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

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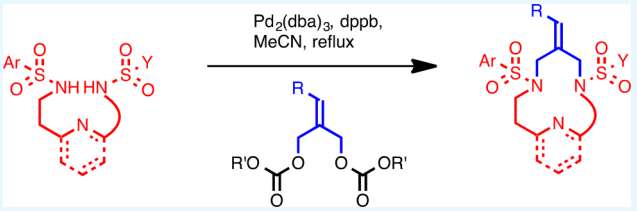
Supporting Information

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-triazacyclododecane disulfonamides, which are of interest as potential immunomodulatory and antiviral drugs.[9−13] Many analogs 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−Trost[14−16] *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(*t*-butylcarbonate) in THF or toluene.[26−28] In addition, palladium-catalyzed

Scheme 1. Atkins−Richman (A) and Tsuji−Trost (B) Approaches to 3-Methylene-1,5,9-triazacyclododecanes

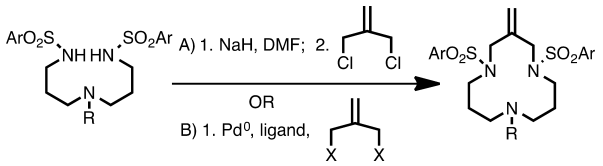


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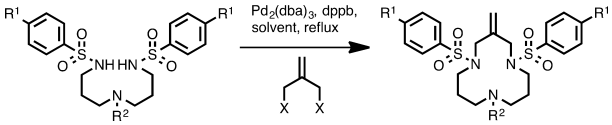
Table 1. Pd-Catalyzed Synthesis of Symmetrical 3-Methylene-1,5-diarenesulfonyl-1,5,9-triazacyclododecanes[a]



starting material	R^1	R^2	X	solvent	product	yield
1	Me	Bn	OBoc	MeOH	**2** (CADA·HCl)[b]	53%
1	Me	Bn	OBoc	THF	**2** (CADA·HCl)[b]	73%
1	Me	Bn	OBoc	MeCN	**2** (CADA·HCl)[b]	95%
1	Me	Bn	Cl	MeCN	**2** (CADA·HCl)[b]	0%
1	Me	Bn	OAc	MeCN	**2** (CADA·HCl)[b]	0%
3	OMe	Bn	OBoc	THF	**4** (KKD023·HCl)[b]	65%
3	OMe	Bn	OBoc	MeCN	**4** (KKD023·HCl)[b]	85%
3	OMe	Bn	OBoc	MeCN	no reaction[c]	
5	Me	H	OBoc	MeCN	**6** (94-129·HCl)[b]	98%
7	Br	Bn	OBoc	MeCN	**8** (ASPB127)[b]	52%
9	NO_2	Bn	OBoc	MeCN	**10** (AS114)[b,d]	56%
11	CN	Bn	OBoc	MeCN	**12** (ES03)	47%[e]

[a]Reaction conditions (unless indicated otherwise): 15−25 mM disulfonamide in anhydrous solvent, 2−2.5 equiv dicarbonate ester, 3 mol % $Pd_2(dba)_3$, and 6 mol % dppb, stirred under reflux for 18−24 h. [b]Ref 10; HCl salts were formed by treatment of the crude product with methanolic HCl and evaporation. [c]The HCl salt of the disulfonamide was used. [d]9 mM disulfonamide; 5 equiv dicarbonate ester. [e]Overall yield for two steps, including synthesis of **11**.

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, cyclotriazadisulfonamide, 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, evaporating, and triturating the residue with hexane. Three bis(electrophiles) were tested: 1,3-dichloro-2-methylenepropane, 2-methylene-1,3-propanediyl diacetate, and 2-methylene-1,3-propanediyl bis(*t*-butylcarbonate). Only the last, a carbonate ester, gave the desired product.

