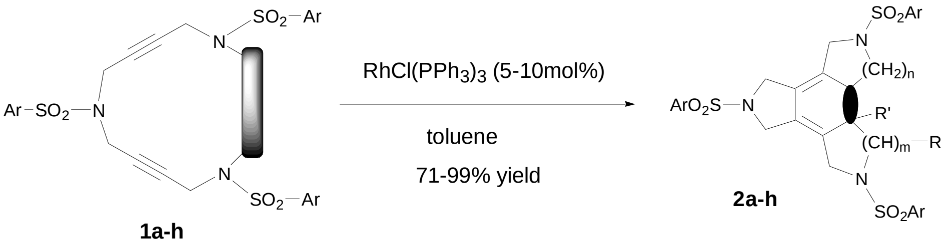
Scheme S2. Synthetic scheme for macrocycles **1f** and **1g**

(*Z*)-3-Phenyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3-ene-,8,13-diyne (1f). A mixture of 1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazaundeca-3,8-diyne, **8** (0.2g, 0.32 mmols) and potassium carbonate (0.23g, 1.63 mmols) in acetonitrile (20 cm^3) was stirred and heated to reflux. (*Z*)-2-phenyl-1,4-dibromo-2-butene (0.10g, 0.35 mmols) in acetonitrile (20 cm^3) was added dropwise to this solution and the resulting mixture was stirred at reflux for 2h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate of increasing polarity (from 8:2 to 6:4) as the eluent to afford **1f** (0.17g, 68% yield) as a colourless solid (Found: C, 62.79 and 62.92; H, 5.44 and 5.48; N, 5.71 and 5.70; S, 12.75 and 12.78. $C_{39}H_{39}N_3O_6S_3$ requires C, 63.13; H, 5.30; N, 5.66; S, 12.97%); mp 201-203 ºC; ν_{max} (ATR)/cm^{-1} 2924, 2855, 1329 and 1154; δ_H(500 MHz, $CDCl_3$, Me_4Si) 2.26 (dd, *J* = 11 and 9.5 Hz, 1H), 2.39 (s, 3H), 2.42 (s, 3H), 2.46 (s, 3H), 2.94 (br abs, 1H), 3.03 (d, *J* = 10 Hz, 1H), 3.13 (br abs, 1H), 3.62 (dd, *J* = 9 and 8 Hz, 1H), 3.68 (d, *J* = 15 Hz, 1H), 3.80 (br abs, 1H), 3.84-3.99 (m, 4H), 4.05 (d, *J* = 15 Hz, 1H), 4.42 (d, *J* = 10 Hz, 1H), 6.88 (d, *J* = 7 Hz, 2H), 7.12-7.18 (m, 3H), 7.19 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.24 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.34 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.47 (BB' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.55 (BB' part of the AA'BB' system, *J* = 8.5 Hz, 2H) and 7.72 (BB' part of the AA'BB' system, *J* = 8.5 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.2, 37.0, 38.6, 38.7, 39.8, 49.0, 54.1, 79.0, 79.2, 80.0, 81.4, 127.9, 128.4, 128.5, 128.8, 129.2, 129.5, 130.1, 130.3, 135.7, 136.3, 136.7, 136.8, 144.3 and 144.7; *m/z* (ESI-MS) 742 $[M+H]^+$ and 759 $[M+NH_4]^+$.

