Tsuji–Trost Cyclization of Disulfonamides: Synthesis of 12-Membered, 11-Membered, and Pyridine-Fused Macrocyclic Triamines

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ABSTRACT: Macrocyclic triamine disulfonamides can be synthesized by double Tsuji−Trost N-allylation reaction of open-chain disulfonamides with 2-alkylidene-1,3-propanediyl bis(carbonates). The previously used Atkins−Richman macrocyclization method generally gives lower yields and requires more tedious purification of the product. Solvent, palladium source, ligand, and concentration have all been varied to optimize the yields of two key 12-membered ring bioactive compounds, CADA and VGD020. The new approach tolerates a wide range of functional groups and gives highest yields for symmetrical compounds in which the acidities of the two sulfonamide groups are matched, although the yields of unsymmetrical compounds are still generally good. The method has also been extended to the synthesis of 11-membered rings, pyridine-fused macrocycles, and products bearing an ester or aryl substituent on the exocyclic double bond.

INTRODUCTION

Macrocyclic polyamines, which are of interest for their biological activity,1 as receptors for anions, or as ligands for transition metals, can be synthesized by a number of methods.2 Among the most common is the Atkins−Richman procedure involving reaction of the dianion of an open-chain ditosylamide with the disulfonate ester of an open-chain diol.3,4 This approach has also been modified to accommodate other dinucleophiles and dielectrophiles, including dihalides.5−8 As shown in Scheme 1 (method A), a modified Atkins−Richman approach was used in the synthesis of 3-methylene-1,5,9-triazacyclododecanes disulfonamides, which are of interest as potential immunomodulatory and antiviral drugs.9−13 Many analogous have been synthesized by this method, but it requires slow addition, large volumes of solvent, and tedious purification to remove oligomeric byproducts.

The exocyclic double bond in the 3-position of the 1,5,9-triazacyclododecane ring, which is important for activity,9 enables an alternate macrocyclization strategy involving double N-allylation, as shown in Scheme 1 (method B). Tsuji−Trost14−16 N-allylation is well-precedented,17−25 and hydroxyl groups in erythromycin A and other macrolide antibiotics have been bridged with an isobutylene unit by palladium-catalyzed reaction with 3-methylene-1,3-propanediyl bis(3-butylcarbonate) in THF or toluene.26−28 In addition, palladium-catalyzed
C-allylation with similar dielectrophiles has been used in natural product total syntheses.29,30

**RESULTS AND DISCUSSION**

The proposed Pd-catalyzed macrocyclization reaction was first tested on the synthesis of the lead compound, cyclo-
triazadisulfonamide, CADA (2), which can be prepared in 54% yield by the Atkins–Richman method.10 As shown in Table 1, various solvents were tried and acetonitrile gave the best yield (95%). No oligomeric side products were detected, and the pure HCl salt was obtained by simply treating the crude product with methanolic HCl and evaporation. The HCl salt of the disulfonamide was used.4,9 mM disulfonamide; 5 equiv dicarbonate ester. Overall yield for two steps, including synthesis of 11.

| starting material | R¹ | R² | X | solvent | product | yield |
|------------------|----|----|---|---------|---------|-------|
| 1                | Me | Bn | OBoc | MeCN | 2 (CADA·HCl) | 53% |
| 1                | Me | Bn | OBoc | MeCN | 2 (CADA·HCl) | 73% |
| 1                | Me | Bn | OBoc | MeCN | 2 (CADA·HCl) | 95% |
| 1                | Me | Bn | OBoc | MeCN | 2 (CADA·HCl) | 0% |
| 1                | Me | Bn | Cl  | MeCN | 2 (CADA·HCl) | 0% |
| 1                | Me | Bn | OAc | MeCN | 2 (CADA·HCl) | 0% |
| 3                | OMe| Bn | OBoc | MeCN | 4 (KKD023·HCl) | 65% |
| 3                | OMe| Bn | OBoc | MeCN | 4 (KKD023·HCl) | 85% |
| 3                | OMe| Bn | OBoc | MeCN | no reaction |
| 5                | Me | H  | OBoc | MeCN | 5 (94-129·HCl) | 98% |
| 7                | Br | Bn | OBoc | MeCN | 8 (ASPB127) | 52% |
| 9                | NO₂| Bn | OBoc | MeCN | 10 (AS114) | 56% |
| 11               | CN | Bn | OBoc | MeCN | 12 (ES030) | 47% |

4 Reaction conditions (unless indicated otherwise): 15–25 mM disulfonamide in anhydrous solvent, 2–2.5 equiv dicarbonate ester, 3 mol % Pd(COD)₂, and 6 mol % dppb, stirred under reflux for 18–24 h. Ref 10; HCl salts were formed by treatment of the crude product with methanolic HCl and evaporation. The HCl salt of the disulfonamide was used.4,9 mM disulfonamide; 5 equiv dicarbonate ester. Overall yield for two steps, including synthesis of 11.
Amines can become partially protonated and form bicarbonate.

**Table 2. Pd-Catalyzed Synthesis of Unsymmetrical 3-Methylene-1,5-diarenesulfonyl-1,5,9-triazacyclododecanes**

| starting material | Ar¹ | Ar² | R² | product | yield (%) |
|-------------------|-----|-----|-----|---------|-----------|
| 13                | p-tolyl Ph | CH₃CH₂H₁₁ | 14 (VGD025) | 37% |
| 15                | p-tolyl 4-ButPh | CH₃CH₂H₁₁ | 16 (VGD017) | 53% |
| 17                | p-tolyl 4-ClPh | CH₃CH₂H₁₁ | 18 (VGD018-HCl) | 27% |
| 19                | p-tolyl 1-naphthyl | CH₃CH₂H₁₁ | 20 (VGD021-HCl) | 38% |
| 21                | p-tolyl 2-naphthyl | CH₃CH₂H₁₁ | 22 (VGD022) | 37% |
| 23                | p-tolyl 5-isquin. | CH₃CH₂H₁₁ | 24 (VGD019) | 38% |
| 25                | 4-MeOPh | CH₃CH₂H₁₁ | 26 (VGD029-HCl) | 46% |
| 27                | p-tolyl | CH₃CH₂H₁₁ | 28 (KKD016-HCl) | 56% |
| 29                | 4-Ac | CH₃CH₂H₁₁ | 30 (Dj005) | 28% |
| 31                | 4-CN | CH₃CH₂H₁₁ | 32 (Dj002) | 36% |
| 33                | 4-MeOPh Bn | CH₃CH₂H₁₁ | 34 (VGD027-HCl) | 56% |
| 35                | 4-NO₂Ph Bn | CH₃CH₂H₁₁ | 36 (CK032) | 32% |
| 37                | 3-NO₂Ph | CH₃CH₂H₁₁ | 38 (CK116) | 39% |
| 39                | 2-NO₂Ph | CH₃CH₂H₁₁ | 40 (CK037) | 43% |
| 41                | 4-CF₃OPh Bn | CH₃CH₂H₁₁ | 42 (CK043) | 41% |
| 43                | 4-MeOPh | CH₃CH₂H₁₁ | 44 (CK078) | 40% |
| 45                | 3-NMe₂Ph | CH₃CH₂H₁₁ | 46 (CK207) | 57% |
| 47                | 4-FPh | CH₃CH₂H₁₁ | 48 (CK201-HCl) | 47% |
| 49                | NMe₂ | CH₃CH₂H₁₁ | 50 (CK195) | 42% |