Macrocyclization results for symmetrical CADA analogs are also shown in Table 1. Bis(4-methoxybenzenesulfonyl) analog **4**[10] was also obtained in 95% yield from reaction in acetonitrile and in lower yield from that in THF. An attempt to prepare **4** from the HCl salt of the precursor disulfonamide (**3**) gave no reaction. Removal of the benzyl tail group also gave nearly quantitative macrocyclization for **6**. This is significant because the Atkins−Richman approach did not work in attempts to prepare **6**, which was prepared previously by debenzylation of **2**. Cyano groups in **11** did not interfere with the reaction, and dibrosyl (**8**)[10] and dinosyl (**10**)[10] analogs were obtained in similar yields.

Pd-catalyzed macrocyclization was also tested on synthesis of unsymmetrical 3-methylene-1,5,9-triazacyclododecanes bearing two different arenesulfonyl side arms (Table 2). Yields obtained were generally somewhat lower than those for the symmetrical analogs, probably because of two factors: different acidities of arenesulfonyl side arms could lead to enhanced formation of oligomeric byproducts (see below), and these unsymmetrical analogs could not be purified as solids. The results do show compatibility with additional functional groups, such as in the chloro (**18**),[11] dimethylamino (**26**, **28**, **44**, **46**, and **50**),[10,11] and nitro (**36**, **38**, and **40**)[11] analogs. In the case of resynthesis of 4-(dimethylamino)naphthalene-1-sulfonyl (dansyl) analog **28**,[10] the disulfonamide precursor (**27**) was prepared by a more expedient route to unsymmetrical compounds[11] that was developed after the original synthesis of **28**.[10]

The expectation that byproducts may be formed when the two arenesulfonamide groups are different is apparent from the catalytic cycle shown in Figure 1. Electron-donating or electron-withdrawing substituents on benzenesulfonamides affect the pK_a of the NH group. The catalytic cycle shows that formation of the π-allyl intermediate generates an alkoxide, which serves as the base sulfonamide. For an unsymmetrical open-chain disulfonamide, the more acidic NH should be selectively allylated. The intermediate must then be deprotonated on the less acidic NH to undergo macrocyclization by intramolecular *N*-allylation, so intermolecular reaction with the more acidic NH of a second open-chain disulfonamide molecule may compete. An oligomer resulting from this effect is shown later in Scheme 2.

An attempt was made to extend the scope of this reaction to macrocycles containing an ether linkage. The result shown in Scheme 2 was formation of the 2+1 oligomer **52** (VGD043), which was obtained in 27% yield after column chromatography. Preferential reaction of the sulfonamide nitrogen relative to the hydroxyl oxygen is consistent with the greater acidity of benzenesulfonamide relative to methanol (pK_a 16.1 vs 29.0, respectively, in DMSO).[31] Similar products have been detected spectroscopically as byproducts from reactions of some unsymmetrical disulfonamides.

Analog **54** (VGD020)[11] is one of the more biologically potent compounds prepared to date, so attempts were made to improve its synthesis. As shown in Table 3, omission of sodium carbonate from the reaction mixture gave variable results, so 0.1−1.0 molar equivalents were included in subsequent reactions to insure complete deprotonation of the tertiary nitrogen. This resulted in high yields with three different Pd catalysts, Pd_2dba_3, $Pd(OAc)_2$, and $Pd(PPh_3)_4$. As shown in Table 1, when the HCl salt of disulfonamide **3** was used in the

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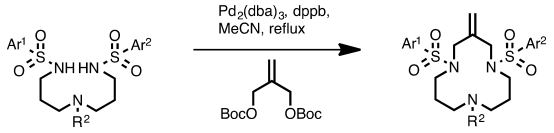
Table 2. Pd-Catalyzed Synthesis of Unsymmetrical 3-Methylene-1,5-diarenesulfonyl-1,5,9-triazacyclododecanes[a]