(*E*)-3-Phenyl-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3-ene-,8,13-diyne (1g). A mixture of **8** (0.2g, 0.32 mmols) and potassium carbonate (0.23g, 1.63 mmols) in acetonitrile (20 cm^3) was stirred and heated to reflux. (*E*)-2-phenyl-1,4-dibromo-2-butene (0.10g, 0.35 mmols) in acetonitrile (20 cm^3) was added dropwise to this solution and the resulting mixture was stirred at reflux for 2h (TLC monitoring). The mixture was cooled to room temperature, the salts filtered off, and the solvent removed by vacuum evaporation. The residue was purified by column chromatography on silica gel using mixtures of hexane/ethyl acetate of increasing polarity (from 8:2 to 7:3) as the eluent to afford **1g** (0.20g, 84% yield) as a colourless solid (Found: C, 62.47 and 62.12; H, 5.67 and 5.75; N, 5.47 and 5.44; S, 12.22 and 12.14. $C_{39}H_{39}N_3O_6S_3$.EtOAc requires C, 62.22; H, 5.71; N, 5.06; S, 11.59%); mp 189-191 ºC; ν_{max} (ATR)/cm^{-1} 2920, 2851, 1341 and 1155; δ_H(600 MHz, $CDCl_3$, Me_4Si) 2.42 (s, 3H), 2.43 (s, 3H), 2.45 (s, 3H), 2.48 (dd, *J* = 12 and 8 Hz, 1H), 2.71 (br abs, 1H), 2.69 (d, *J* = 9.6 Hz, 1H), 3.60-3.63 (m, 1H + 1H + 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.75-3.79 (m, 1H + 1H), 3.84 (d, *J* = 15 Hz, 1H), 3.90 (d, *J* = 9 Hz, 1H), 4.02 (d, *J* = 15 Hz, 1H), 4.07 (d, *J* = 15 Hz, 1H), 6.95-6.98 (m, 2H), 7.15-

7.18 (m, 3H), 7.18 (AA' part of the AA'BB' system, *J* = 8.4 Hz, 2H), 7.20 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.34 (AA' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.46 (BB' part of the AA'BB' system, *J* = 8 Hz, 2H), 7.64 (BB' part of the AA'BB' system, *J* = 8.5 Hz, 2H) and 7.68 (BB' part of the AA'BB' system, *J* = 8.5 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.2, 22.3, 35.9, 37.2, 38.3, 38.5, 44.1, 44.2, 79.6, 79.9, 80.1, 80.2, 127.5, 128.3, 128.8, 128.9, 129.8, 130.1, 130.3, 130.4, 136.0, 136.1, 136.7, 138.9, 139.4, 144.7 and 144.8; *m*/*z* (ESI-MS) 742 $[M+H]^+$.

S.3. [2+2+2] Cycloisomerization reactions of macrocycles 1a-1h



Scheme S3. [2+2+2] Cycloisomerization reactions of macrocycles **1**

2,6,9-Tris[(2,4,6-triisopropylphenyl)sulfonyl]-1,2,3,4,5,6,7,8,9,10-decahydrodipyrrolo-[3,4-*f*,*h*]isoquinoline (2a). A degassed mixture of triynic macrocycle **1a** (0.05g, 0.05 mmol) and chlorotris(triphenylphosphane)rhodium(I) (Wilkinson's catalyst) (0.0023g, 0.0025 mmol) in anhydrous and degassed toluene (10 cm^3) was stirred and heated to 90ºC for 28h under a nitrogen atmosphere (TLC monitoring). The solvent was removed and the residue was purified by column chromatography on silica gel using mixtures of hexane:dichloromethane of increasing polarity (1:10 to 1:12) as the eluent to afford **2a** (0.04g, 81% yield) as a colourless solid. mp 235-237 ºC (dec); ν_{max} (ATR)/cm^{-1} 2958, 1315 and 1151; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.13-1.32 (m, 54H), 2.69 (br abs, 2H), 2.80-3.10 (m, 3H), 3.49 (t, *J* = 5.2 Hz, 2H), 4.03-4.31 (m, 6H), 4.12 (br s, 2H), 4.39 (br s, 2H), 4.49 (br s, 6H), 7.16 (s, 2H) and 7.19 (s, 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 24.2, 25.5, 26.7, 30.1, 34.9, 41.9, 44.3, 51.6, 52.0, 124.6, 124.7, 127.4, 128.7, 129.5, 129.7, 130.3, 131.5, 131.6, 134.1, 136.1, 152.0, 152.4, 154.1, 154.2

and 154.3; *m*/*z* (ESI-MS) 1014 $[M+H]^+$, 1036 $[M+Na]^+$ and 1052 $[M+K]^+$; HRMS calcd. for $[C_{58}H_{83}N_3O_6S_3 + H]^+$: 1014.5517. Found: 1014.5515.