“Reaction conditions: 15–20 mM disulfonamide in anhydrous acetonitrile, 2.5 equiv dicarbonate ester, 3 mol % Pd₂(dba)₃, 6 mol % dppb, stirred under reflux for 18–24 h. Ref 11. 5-Dimethylamino-1-naphthyl. Ref 10. 0.1–0.5 equiv Na₂CO₃ was added to the reaction mixture. Ref 13.”

Figure 1. Catalytic cycle for palladium-catalyzed N-allylation of sulfonamides with allylic carbonates.

**Table 3. Yield Optimization for Synthesis of VGD020 (54)**

| catalyst (equiv) | ligand (equiv) | base (equiv) | R yield (%) |
|------------------|----------------|-------------|-------------|
| Pd₂(dbp) (0.03) | dppb (0.06) | none | tBu | variable |
| Pd₂(dbp) (0.03) | dppb (0.06) | Na₂CO₃ (0.1) | tBu | 25–26 |
| Pd₂(dbp) (0.03) | dppb (0.06) | Na₂CO₃ (1.0) | tBu | 25–26 |
| Pd(OAc)₂ (0.03) | dppb (0.06) | Na₂CO₃ (0.1) | tBu | 20 |
| Pd(PPh₃) (0.06) | dppb (0.06) | Na₂CO₃ (1.0) | tBu | 10 |
| Pd₂(dbp) (0.03) | none | Na₂CO₃ (1.0) | tBu | 0 |
| Pd₂(dbp) (0.03) | PPh₃ (0.06) | Na₂CO₃ (1.0) | tBu | 20 |
| Pd₂(dbp) (0.03) | dppf (0.06) | Na₂CO₃ (1.0) | tBu | 9 |
| Pd₂(dbp) (0.03) | dppb (0.06) | Na₂CO₃ (0.1) | Me | 40 |
| Pd₂(dbp) (0.03) | dppb (0.06) | Na₂CO₃ (1.0) | tBu | 50–56 |
| Pd₂(dbp) (0.03) | dppb (0.06) | Na₂CO₃ (1.0) | tBu | 48^e |

“Reaction conditions (unless indicated otherwise): 15–20 mM disulfonamide in anhydrous acetonitrile, stirred under reflux for 18–24 h. 9 mM disulfonamide. ^4 mM disulfonamide.

Salts when exposed to water and atmospheric carbon dioxide. The added Na₂CO₃ apparently scavenges protons that can quench the N-allylation reaction by protonating t-butoxide, which is needed for sulfonamide deprotonation (see catalytic cycle in Figure 1).

With Pd₂(dbp) as a source of Pd, reactions failed when a phosphine ligand was omitted. While reactions worked with triphenylphosphine and dppe as ligands, somewhat lower yields were observed. Other sources of Pd such as Pd(PPh₃)₃ and Pd(OAc)₂ can also be used, although Pd₂(dbp) gave the highest yield. When the bis(electrophile) 2-methylene-1,3-propanediyl bis(t-butoxide) was replaced with 2-methylene-1,3-propanediyl bis(methylcarbonyl), the reaction succeeded in good yields. This is significant for large-scale reactions, because the bis(methylcarbonyl) reagent is less expensive to prepare than the diBoc compound. When the concentration of the reagents and catalyst were decreased from 15 to 20 mM by about half (9 mM), the yield almost doubled. The last entry in Table 3 shows that greater dilution did not improve the yield further. Slow addition of mixtures of the two reactants to hot solvent containing the catalyst was also attempted but did not improve the yield.

Hydroxytosylate is considered a difficult leaving group in Tsuji–Trost chemistry, although allylic alcohols have been used for N-allylations under certain conditions. Because of its lower cost and need to prepare S4 on a larger scale, we also attempted macrocyclization with 2-methylene-1,3-propanediol under conditions used with dicarbonates, but no product (S4) was isolated.

**Scheme 2. Attempted Macrocyclization of a Hydroxytosylate, Resulting in Oligomerization to S2**
Other variations attempted were to change the size of the macrocyclic ring and to fuse a pyridine ring in the position of the tertiary nitrogen bearing the tail group (Scheme 3).

Compound 56 (ES-US$^5$) with an 11-membered macrocyclic ring was successfully isolated in modest yield (37%), and compound 58 (SH28) consisting of a 12-membered macrocycle fused to pyridine was prepared in 56% yield. An attempt to carry out an analogous cyclization to form a 10-membered ring failed, but after adjusting the reaction conditions, the 20-membered 2+2 macrocycle 60 (LAL012) was isolated in 50% yield.

Further experiments were conducted to determine if substituents on the isobutylene head group could be tolerated (Scheme 4). Use of diBoc reagents with an ester or a phenyl substituent gave the macrocyclic products in modest yield. Ester 62 (RA014) was isolated as a 1:1 mixture of E/Z stereoisomers that could not be separated by chromatography, but recrystallization gave a crystalline 1.4:1 mixture that yielded to full characterization, including combustion microanalysis. Attempts to prepare an analog with two methyl substituents on the exocyclic double bond failed to give the 12-membered macrocycle. Chromatography of the reaction mixture gave bis(diene) 64 (TL002) instead. This side product was initially identified by mass spectrometry, then the diBoc reagent was used in larger excess, and 64 was isolated in 88% yield. The formation of this open-chain bis(diene) can be attributed to steric hindrance of macrocyclization and base-mediated E2' elimination of the allylic BocO$^-$ group of the monoauxilated intermediate (cf. Figure 1). The successful macrocyclization of 1 with the phenyl-substituted di(Boc) reagent 65 to form 66 with an exocyclic benzylidine substituent in the head group is also shown in Scheme 4.