starting material	Ar^1	Ar^2	R^2	product	yield
13	*p*-tolyl	Ph	$CH_2C_6H_{11}$	**14** (VGD025)[b]	37%
15	*p*-tolyl	4-*t*BuPh	$CH_2C_6H_{11}$	**16** (VGD017)[b]	53%
17	*p*-tolyl	4-ClPh	$CH_2C_6H_{11}$	**18** (VGD018·HCl)[b]	27%
19	*p*-tolyl	1-naphthyl	$CH_2C_6H_{11}$	**20** (VGD021·HCl)[b]	38%
21	*p*-tolyl	2-naphthyl	$CH_2C_6H_{11}$	**22** (VGD022)[b]	37%
23	*p*-tolyl	5-isoquin.	$CH_2C_6H_{11}$	**24** (VGD019)[b]	38%
25	dan[c]	4-MeOPh	$CH_2C_6H_{11}$	**26** (VGD029·HCl)[b]	46%
27	dan[c]	*p*-tolyl	$CH_2C_6H_{11}$	**28** (KKD016·HCl)[d]	56%
29	*p*-tolyl	4-Ac	$CH_2C_6H_{11}$	**30** (DJ005)[e]	28%
31	*p*-tolyl	4-CN	$CH_2C_6H_{11}$	**32** (DJ002)[e]	36%
33	*p*-tolyl	4-MeOPh	Bn	**34** (VGD027·HCl)[b]	56%
35	*p*-tolyl	4-NO_2Ph	Bn	**36** (CK032)[e,f]	32%
37	*p*-tolyl	3-NO_2Ph	Bn	**38** (CK116)[e,f]	39%
39	*p*-tolyl	2-NO_2Ph	Bn	**40** (CK037)[e,f]	43%
41	*p*-tolyl	4-CF_3OPh	Bn	**42** (CK043)[e,f]	41%
43	*p*-tolyl	4-NMe_2Ph	Bn	**44** (CK078)[e,f]	40%
45	*p*-tolyl	3-NMe_2Ph	Bn	**46** (CK207)[e,f]	57%
47	*p*-tolyl	4-FPh	Bn	**48** (CK201·HCl)[e,f]	47%
49	*p*-tolyl	NMe_2	Bn	**50** (CK195)[e,f]	42%

[a]Reaction conditions: 15−20 mM disulfonamide in anhydrous acetonitrile, 2.5 equiv dicarbonate ester, 3 mol % $Pd_2(dba)_3$, 6 mol % dppb, stirred under reflux for 18−24 h. [b]Ref 11. [c]5-Dimethylamino-1-naphthyl. [d]Ref 10. [e]0.1−0.5 equiv Na_2CO_3 was added to the reaction mixture. [f]Ref 13.

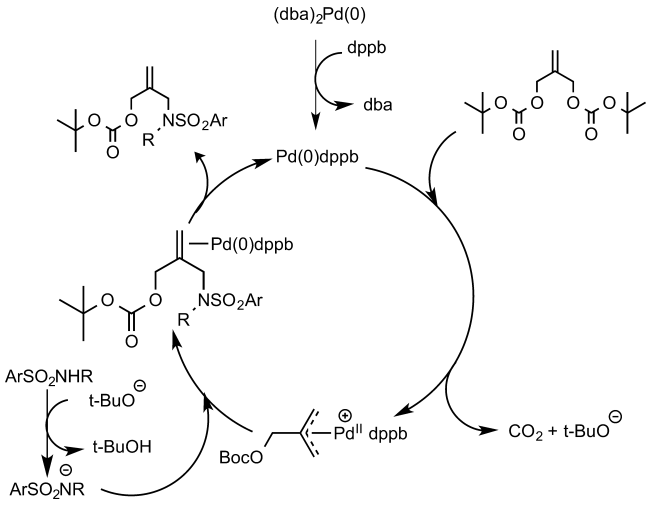


Figure 1. Catalytic cycle for palladium-catalyzed *N*-allylation of sulfonamides with allylic carbonates.

attempted reaction, no product (**4**) was obtained. Tertiary amines can become partially protonated and form bicarbonate salts when exposed to water and atmospheric carbon dioxide. The added Na_2CO_3 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).