***trans*-2,6,9-Tris[(4-methylphenyl)sulfonyl]1,2,3,4,4a,4b,5,6,7,8,9,10-dodecahydrodipyrrolo-[3,4-*f,h*]isoquinoline (2b)**. **2b** was prepared according to the method described above for **2a**. (90% yield) Colourless solid; mp 141-143 ºC; ν_{max} (ATR)/cm^{-1} 2929, 1341, 1161 and 1092; δ_H(500 MHz, $CDCl_3$, Me_4Si) 1.50 (apparent dq, *J* = 12 and 4 Hz, 1H), 1.85-1.95 (m, 1H + 1H), 2.26 (apparent t, *J* = 10 Hz, 1H), 2.46 (s, 9H), 2.50-2.62 (m, 1H + 1H), 2.80 (d, *J* = 14.3 Hz, 1H), 3.65 (d, *J* = 16.8 Hz, 1H), 3.68 (d, *J* = 14.0 MHz, 1H), 3.77-3.90 (m, 1H + 1H + 1H), 3.92 (d, *J* = 14 Hz, 1H), 3.95-4.03 (m, 1H + 1H), 4.11-4.19 (m, 1H), 7.32-7.38 (m, 6H), 7.65 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H), 7.69 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H) and 7.72 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.9, 33.0, 38.7, 45.9, 46.1, 47.7, 49.5, 49.7, 49.9, 53.9, 122.5, 125.2, 127.4, 128.0, 128.1, 128.2, 129.6, 130.2, 130.3, 132.9, 133.1, 133.2, 144.4, 144.5 and 144.6; HRMS calcd. for $[C_{34}H_{37}N_3O_6S_3 + Na]^+$: 702.1737. Found: 702.1727.

***cis*-2,6,9-Tris[(4-methylphenyl)sulfonyl]1,2,3,4,4a,4b,5,6,7,8,9,10-dodecahydrodipyrrolo-[3,4-*f,h*]isoquinoline (2c).** **2c** was prepared according to the method described above for **2a**. (87% yield) Colourless solid; mp 212-215 ºC; ν_{max} (ATR)/cm^{-1} 2921, 1343, 1159 and 1090; δ_H(500 MHz, $CDCl_3$, Me_4Si) 1.19 (br abs, 1H), 1.24 (br abs, 1H), 2.27 (apparent t, 1H), 2.37 (apparent dt, *J* = 11.7 and 3.4 Hz, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 2.47 (s, 3H), 2.67 (dd, *J* = 11.4 and 9.0 Hz, 1H), 2.82 (d, *J* = 11.6 Hz, 1H), 3.07 (br abs, 1H), 3.50 (d, *J* = 16 Hz, 1H), 3.65 (apparent t, *J* = 7.9 Hz, 1H), 3.71 (br abs, 1H), 3.84 (br abs, 2H), 3.91 (d, *J* = 14 Hz, 1H), 3.98 (d, *J* = 16 Hz, 1H), 4.06 (d, *J* = 11.6 Hz, 1H), 4.13 (d, *J* = 14 Hz, 1H), 7.29-7.39 (m, 6H), 7.61 (BB' part of the AA'BB' system, *J* = 8.3 Hz, 2H), 7.69 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H) and 7.70 (BB' part of the AA'BB' system, *J* = 8.2 Hz, 2H); δ_C(125 MHz, $CDCl_3$, Me_4Si) 21.4, 21.5, 21.6, 27.8, 37.1, 40.2, 46.4, 48.7, 48.9, 49.6, 49.8, 123.6, 123.7, 125.2, 127.6, 127.7, 127.8, 129.1, 129.8, 129.9, 132.4, 132.7, 132.8, 143.8, 143.9 and 144.1; HRMS calcd. for $[C_{34}H_{37}N_3O_6S_3 + Na]^+$: 702.1737. Found: 702.1714.