**CONCLUSIONS**

We conclude that Pd-catalyzed reaction of disulfonamides with doubly allylic bis(carbonates) is a versatile approach to useful macrocyclic polyamines that give good yields, when compared with other macrocyclization methods. The reaction tolerates a wide range of substituents and can be used to prepare 11-membered rings and pyridine-fused analogs, as well as macrocyclic triamines with monosubstituted isobutylene head groups.

**EXPERIMENTAL SECTION**

**General Methods.** All reactions were performed under anhydrous nitrogen. Solvents and reagents obtained from Sigma-Aldrich Chemical Company or Fisher Scientific were of ACS reagent grade or better. They were used without purification, unless stated otherwise. HCl (2 N) solutions in methanol/water were made from 42 mL of concentrated aq. HCl (12.1 N) and 210 mL of methanolic HCl salts were triturated by sonication in anhydrous diethyl ether (5−15 mL, unless stated otherwise) for 5 min and filtration, repeating the process at least twice. "Overnight" periods are approximately 16 h. Organic solutions were dried over anhydrous Na$_2$SO$_4$ and then filtered. Drying in vacuo was done at 0.1 mm and at room temperature, unless stated otherwise. Column chromatography employed Sorbent Technologies neutral alumina (50−200 μm) or standard grade silica (32−63 μm), unless stated otherwise. Melting points were measured with Thomas-Hoover or Mel-Temp apparatus and are uncorrected. $^1$H NMR (400 or 500 MHz) and $^{13}$C NMR (100 or 125 MHz) spectra were acquired on Varian 400 or Varian Unity+ 500 spectrometers. Chemical shifts (δ) are reported in ppm values relative to solvent peaks as follows: $^1$H, CDCl$_3$/TMS = 0.00, DMSO-$d_6$ = 2.50, CD$_2$OD = 3.31; $^{13}$C, CDCl$_3$ = 77.23, DMSO-$d_6$ = 39.7, CD$_3$OD = 49.15 ppm. Infrared spectra (IR) were acquired on a Nicolet 6700 FTIR spectrometer. Low-resolution mass spectra (MS) were recorded on a Waters Micromass ZQ electrospray ionization quadrupole mass spectrometer. Low-resolution mass spectra (MS) were recorded on a Waters Micromass ZQ electrospray ionization quadrupole mass spectrometer employing positive-ion detection (cap. voltage = 3.5 kV). High-resolution mass spectra (HRMS) were obtained on an Agilent 6230 TOF mass spectrometer. Combustion analysis samples were dried at 78°C (0.1 mm, 2 d), unless noted otherwise, and microanalysis was done by NuMega Resonance Labs, Inc. After purification, all products were at least 95% pure, as proven by C,H,N microanalysis or NMR spectroscopy.
General Procedure for Tsuji–Trost Macrocyclization
Synthesis of 2, 4, 6, 8, 10, and 28. All glassware and equipment used in macrocyclization reactions, including stir bars, spatulas, syringes, and needles, were dried overnight at 110 °C. Anhydrous acetonitrile (AN) used in macrocyclization was dried by distillation from CaH₂. All reagents were dried at 0.1 mm before use.

In a 250 mL flask equipped with an inlet for N₂ and a stirring bar, a mixture of 1.9 mmol of the disulfonamide, 4.7 mmol of the bis(electrophile), 0.06 mmol of tris(dibenzyldieneacetone)dipalladium(0) (Pd₂(dba)₃), 0.11 mmol of 1,1-bis(diphenylphosphino)butane (dpbb), and 120 mL of anhydrous AN was stirred and boiled under reflux for 18–24 h under N₂. The solvent was removed by rotary evaporation. A solution of the residue in 90 mL of dichloromethane (DCM) was extracted with saturated aq. NaHCO₃ solution (2 × 30 mL), dried (Na₂SO₄), filtered, and evaporated to dryness. A solution of the crude product in 10 mL of 2 N HCl (as a viscous oil). ¹H NMR (500 MHz, CDCl₃) δ 8.52 (d, 9 Hz, 1 H, 2-Dn), 8.33 (d, 9 Hz, 1 H, 4-Dn), 8.22 (d, 7 Hz, 1 H, 8-Dn), 7.71 (d, 8 Hz, 2 H, o-Ts), 7.54 (t, 8 Hz, 1 H, 3-Dn), 7.50 (t, 8 Hz, 1 H, 7-Dn), 7.26 (d, 8 Hz, 2 H, m-Ts), 7.17 (d, 8 Hz, 1 H, 6-Dn), 6.00 (s, 2 H, NH), 2.94 (m, 4 H, CH₂NH₂), 2.87 (s, 6 H, NCH₃), 2.40 (s, 3 H, ArCH₃), 2.26 (m, 4 H, CH₂NH), 1.98 (d, 4 H, Cy), 1.30 (m, 2 H, Cy), 1.12 (m, 3 H, Cy), 0.80 g (1.35 mmol) of 3, which was prepared as described previously, ¹³C NMR (100 MHz, CDCl₃) δ 152.0, 143.3, 137.2, 135.2, 130.4, 130.1, 129.9, 129.8, 128.4, 127.2, 134.3, 119.3, 115.3, 62.0, 53.2, 53.0, 45.6, 42.8, 42.7, 35.8, 32.0, 20.6, 26.2, 25.9, 21.7. For the synthesis of 27-HCl, a mixture of 0.55 g of 27 in 10 mL of 2 N HCl in methanol/water was stirred at room temperature for 3 h and then concentrated by rotary evaporation. The residue was dried in vacuo and purified by column chromatography on alumina, eluting with hexane/ErOAc to give 0.70 g (67%) of 27 as a viscous oil. ¹H NMR (500 MHz, CDCl₃) δ 8.78 (d, 9 Hz, 1 H, 2-Dn), 8.57 (d, 9 Hz, 1 H, 4-Dn), 8.37 (d, 8 Hz, 1 H, 8-Dn), 7.94 (d, 8 Hz, 1 H, 6-Dn), 7.85 (m, 2 H, 3,7-Dn), 7.74 (d, 8 Hz, 2 H, o-Ts), 7.41 (d, 8 Hz, 2 H, m-Ts), 3.36 (s, 6 H, NCH₃), 3.21 (m, 4 H, CH₂NH), 2.99 (t, 6 Hz, 2 H, CH₂Cy), 2.93 (m, 3 H, CH₂NH), 2.44 (s, 3 H, ArCH₃), 1.90 (m, 4 H, CH₂CH₃), 1.76 (m, 6 H, Cy), 1.39 (m, 2 H, Cy), 1.25 (m, 1 H, Cy), 1.05 (m, 2 H, Cy). ¹³C NMR (125 MHz, CD₂Cl₂) δ 145.1, 138.5, 138.1, 131.4, 131.1, 130.8, 130.9, 129.1, 128.2, 128.0, 127.6, 120.2, 67.0, 61.1, 52.64, 52.56, 47.6, 41.2, 41.1, 34.7, 31.9, 27.0, 26.6, 25.4, 25.1, 24.9, 21.6. Anal. calc. for C₂₆H₁₄N₂O₂S₂: 3HCl: C, 55.88; H, 7.03; N, 8.15. Found: C, 55.49; H, 7.41; N, 8.07.