Scheme 2. Attempted Macrocyclization of a Hydroxytosylate, Resulting in Oligomerization to 52

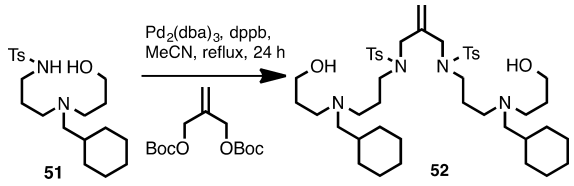
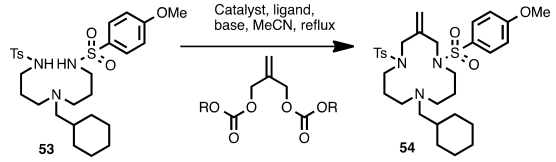


Table 3. Yield Optimization for Synthesis of VGD020 (54)[a]



catalyst (equiv)	ligand (equiv)	base (equiv)	R	yield (%)
Pd_2dba_3 (0.03)	dppb (0.06)	none	*t*Bu	variable
Pd_2dba_3 (0.03)	dppb (0.06)	Na_2CO_3 (0.1)	*t*Bu	25−26
Pd_2dba_3 (0.03)	dppb (0.06)	Na_2CO_3 (1.0)	*t*Bu	25−26
$Pd(OAc)_2$ (0.03)	dppb (0.06)	Na_2CO_3 (1.0)	*t*Bu	20
$Pd(PPh_3)_4$ (0.06)	dppb (0.06)	Na_2CO_3 (1.0)	*t*Bu	10
Pd_2dba_3 (0.03)	none	Na_2CO_3 (1.0)	*t*Bu	0
Pd_2dba_3 (0.03)	PPh_3 (0.06)	Na_2CO_3 (1.0)	*t*Bu	20
Pd_2dba_3 (0.03)	dppf (0.06)	Na_2CO_3 (1.0)	*t*Bu	9
Pd_2dba_3 (0.03)	dppb (0.06)	Na_2CO_3 (1.0)	Me	40
Pd_2dba_3 (0.03)	dppb (0.06)	Na_2CO_3 (1.0)	*t*Bu	50−56[b]
Pd_2dba_3 (0.03)	dppb (0.06)	Na_2CO_3 (1.0)	tBu	48[c]

[a]Reaction conditions (unless indicated otherwise): 15−20 mM disulfonamide in anhydrous acetonitrile, stirred under reflux for 18−24 h. [b]9 mM disulfonamide. [c]4 mM disulfonamide.

With Pd_2dba_3 as a source of Pd, reactions failed when a phosphine ligand was omitted. While reactions worked with triphenylphosphine and dppf as ligands, somewhat lower yields were observed. Other sources of Pd such as $Pd(PPh_3)_4$ and $Pd(OAc)_2$ can also be used, although Pd_2dba_3 gave the highest yield. When the bis(electrophile) 2-methylene-1,3-propanediyl bis(*t*-butylcarbonate) was replaced with 2-methylene-1,3-propanediyl bis(methylcarbonate), the reaction succeeded in good yields. This is significant for large-scale reactions, because the bis(methylcarbonate) 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.

Hydroxyl is considered a difficult leaving group in Tsuji−Trost chemistry,[15] although allylic alcohols have been used for *N*-allylations under certain conditions.[32−35] Because of its lower cost and our need to prepare **54** on a larger scale, we also attempted macrocyclization with 2-methylene-1,3-propanediol under conditions used with dicarbonates, but no product (**54**) was isolated.

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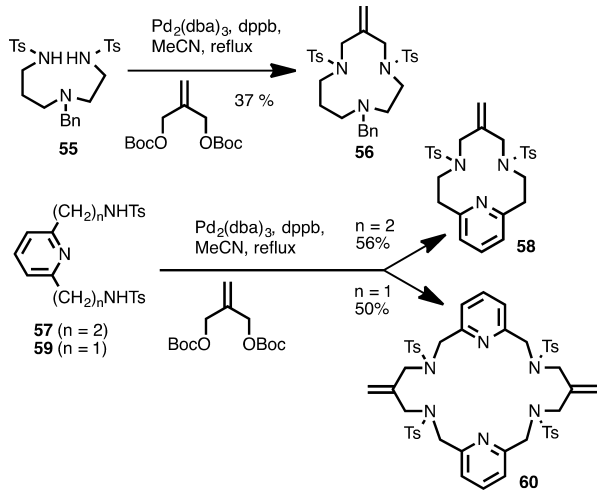
Other variations attempted were to change the size of the macrocyclic ring and to fuse a pyridine ring in the position of the tertiary nitrogen bearing the tail group (Scheme 3).