***trans*-2,5,10-Tris[(4-methylphenyl)sulfonyl]-2,3,4,5,6,7,7a,7b,8,9,10,11-dodecahydro-1*H*-pyrrolo[3,4-f][3,8]phenanthroline (2d). 2d** was prepared according to the method described above for **2a**. (98% yield) Colourless solid; mp 256-257 ºC (dec); ν_{max} (ATR)/cm^{-1} 2917, 2850, 1348, 1162 and 1093; δ_H(600 MHz, $CDCl_3$, Me_4Si) 1.40-1.43 (m, 2H), 1.84-1.89 (m, 2H + 2H), 2.30 (apparent t, *J* = 11.2 Hz, 2H), 2.45 (s, 6H), 2.46 (s, 3H), 2.78 (d, *J* = 13.7 Hz, 2H), 3.84 (br abs, 2H), 3.86 (d, *J* = 13.6 Hz, 2H), 4.01 (d, *J* = 13.6 Hz, 2H), 4.11 (d, *J* = 13.7 Hz, 2H), 7.34 (AA' part of the AA'BB' system, *J* = 8.0 Hz, 4H), 7.38 (AA' part of the AA'BB' system, *J* = 8.0 Hz, 2H), 7.64 (BB' part of the AA'BB' system, *J* = 8.0 Hz, 4H) and 7.76 (BB' part of the AA'BB' system, *J* = 8.0 Hz, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.2, 32.5, 40.9, 46.8, 47.9, 50.4, 123.2, 128.2, 128.5, 128.6, 130.5, 130.6, 133.3, 144.6 and 144.7; *m*/*z* (ESI-MS) 694 $[M+H]^+$, 716 $[M+Na]^+$ and 732 $[M+K]^+$; HRMS calcd. for $[C_{35}H_{39}N_3O_6S_3 + K]^+$: 732.1633. Found: 732.1619.

***trans*-2,5,8-Tris[(4-methylphenyl)sulfonyl]-3a-phenyl-3b-1*H*-2,5,8-triazatrindane (2f). 2f** was prepared according to the method described above for **2a**. (95% yield) Colourless solid (Found: C, 62.58 and 62.59; H, 5.45 and 5.48; N, 5.58 and 5.64; S, 12.63 and 12.69. $C_{39}H_{39}N_3O_6S_3$.1/2EtOAc requires C, 62.65; H, 5.51; N, 5.35; S, 12.24%); mp 159-161 ºC; ν_{max} (ATR)/cm^{-1} 2923, 1342 and 1161; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.15-2.30 (m, 1H), 2.37 (s, 3H), 2.39 (s, 3H), 2.43 (s, 3H), 2.90-3.19 (m, 3H), 3.50-4.10 (m, 8H), 4.39 (d, *J* = 9.6 Hz, 1H), 6.80-6.90 (m, 2H), 7.00-7.35 (m, 9H), 7.40-7.56 (m, 4H) and 7.66-7.72 (m, 2H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.0, 22.1, 22.2, 48.3, 49.1, 49.2, 50.0, 50.4, 53.1, 61.0, 125.7, 127.6, 128.1, 128.2, 128.3, 128.4, 129.1, 129.4, 129.8, 130.3, 130.4, 130.6, 132.7, 133.4, 133.7, 135.0, 144.4, 144.5 and 144.9; *m*/*z* (ESI-MS) 742 $[M+H]^+$.