Using the general macrocyclization procedure, 0.47 g (0.76 mmol) of 27 was converted to 0.30 g (56%) of pure 9-cyclohexylmethyl-1-(5-dimethylaminonaphthalenesulfonyl)-3-methylene-5-(p-toluenesulfonyl)-1,5,9-triazacyclodecane 28 (KKD016-HCl) as a tan solid.

Improved Procedure for Tsuji–Trost Macrocyclization
Apparatus, reagents, and solvent were dried as described in the general macrocyclization procedure. In a 250 mL round bottom flask equipped with a nitrogen inlet and a stirring bar, a mixture of 6.3 mmol of the disulfonamide, 30 mmol of the bis(electrophile), 0.76 mmol of anhydrous Na₂CO₃, 0.37 mmol of tris(dibenzyldieneacetone)dipalladium(0) (Pd₂(dba)₃), 0.72 mmol of 1,1-bis(diphenylphosphino)butane (dpbb), and 730 mL of anhydrous AN was stirred and boiled under reflux for 24 h under nitrogen. The solvent was removed by rotary evaporation, and the residue was partitioned between 100 mL of saturated aqueous NaHCO₃ and 100 mL of dichloromethane (DCM). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The

Resynthesis of 2 (KKD023-HCl).¹⁰ Using the general macrocyclization procedure, 1.0 g (1.9 mmol) of 1, which was prepared as described previously, was converted to 1.1 g (95%) of pure 9-benzyl-3-methylene-1,5-di(p-toluenesulfonyl)-1,5,9-triazacyclodecane hydrochloride (2, KKD016-HCl) as a tan solid.

Resynthesis of 4 (KKD023-HCl).¹⁰ Using the general macrocyclization procedure, 1.0 g (1.8 mmol) of 3, which was prepared as described previously, was converted to 1.0 g (85%) of pure 9-benzyl-3-methylene-1,5-di(p-methoxybenzenesulfonyl)-1,5,9-triazacyclodecane hydrochloride 4 (KKD023-HCl) as a tan solid.

Resynthesis of 6 (94-129-HCl).¹⁰ Using the general macrocyclization procedure, 0.82 g (1.9 mmol) of 5, which was prepared as described previously, was converted to 1.0 g (98%) of pure 3-methylene-1,5-di(p-toluenesulfonyl)-1,5,9-triazacyclodecane hydrochloride 6 (94-129-HCl) as a tan solid.

Resynthesis of 8 (ASPB127).¹⁰ Using the general macrocyclization procedure, 4.2 g (6.3 mmol) of 7, which was prepared as described previously, was converted to 1.46 g (52%) of pure 9-benzyl-3-methylene-1,5-di(p-bromobenzensulfonyl)-1,5,9-triazacyclodecane 8 (ASPB127). In this case, the triturated HCl salt was converted to the free base by stirring for several hours with 40 mL of DCM, 40 mL of saturated aq. NaCl solution, and 50 mL of 2 N aq. KOH solution. The layers were separated, and the aqueous layer was extracted with DCM (2 × 25 mL). The combined aqueous solutions were dried (Na₂SO₄), filtered, and evaporated to dryness. The residue was purified by column chromatography on alumina, eluting with hexane/ethyle acetate (3:1, v/v).

Resynthesis of 10 (AS114).¹⁰ Using the general macrocyclization procedure, except for dilution of all reagents and catalysts to a concentration of 9 mM for the disulfonamide, 0.80 g (1.35 mmol) of 9, which was prepared as described previously, was converted to 0.49 g (56%) of pure 9-benzyl-3-methylene-1,5-di(p-nitrobenzenesulfonyl)-1,5,9-triazacyclodecane 10 (AS114). The free base was generated from the HCl salt and purified as described for 8.

Resynthesis of 28 (KKD016-HCl).¹⁰ N-(5-Dimethylamino-naphthalene-1-sulfonyl)-N’-(p-toluenesulfonyl)bis(3-aminopropyl)cyclohexylmethylamine (27). A mixture of 0.65 g (1.7 mmol) of N-(p-toluenesulfonyl)bis(3-aminopropyl)-cyclohexylmethylamine, which was prepared as described previously, was converted to 1.0 g (1.9 mmol) of 9-benzyl-3-methylene-1,5-di(p-toluenesulfonyl)-1,5,9-triazacyclodecane hydrochloride (2, KKD016-HCl) as a tan solid.
combined organic solutions were concentrated to dryness by rotary evaporation, and the residue was dried in vacuo. The products were purified by column chromatography on neutral alumina, eluting with hexane/EtOAc.

**Synthetic procedures and Characterization Data for 12.** A mixture of 0.61 g (2.8 mmol) of N,N-bis[(3-aminopropyl)benzylamine, 0.88 g (8.3 mmol) of anhydrous Na2CO3, and 20 mL of anhydrous AN was vigorously stirred under nitrogen for 10 min at room temperature. A solution of 1.2 g (6.1 mmol) of p-cyanobenzensulfonyl chloride in 20 mL of anhydrous AN was added dropwise over 30 min. The reaction mixture was stirred overnight and filtered. The filtrate was concentrated to dryness by rotary evaporation, and the residue was shaken with 50 mL of DCM and 50 mL of saturated aq. NaCl solution. The layers were separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic solutions were dried and concentrated to dryness by rotary evaporation. The residue was dried overnight in vacuo (0.2 mm, 40 °C) to give 1.6 g (100%) of N,N′-bis{(p-cyanobenzenesulfonyl)aryl-N,N′-bis(3-aminopropyl)benzylamine} (11, ES02) as a viscous oil, which was determined to be sufficiently pure for use in the next step. Using the improved Tsuji–Trost macrocyclization procedure, 1.5 g (2.7 mmol) of intermediate 11 was converted to 12, which was purified by column chromatography on neutral alumina, eluting with 9:1 (v/v) chloroform/ethyl acetate, resulting in 0.82 g (47%) of 9-(p-toluenesulfonyl)-1,5-bis((3-acetamidopropyl)-N,N′-bis(3-aminopropyl)cyclohexylmethylamine) (DJ005).