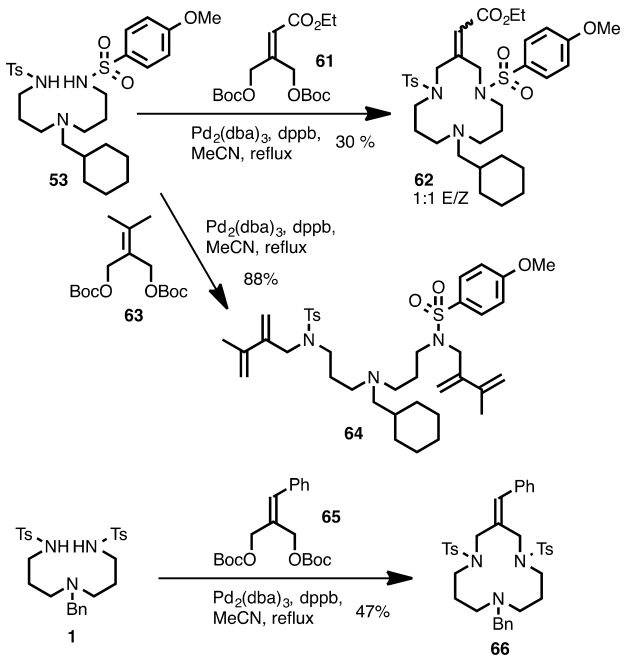
Scheme 3. Ring Size and Pyridine Ring Fusion Variations



Compound **56** (ES-US5) 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 monoallylated 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.

Scheme 4. Head Group Variations



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_2SO_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_3OD = 3.31; ^{13}C, $CDCl_3$ = 77.23, DMSO-d_6 = 39.7, CD_3OD = 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 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.

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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 macrocyclizations was dried by distillation from CaH_2. All reagents were dried at 0.1 mm overnight before use.

In a 250 mL flask equipped with an inlet for N_2 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(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 0.11 mmol of 1,1-bis(diphenylphosphino)butane (dppb), and 120 mL of anhydrous AN was stirred and boiled under reflux for 18–24 h under N_2. The solvent was removed by rotary evaporation. A solution of the residue in 90 mL of dichloromethane (DCM) was extracted with saturated aq. $NaHCO_3$ solution (2 × 30 mL) and saturated aq. NaCl solution (30 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. A solution of the crude product in 10 mL of 2 N HCl in methanol/water was stirred for a few hours, and then, the solvent was removed by rotary evaporation. The residue was dried in vacuo (0.1 mm), triturated with diethyl ether (5 × 15 mL) and then again dried in vacuo.