***cis*-2,5,8-Tris[(4-methylphenyl)sulfonyl]-3a-phenyl-3b-1*H*-2,5,8-triazatrindane (2g). 2g** was prepared according to the method described above for **2a**. (71% yield) Colourless solid (Found: C, 62.71 and 62.64; H, 5.40 and 5.52; N, 5.59 and 5.62; S, 12.65 and 12.65. $C_{39}H_{39}N_3O_6S_3$.1/2EtOAc requires C, 62.65; H, 5.51; N, 5.35; S, 12.24%); mp 136-138 ºC; ν_{max} (ATR)/cm^{-1} 2922, 1340 and 1157; δ_H(200 MHz, $CDCl_3$, Me_4Si) 2.40-2.50 (m, 10H), 2.64 (d, *J* = 10 Hz, 2H), 3.54-4.15 (m, 10H), 6.92-6.71 (m, 2H), 7.12-7.22 (m, 7H), 7.29-7.36 (m, 2H), 7.40-7.48 (m, 2H) and 7.60-7.70 (m, 4H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 22.1, 22.2, 47.9, 48.5, 48.9, 49.0, 50.8, 50.9, 51.0, 53.1, 125.5, 125.7, 126.0, 126.7, 127.7, 127.8, 128.0, 128.2, 129.1, 129.8, 130.4, 130.6, 130.7, 133.4, 134.2, 134.8, 144.3, 144.8, 144.9 and 147.2; *m*/*z* (ESI-MS) 742 $[M+H]^+$ and 764 $[M+Na]^+$.

1-Phenyl-2,5,8-tris[(4-methylphenyl)sulfonyl)]-1*H*-2,5,8-triazatrindane (2h). 2h was prepared according to the method described above for **2a**. Colourless solid (quantitative yield); mp 136-139 ºC; ν_{max} (ATR)/cm^{-1} 2920, 1344, 1163 and 1095; δ_H(200 MHz, $CDCl_3$, Me_4Si) 1.50 (d, *J* = 6.3 Hz, 3H), 2.38 (s, 3H), 2.41 (s, 6H), 4.33-4.54 (m, 10H), 4.86 (apparent q, *J* = 6.3 Hz, 1H), 7.28-7.35 (m, 6H) and 7.60-7.76 (m, 6H); δ_C(50 MHz, $CDCl_3$, Me_4Si) 21.7, 22.2, 51.8, 52.0, 52.1, 60.9, 127.5, 127.7, 130.0, 130.1, 130.6, 130.9, 131.4, 133.7, 134.8, 136.5, 144.1 and 144.2; HRMS calcd. for $[C_{34}H_{35}N_3O_6S_3 + Na]^+$: 700.1580. Found: 700.1586.

S.4. General procedure for the enantioselective [2+2+2] cycloisomerization of macrocycles 1e and 1b

With the introduction of H_2 gas to the catalytic system

A degassed mixture of $[Rh(COD)Cl]_2$ (0.006 mmol) and chiral phosphane (0.006 mmol) in anhydrous and degassed toluene (2 cm^3) was stirred at room temperature. The flask was purged with hydrogen gas and the solution was stirred for 1 h. The hydrogen was then removed and nitrogen gas was introduced. A solution of macrocycle (0.06 mmol) in anhydrous toluene (6 cm^3) was added to the previous mixture and the resulting solution was heated to 65ºC and stirred for 24h under a nitrogen atmosphere (TLC monitoring). The solvent was removed and the residue was purified by column chromatography on silica gel to afford the corresponding cycloisomerized compound **2**.

Without the introduction of H_2 gas to the catalytic system

A degassed mixture of $[Rh(COD)Cl]_2$ (0.006 mmol) and chiral phosphane (0.006 mmol) in anhydrous and degassed toluene (2 cm^3) was stirred at room temperature. A solution of macrocycle (0.06 mmol) in anhydrous toluene (6 cm^3) was added to this solution and the mixture was heated to 65ºC and stirred for 24h under a nitrogen atmosphere (TLC monitoring). The solvent was removed and the residue was purified by column chromatography on silica gel to afford the corresponding cycloisomerized compound **2**.

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