**Synthetic Procedures and Characterization Data for 30.** N-(p-Acetylbenzenesulfonyl)-N″-(p-toluenesulfonyl)-[N,N′-bis(3-aminopropyl)cyclohexymethylamine] (31, DJ005). A mixture of 3.0 g (7.9 mmol) of N-(3-aminopropyl)-N-(3-p-toluenesulfonyl)propyl-cyclohexymethylamine, 1.6 g (7.9 mmol) of p-cyanobenzensulfonyl chloride, 51 mL of saturated aq. Na2CO3 solution, 51 mL of saturated aq. NaCl solution, and 51 mL of DCM was stirred at room temperature for 24 h, and then, the layers were separated. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic solutions were dried and concentrated by rotary evaporation to give a light yellow oil, which was dried in vacuo to give 2.64 g (78%) of pure 29 free base. 1H NMR (400 MHz, CDCl3) δ 8.07 (d, 9 H, 2 H, o-ArSO2), 7.95 (d, 9 H, 2 H, m-ArSO2), 7.72 (d, 8 H, 2 H, o-Ts), 7.30 (d, 8 H, 2 H, m-Ts), 6.10 (br., 2 H, NH), 3.04 (t, 6 H, 2 H, CH2NH2SO2Ar), 2.97 (t, 6 H, 2 H, CH2NHTs), 2.65 (s, 3 H, Ac), 2.43 (s, 3 H, ArCH2), 2.38 (t, 7 H, 2 H, CH2NC3H7Cy), 2.05 (d, 7 H, 2 H, CH2Cy), 1.65 (m, 10 H, H7,11, Cy), 1.14 (m, 3 H, 3 H, Cy), 0.78 (m, 2 H, 2 H, Cy).13C NMR (100 MHz, CDCl3) δ 196.9, 143.7, 143.3, 139.8, 136.5, 129.7, 128.9, 127.4, 127.1, 61.0, 52.3, 41.1, 34.2, 31.6, 26.9, 26.1, 25.6, 21.5. MS (ESI+) m/z 64 (M+H)+.

1-(p-Acetylbenzenesulfonyl)-9-cyclohexymethyl-3-methylene-5-(p-toluenesulfonyl)-1,5,9-triazacyclododecane (30, DJ005). Using the improved Tsuji–Trost macrocyclization procedure, intermediate 29 was cyclized to 30, which was converted to the HCl salt and purified as described for 29. A sample of 30-HCl was dried in vacuo at 78 °C and found to be pure (anal. calc. for C28H42N3O5S2·HCl: C, 47.72; N, 6.20. Found: C, 47.72; N, 6.18). This sample of 30-HCl was converted to the free base as described for 29 and isolated by column chromatography on neutral alumina, eluting with 3:7 (v/v) ethyl acetate/hexane, resulting in 0.41 g (28%) of a pale yellow solid. 1H NMR (400 MHz, CDCl3) δ 8.08 (d, 9 H, 2 H, o-ArSO2), 7.89 (d, 9 H, 2 H, m-ArSO2), 7.64 (d, 8 H, 2 H, o-Ts), 7.32 (d, 8 H, 2 H, m-Ts), 5.15 (s, 2 H, C=CH), 3.91 (s, 2 H, H6/12), 3.71 (s, 2 H, H4/2), 3.28 (t, 7 H, 2 H, H6/12), 3.04 (t, 7 H, 2 H, H12/6), 2.65 (s, 3 H, Ac), 2.43 (s, 3 H, ArCH2), 2.25 (m, 4 H, H8,10), 1.95 (d, 7 H, 2 H, CH2Cy), 1.65 (m, 10 H, H7,11, Cy), 1.13 (m, 3 H, Cy), 0.73 (m, 2 H, Cy).13C NMR (100 MHz, CDCl3) δ 196.6, 143.4, 140.5, 139.9, 136.2, 129.7, 127.4, 127.1, 61.4, 60.3, 51.9, 51.6, 47.8, 36.0, 31.8, 29.7, 27.7, 26.8, 26.1, 21.5. MS (ESI+) m/z 616 (M+H)+.

**Synthetic Procedures and Characterization Data for 32.** N′-(p-Cyanobenzenesulfonyl)-N″-(p-toluenesulfonyl)-(N,N′-bis(3-aminopropyl)cyclohexymethylamine) (31, DJ005). A mixture of 3.0 g (7.9 mmol) of N-(3-aminopro p) -N-(3-p-toluenesulfonyl)propyl-cyclohexymethylamine, 1.6 g (7.9 mmol) of p-cyanobenzensulfonyl chloride, 51 mL of saturated aq. Na2CO3 solution, 51 mL of saturated aq. NaCl solution, and 51 mL of DCM was stirred at room temperature for 24 h, and then, the layers were separated. The aqueous layer was extracted with DCM (3 × 30 mL). The combined organic solutions were dried and concentrated to dryness by rotary evaporation to give a light orange oil. A solution of the crude product in 140 mL of 2 N HCl in aq. MeOH was stirred at room temperature for 4 h, and then, the solvent was removed via rotary evaporation. The residue was dried in vacuo, triturated with anhydrous diethyl ether (3 × 20 mL), and then, dried in vacuo to give 1.26 g (28%) of 33-HCl. The HCl salt was converted back to the free base by stirring with 138 mL of 2 N aq. NaOH solution, 138 mL of saturated aq. NaCl solution, and 138 mL of DCM for 6 h, and then, the layers were separated. The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic solutions were dried and concentrated by rotary evaporation to give a light orange oil that was dried overnight in vacuo to yield 1.09 g (25%) of 31, which was determined to be sufficiently pure for conversion to 32. 1H NMR (400 MHz, CDCl3) δ 7.97 (d, 8 H, 2 H, o-ArSO2), 7.78 (d, 8 H, 2 H, o-Ts), 7.70 (d, 8 H, 2 H, m-ArSO2), 7.29 (d, 8 H, 2 H, m-Ts), 3.04 (t, 6 H, 2 H, CH2,NH2SO2Ar), 2.96 (t, 6 H, 2 H, CH2NHTs), 2.41 (s, 3, 1259 DOI: 10.1021/acsomega.8b02555
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H, CH₃), 2.38 (d, 7 Hz, 4 H, CH₂NCH₂Cy), 2.04 (d, 7 Hz, 2 H, CH₂Cy), 1.64 (m, 10 H, CH₂CH₂, Cy), 1.36 (m, 1 H, Cy), 1.12 (m, 2 H, Cy), 0.82 (m, 2 H, Cy). ¹³C NMR (100 MHz, CDCl₃) δ 144.6, 143.3, 138.4, 132.8, 129.7, 127.7, 127.0, 117.4, 116.0, 62.1, 53.1, 42.7, 42.5, 35.6, 31.9, 26.5, 26.0, 25.8, 21.5. MS (ESI⁺) m/z 547 (MH⁺).