*Resynthesis of **2** (CADA·HCl).*[10] Using the general macrocyclization procedure, 1.0 g (1.9 mmol) of **1**, which was prepared as described previously,[10] was converted to 1.1 g (95%) of pure 9-benzyl-3-methylene-1,5-di(*p*-toluenesulfonyl-1,5,9-triazacyclododecane hydrochloride (**2**, CADA·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,[10] was converted to 1.0 g (85%) of pure 9-benzyl-3-methylene-1,5-di(*p*-methoxybenzenesulfonyl-1,5,9-triazacyclododecane 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,[36] was converted to 1.0 g (98%) of pure 3-methylene-1,5-di(*p*-toluenenesulfonyl-1,5,9-triazacyclododecane 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,[10] was converted to 1.46 g (52%) of pure 9-benzyl-3-methylene-1,5-di(*p*-bromobenzenesulfonyl-1,5,9-triazacyclododecane **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 (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by column chromatography on alumina, eluting with hexane/ethyl 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,[10] was converted to 0.49 g (56%) of pure 9-benzyl-3-methylene-1,5-di(*p*-nitrobenzenesulfonyl-1,5,9-triazacyclododecane **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-Dimethylaminonaphthalene-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,[11] 0.46 g (1.7 mmol) of 5-dimethylaminonaphthalene-1-sulfonyl chloride, 11 mL of DCM, 11 mL of saturated aq. Na_2CO_3 solution, and 11 mL of saturated aq. NaCl solution was stirred vigorously at room temperature for 24 h. The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated to dryness by rotary evaporation. The residue was dried in vacuo and purified by column chromatography on alumina, eluting with hexane/EtOAc to give 0.70 g (67%) of **27** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2NH), 2.87 (s, 6 H, NCH_3), 2.40 (s, 3 H, $ArCH_3$), 2.26 (m, 4 H, CH_2N), 1.98 (d, 7 Hz, 2 H, CH_2Cy), 1.61 (t, 8 Hz, 6 H, CCH_2C, Cy), 1.52 (m, 4 H, Cy), 1.30 (m, 2 H, Cy), 1.12 (m, 3 H, Cy), 0.74 (m, 2 H, Cy). ^{13}C (100 MHz, $CDCl_3$) δ 152.0, 143.3, 137.2, 135.2, 130.4, 130.1, 129.9, 129.8, 129.6, 128.4, 127.2, 123.4, 119.3, 115.3, 62.0, 53.2, 53.0, 45.6, 42.8, 42.7, 35.8, 32.0, 26.8, 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 to dryness by rotary evaporation. The residue was dried in vacuo and then triturated with anhydrous diethyl ether (3 × 10 mL) to give 0.57 g (93%) of **27**·HCl as a yellowish powder. ^{1}H NMR (500 MHz, CD_3OD) 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, NCH_3), 3.21 (m, 4 H, CH_2N), 2.99 (t, 6 Hz, 2 H, CH_2Cy), 2.93 (m, 4 H, CH_2NH), 2.44 (s, 3 H, $ArCH_3$), 1.90 (m, 4 H, CCH_2C), 1.76 (m, 6 H, Cy), 1.39 (m, 2 H, Cy), 1.25 (m, 1 H, Cy), 1.05 (m, 2 H, Cy). ^{13}C NMR (125 MHz, CD_3OD) δ 145.1, 138.5, 138.1, 131.4, 131.1, 130.8, 129.2, 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. calcd. for $C_{32}H_{46}N_4O_4S_2$·2HCl: 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-triazacyclododecane **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 Na_2CO_3, 0.37 mmol of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 0.72 mmol of 1,1-bis(diphenyl-phosphino)butane (dppb), 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 $NaHCO_3$ and 100 mL of dichloromethane (DCM). The layers were separated, and the aqueous layer was extracted with DCM (2 × 100 mL). The

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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,[10] 0.88 g (8.3 mmol) of anhydrous Na_2CO_3, 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*-cyanobenzenesulfonyl 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)[*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-benzyl-3-methylene-1,5-bis(*p*-cyanobenzenesulfonyl)-1,5,9-triazacyclododecane (**12**, ES03) as fine white crystals, mp 190−193 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, 9 Hz, 4 H, *o*-$ArSO_2$), 7.84 (d, 9 Hz, 4 H, *m*-$ArSO_2$), 7.25 (m, 3 H, *m,p*-Ph), 7.13 (m, 2 H, *o*-Ph), 5.21 (s, 2 H, C═CH), 3.90 (s, 4 H, H2,4), 3.41 (s, 2 H, CH_2Ph), 3.17 (t, 6.7 Hz, 4 H, H6,12), 2.39 (t, 5.8 Hz, 4 H, H8,10), 1.67 (quint., 6 Hz, 4 H, H7,11). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 137.4, 133.0, 128.7, 127.1, 121.9, 117.1, 116.6, 116.5, 105.2, 59.0, 49.4, 48.0, 44.2, 24.8. MS (ESI$^+$) *m/z* 604 (MH^+). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd. for $C_{31}H_{34}N_5O_4S_2$ 604.2052; found: 604.2046.