1-[(p-Cyanobenzensulfonyl)-9-cyclohexylmethyl-3-methylene-5-(6-toluenesulfonyl)-1,5,9-triazacyclodecane (32, DJ002). Using the improved Tsuji–Trost macrolization procedure, intermediate 31 was converted to 32, which was purified by column chromatography on neutral alumina, eluting with 3:7 (v/v) ethyl acetate/hexane, resulting in 0.42 g (36%) of a light orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, 8 Hz, 2 H, o- ArSO₂), 7.81 (d, 8 Hz, 2 H, o-Ts), 7.63 (d, 8 Hz, 2 H, m-ArSO₂), 7.32 (d, 8 Hz, 2 H, m-Ts), 5.14 (s, 2 H, C═CH), 3.96 (s, 2 H, H₂/4), 3.67 (s, 2 H, H₂/2), 3.36 (m, 2 H, H/6/12), 2.99 (t, 6 Hz, 2 H, H12/6), 2.43 (s, 3 H, CH₃), 2.33 (m, 4 H, H8/10), 1.96 (d, 7 Hz, 2 H, CH₂Cy), 1.60 (m, 10 H, H7/10, Cy) 1.13 (m, 3 H, Cy), 0.73 (m, 2 H, Cy). ¹³C NMR (125 MHz, CDCl₃) δ 144.0, 143.6, 137.6, 134.4, 133.0, 129.8, 127.7, 127.3, 117.2, 116.5, 116.3, 62.1, 53.0, 50.6, 49.6, 45.5, 43.3, 36.8, 31.9, 27.7, 26.7, 26.0, 25.5, 23.8, 21.5. MS (ESI⁺) m/z 599 (MH⁺). Anal. calc. for C₆H₆NO₅S₂: HCl·CH₂OH·0.5H₂O: C, 56.83; H, 7.15; N, 8.28. Found: C, 56.64; H, 6.82; N, 8.01.

Resynthesis of 48 (CK201-HCl).¹³ Using the improved Tsuji–Trost macrolization procedure, 0.98 g (1.8 mmol) of 47, which was prepared as described previously, was converted to 0.51 g (47%) of pure 9-benzyl-1-(p-fluorobenzensulfonyl)-3-methylene-5-(6-toluenesulfonyl)-1,5,9-triazacyclodecane hydrochloride 48 (CK201-HCl). The chromatographed free base was converted to the HCl salt as described in the general macrolization procedure.

Synthetic Procedures and Characterization Data for 52. N-(3-Hydroxypropyl)-N-(3-5-toluenesulfonylaminidopropyl)cyclohexylmethylamine (51, VGD043). A mixture of 4.11 g (12.7 mmol) of N-(3-toluenesulfonylaminidopropyl)cyclohexylmethylamine,¹¹ 1.48 g (14.0 mmol) of Na₂CO₃, 0.21 g (1.4 mmol) of NaI, 1.94 g (14.0 mmol) of 3-bromopropan-1-ol, and 40 mL of AN was stirred under nitrogen, boiled under reflux for 24 h, and then cooled to room temperature. The resulting white mixture was filtered through a fine-porosity sintered glass funnel, and the residue was washed with 20 mL of AN. The combined filtrates were concentrated by rotary evaporation, and the residue was dried in vacuo to give an oil, which was purified by filtration chromatography on neutral alumina, eluting with 9:1 (v/v) EtOH/DCM/ EtOH followed by neat EtOH to give 2.30 g (47%) of 51, which was converted to 52 without further purification.¹ H NMR (500 MHz, CDCl₃) δ 7.74 (d, 8 Hz, 2 H, o-Ts), 7.30 (d, 8 Hz, 2 H, m-Ts), 3.73 (t, 6 Hz, 2 H, CH₂OH), 2.96 (t, 6 Hz, 2 H, CH₂NCH₂Cy), 2.54 (t, 6 Hz, 2 H, CH₂NCH₂Cy), 2.42 (m, 5 H, CH₃N, CH₂N), 2.11 (d, 7 Hz, 2 H, CH₂Cy), 1.67 (m, 8 H, CH₂CH₂Cy), 1.44 (m, 1 H, Cy), 1.17 (m, 4 H, Cy), 0.82 (m, 2 H, Cy). ¹³C NMR (125 MHz, CDCl₃) δ 143.2, 137.3, 129.7, 127.2, 63.3, 62.1, 54.3, 52.5, 42.1, 35.7, 32.0, 28.2, 26.7, 26.3, 21.6. IR (neat, cm⁻¹): 3280 (w), 2923 (m), 2850 (m), 1598 (w), 1449 (m), 1326 (m), 1159 (s), 1094 (m), 912 (w), 815 (m), 737 (w), 661 (m). HRMS calc. for C₃₀H₂₅N₃O₄S (M⁺) 532.2285, found 532.2273; calc. for C₂₉H₂₅N₃O₄SnA (M + Na)⁺ 405.2182, found 405.2184.

N,N′-Bis[(N-cyclohexylmethyl-3-hydroxypropyl)-3-amino- propyl]-N,N′-di[(p-toluenesulfonyl)-2-methylene-1,3-dia- minopropyl]-N,N′-bis[(N-cyclohexylmethyl-3-hydroxypropyl)-3-amino-propyl]-N,N′-di[(p-toluenesulfonyl)-2-methylene-1,3-dia- minopropyl] (52, VGD043). A mixture of 0.76 g (2.0 mmol) of 51, 1.42 g (4.93 mmol) of 2-methylen-1,3-propanediol (t-butyldimethylsilyl), 10 mL of CHCl₃ was stirred at 50 °C for 2 h and then allowed to cool to room temperature. The layers were separated, and the aqueous layer was extracted with CHCl₃ (2 × 25 mL). The combined organic solutions were concentrated by rotary evaporation, and the residue was dried in vacuo at 50 °C yielding 1.49 g (99%) of N-[(3-5-toluenesulfonylaminidopropyl)-N-(2-p-toluenesulfonyldiethyl)benzylamine (55, ES26) as a light brown oil, which was sufficiently pure for use in the next step. Using the improved Tsuji–Trost macrolization procedure, intermediate 55 was converted to 56, which was purified by chromatography on neutral alumina, eluting with 2:3 (v/v) ethyl acetate/hexane, giving 0.77 g (50%) of 8-benzyl-3-
methylene-1,5-di(p-toluenesulfonyl)-1,5,8-triazacyclodecane (56) as a fine beige powder. A sample was washed at the HCl salt, which was found to be pure by combustion microanalysis after drying overnight in vacuo at 78 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, 8 Hz, 2 H, o-Ts), 7.60 (d, 8 Hz, 2 H, o-Ts), 7.33 (d, 8 Hz, 2 H, m-Ts), 7.28 (d, 8 Hz, 2 H, m-Ts), 7.23 (m, 5 H, Ph), 5.43 (s, 1 H, C≡CH), 5.28 (s, 1 H, C≡CH), 3.95 (m, 2 H, H₂/H₂), 3.82 (m, 2 H, H₄/H₂), 3.50 (s, 2 H, CH₂Ph), 3.15 (m, 4 H, H₆/H₁₁), 2.59 (m, 2 H, H₇), 2.44 (m, 8 H, H₉, CH₃), 1.87 (m, 2 H, H₁₀). ¹³C NMR (125 MHz, CDCl₃) δ 143.5, 141.8, 138.0, 129.9, 129.6, 128.3, 127.5, 127.4, 127.1, 116.7, 57.6, 54.0, 53.3, 50.4, 48.2, 47.2, 26.8, 21.7. ES-US-SCI: MS (ESI⁺) m/z 568 (MH⁺). Anal. calcd. for C₆₀H₅₄N₆O₈S₄: C, 60.34; H, 5.66; N, 5.18. Found: C, 61.24; H, 5.64; N, 5.25.

**Synthetic Procedure and Characterization Data for 58.** 6-Methylene-4,8-di(p-toluenesulfonyl)-4,8,15-triazabicyclo[9,3,1]pentadeca-1(15),11,13-triene (58, SH28).

A mixture of 71 mg (0.15 mmol) of NaHCO₃, 8.5 mL of anhydrous AN, and 4 mg (4 mmol) of 2-methylene-1,3-propanediyl bis(6-Methylene-4,8-di(p-toluenesulfonyl)-4,8,15-triazacyclodecane (56) was dissolved in 10 mL of DCM and cooled to 0 °C. A solution of 2.5 g (11 mmol) of triethyl phosphonoacetate in 150 mL of anhydrous THF was stirred under nitrogen at 0 °C. After 15 min, LAL009 was added. The mixture was stirred for 15 min at room temperature and then boiled under reflux for 15 min. 2-Oxo-1,3-propanesultone (26) was added to the reaction mixture, which was boiled under reflux for 24 h, cooled to room temperature, and concentrated to a minimum volume by rotary evaporation. A solution of 2.5 g (11 mmol) of triethyl phosphonoacetate in 150 mL of anhydrous THF was stirred under nitrogen at 0 °C. After 15 min, LAL009 was added. The mixture was stirred for 15 min at room temperature and then boiled under reflux for 15 min. 2-Oxo-1,3-propanesultone (26) was added to the reaction mixture, which was boiled under reflux for 24 h, cooled to room temperature, and concentrated to a minimum volume by rotary evaporation. A suspension of the residue in ethyl acetate was filtered, washed with saturated NaCl solution, and concentrated to dryness by rotary evaporation. The residue was dried in vacuo and then purified by column chromatography on silica gel, eluting with 91:1 (v/v) chloroform/ethyl acetate, giving 0.28 g (50%) of a white solid, mp 121–215 °C (dec). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, 9 Hz, 8 H, o-Ts), 7.41 (t, 9 Hz, 2 H, H₁₁,2₃), 7.27 (m, 8 H, m-Ts), 7.09 (d, 9 Hz, 4 H, H₁₀,1₂,2₂,2₄), 4.87 (s, 4 H, C≡CH), 4.07 (s, 8 H, ArCH₂N), 3.70 (s, 8 H, CCH₂N), 2.43 (s, 12 H, Me). ³¹P NMR (100 MHz, CDCl₃) δ 156.2, 143.5, 138.5, 137.2, 136.3, 129.7, 127.4, 121.3, 116.8, 53.2, 51.8, 21.6. IR (neat, cm⁻¹): 1593 (m), 1445 (w), 1341 (s), 1289 (w), 1155 (s), 1089 (s), 1074 (w), 1060 (w), 962 (m), 926 (w), 906 (w), 805 (m), 784 (m), 763 (w), 752 (m), 709 (m), 727 (w), 695 (w), 649 (s), 613 (s), 596 (m). MS (ESI+) m/z 1016 [M−1+Na⁺]. Anal. calcld. for C₅₀H₄₈N₄O₄S₁₂: C, 60.34; H, 5.47; N, 7.84. Found: C, 60.48; H, 5.60; N, 8.53.

**Synthetic Procedures and Characterization Data for 60.** 2-Carboethoxymethylene-1,3-propanediyld bis(3,5,7,61,62-Acetyl-61,62-di(p-toluenesulfonyl)-2,6-bis(2-aminomethyl)-4,8,15-triazacyclodecane (60). A solution of 2.5 g (11 mmol) of triethyl phosphonoacetate in 150 mL of anhydrous THF was stirred under nitrogen as a white solid, mp 121–215 °C (dec). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, 9 Hz, 8 H, o-Ts), 7.45 (t, 9 Hz, 2 H, H₁₁,2₃), 7.25 (m, 8 H, m-Ts), 7.09 (d, 9 Hz, 4 H, H₁₀,1₂,2₂,2₄), 4.87 (s, 4 H, C≡CH), 4.07 (s, 8 H, ArCH₂N), 3.70 (s, 8 H, CCH₂N), 2.43 (s, 12 H, Me). ³¹P NMR (100 MHz, CDCl₃) δ 156.2, 143.5, 138.5, 137.2, 136.3, 129.7, 127.4, 121.3, 116.8, 53.2, 51.8, 21.6. IR (neat, cm⁻¹): 1593 (m), 1445 (w), 1341 (s), 1289 (w), 1155 (s), 1089 (s), 1074 (w), 1060 (w), 962 (m), 926 (w), 906 (w), 805 (m), 784 (m), 763 (w), 752 (m), 709 (m), 727 (w), 695 (w), 649 (s), 613 (s), 596 (m). MS (ESI+) m/z 1016 [M−1+Na⁺]. Anal. calcld. for C₅₀H₄₈N₄O₄S₁₂: C, 60.34; H, 5.47; N, 7.84. Found: C, 60.48; H, 5.60; N, 8.53.
N'-(p-toluenesulfonyl)[N,N-bis(3-aminopropyl)-
cyclohexylmethylamine (53)\(^{[11]}\) was converted to 62, which was purified by column chromatography on neutral alumina, eluting with 3:1 (v/v) ethylene/hexyl acetate, yielding 0.68 g (30\%) of a 1:1 E/Z mixture as a white solid. Recrystallization from ethyl acetate gave crystals consisting of a 1:1 mixture of stereoisomers. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.74 (d, 9 Hz, 2 H, \(-\text{o-AsO}_2\), major), 7.69 (d, 8 Hz, 2 H, \(-\text{o-Ts}\), 7.30 (d, 8 Hz, 2 H, \(-\text{m-Ts}\), 6.97 (d, 9 Hz, 2 H, \(-\text{m-AsO}_2\), 5.26 (s, 2 H, C\(=\text{CH}\)), 5.24 (s, 2 H, C\(=\text{CH}\)), S.15 (s, 2 H, C\(=\text{CH}\)), S.07 (s, 2 H, C\(=\text{CH}\)), 3.92 (s, 3 H, OCH\(_3\)), 3.87 (m, 4 H, C\(=\text{CH}_2\text{NOSO}_2\)), 3.02 (m, 4 H, CH\(_2\text{CH}_2\text{NOSO}_2\)), 2.42 (s, 3 H, ArCH\(_3\)), 2.17 (s, 7 Hz, 4 H, CH\(_2\text{NCH}_2\text{Cy}\)), 1.95 (d, 7.1 Hz, 2 H, CH\(_2\text{Cy}\), 1.91 (s, 6 H, C\(=\text{CH}_2\)), 1.64 (m, 10 H, CH\(_2\text{Cy}\), Cy), 1.19 (m, 3 H, Cy), 0.72 (m, 2 H, Cy).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 162.7, 143.1, 142.4, 142.3, 140.4, 136.3, 131.0, 129.6, 129.3, 127.2, 115.7, 115.6, 114.41, 114.39, 114.1, 61.3, 61.2, 55.5, 52.1, 52.0, 51.71, 51.68, 47.03, 47.00, 36.0, 31.8, 27.7, 26.9, 26.2, 26.1, 21.5, 21.3. HRRMS (ESI-TOF) m/z: [M + H]\(^+\) calc. for C\(_{20}\)H\(_{29}\)N\(_4\)O\(_8\)S\(_2\): 712.3818; found 712.3788.

**Synthetic Procedures and Characterization Data for 64. 2-Isopropylidene-1,3-propanediyl bis(t-butylcarbonate) (65, TL004).** A mixture of 1.50 g (9.14 mmol) of 2-benzylidenepropene-1,3-diol, \(^{40}\) 0.11 g (0.91 mmol) of 4-N,N-dimethyaminopyridine, 4.18 g (19.2 mmol) of di-tert-butyl dicarbonate, and 100 mL of diethyl ether was stirred at room temperature under nitrogen for 24 h. The resulting solution was washed with saturated aq. CuSO\(_4\) (3 x 20 mL), saturated aq. NaHCO\(_3\) (3 x 20 mL), and saturated aq. NaCl (3 x 20 mL) solutions, dried, and concentrated to dryness by rotary evaporation. The residue was dried in vacuo and purified by column chromatography on silica gel, eluting with 1:15 (v/v) ethyl acetate/hexane, giving 3.1 g (94\%) of 65 as a viscous clear oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 (m, 2 H, \(-\text{p-Ph}\)), 7.27 (m, 3 H, \(-\text{m-p-Ph}\)), 6.85 (s, 1 H, C\(=\text{CH}\)), 4.76 (s, 2 H, CH\(_2\)), 4.74 (s, 2 H, CH\(_2\)), 1.49 (s, 9 H, t-Bu), 1.46 (s, 9 H, t-Bu). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 153.3, 153.2, 153.3, 134.9, 130.5, 128.8, 128.4, 127.8, 82.3, 68.6, 62.9, 27.6, 27.4. IR (neat, cm\(^{-1}\)): 2979 (w), 1736 (s), 1457 (w), 1394 (w), 1367 (m), 1337 (m), 1160 (s), 1088 (m), 1017 (w), 993 (w), 925 (w), 854 (m), 790 (w), 765 (m), 752 (w), 729 (m), 698 (m), 619 (m), 595 (w), 591 (w). MS (ESI\(^+\)) m/z 387 (M + Na\(^+\)). Anal. calc. for C\(_{20}\)H\(_{28}\)O\(_6\): C, 69.52; H, 7.74. Found: C, 69.52; H, 7.66.

- 9-Benzyl-3-benzylidene-1,5-di(p-toluenesulfonyl)-1,5,9-triazacyclodecane (66, TL005). Using the improved Tsuji–Trost macrocyclization procedure, 0.15 g (0.29 mmol) of N\(^{-}\)-di(p-toluenesulfonyl)-N\(^{-}\)-bis(3-aminopropyl)-benzylamine and 0.50 g (1.37 mmol) of 65 were converted to 66, which was purified by column chromatography on neutral alumina, eluting with 1:4 (v/v) ethyl acetate/hexane, and 82 mg (47\%) of the HCl salt was isolated as a white solid, mp 58–67 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.73 (d, 8 Hz, 2 H, \(-\text{t-Ts}\)), 7.55 (d, 8 Hz, 2 H, \(-\text{o-Ts}\)), 7.29 (m, 4 H, \(-\text{m-Ts}\), 7.23 (m, 5 H, Ph), 7.15 (m, 2 H, Ph), 7.12 (m, 3 H, Ph), 6.80 (s, 1 H, C\(=\text{CH}\)), 4.27 (s, 2 H, CH\(_2\text{C}(\text{OC})\)), 3.40 (s, 2 H, CH\(_2\text{C}(\text{OC})\)), 2.74 (m, 2 H, H12/6), 2.53 (m, 2 H, H8/10), 2.43 (s, 3 H, ArCH\(_3\)), 2.41 (s, 3 H, ArCH\(_3\)), 2.28 (s, 2 H, H10/8), 1.81 (m, 2 H, H7/11), 1.47 (m, 2 H, H11/7). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 143.7, 143.1, 139.5, 138.0, 136.0, 133.5, 130.9, 129.8, 128.9, 128.3, 127.5, 127.0, 59.5, 50.4, 49.6, 48.7, 47.6, 47.2, 42.6, 26.6, 22.6, 21.5. IR (neat, cm\(^{-1}\)): 3057 (w), 3027 (w), 2923 (w), 2236 (w), 1712 (w), 1597 (w), 1493 (w), 1452 (w), 1377 (w), 1337 (m), 1160 (s), 1088 (m), 1017 (w), 993 (w), 925 (w).
ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02555.

Notes
The authors declare no competing financial interest.

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