Synthetic Procedures and Characterization Data for 30. *N′-(p-Acetylbenzenesulfonyl)-N″-(p-toluenesulfonyl)-[N,N-bis(3-aminopropyl)cyclohexylmethylamine] (**29**, DJ004).* A mixture of 4.0 g (10.5 mmol) of *N*-(3-aminopropyl)-*N*-(3-*p*-toluenesulfonamidopropyl)-cyclohexylmethylamine,[11] 2.33 g (10.7 mmol) of *p*-acetylbenzenesulfonyl chloride, 69 mL of saturated aq. Na_2SO_4 solution, 69 mL of saturated aq. NaCl solution, and 69 mL of DCM was stirred at room temperature for 24 h, then the layers were separated, and the aqueous layer was extracted with DCM (3 × 40 mL). The combined organic solutions were dried and concentrated 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 concentrated to dryness by rotary evaporation. The residue was dried in vacuo, triturated with anhydrous diethyl ether (3 × 30 mL) and again dried in vacuo to give 3.24 g (87%) of **29**·HCl. A sample was dried overnight in vacuo at 78 °C and found to be pure (anal. calcd. for $C_{28}H_{42}N_3O_5S_2$·HCl·0.2H_2O: C, 55.70; H, 7.08; N, 6.96. Found: C, 55.64; H, 6.89; N, 6.89). The HCl salt was converted back to the free base by stirring with 185 mL of 2 N aq. NaOH solution, 185 mL of saturated aq. NaCl solution, and 185 mL of DCM for 5 h. The layers were separated, and the aqueous phase was extracted with DCM (2 × 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 9 Hz, 2 H, *o*-$ArSO_2$), 7.95 (d, 9 Hz, 2 H, *m*-$ArSO_2$), 7.72 (d, 8 Hz, 2 H, *o*-Ts), 7.30 (d, 8 Hz, 2 H, *m*-Ts), 6.10 (br., 2 H, NH), 3.04 (t, 6 Hz, 2 H, CH_2NHSO_2At), 2.97 (t, 6 Hz, 2 H, CH_2NHTs), 2.65 (s, 3 H, Ac), 2.43 (s, 3 H, $ArCH_3$), 2.38 (t, 7 Hz, 4 H, CH_2NCH_2Cy), 2.05 (d, 7 Hz, 2 H, CH_2Cy), 1.65 (m, 10 H, CCH_2C, Cy), 1.35 (m, 1 H, Cy) 1.14 (m, 2 H, Cy), 0.78 (m, Hz, 2 H, Cy).^{13}C NMR (100 MHz, $CDCl_3$) 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* 564 (MH^+).

*1-(p-Acetylbenzenesulfonyl)-9-cyclohexylmethyl-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. calcd. for $C_{32}H_{45}N_3O_5S_2$·HCl·0.2H_2O: C, 57.52; H, 7.22; N, 6.27. Found: C, 57.52; H, 7.51; N, 6.12). 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 9 Hz, 2 H, *o*-$ArSO_2$), 7.89 (d, 9 Hz, 2 H, *m*-$ArSO_2$), 7.64 (d, 8 Hz, 2 H, *o*-Ts), 7.32 (d, 8 Hz, 2 H, *m*-Ts), 5.15 (s, 2 H, C═CH), 3.91 (s, 2 H, H2/4), 3.71 (s, 2 H, H4/2), 3.28 (t, 7 Hz, 2 H, H6/12), 3.04 (t, 7 Hz, 2 H, H12/6), 2.65 (s, 3 H, Ac), 2.43 (s, 3 H, $ArCH_3$), 2.25 (m, 4 H, H8,10), 1.95 (d, 7 Hz, 2 H, CH_2Cy), 1.65 (m, 10 H, H7,11, Cy), 1.13 (m, 3 H, Cy), 0.73 (m, 2 H, Cy). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 143.4, 140.5, 139.9, 136.2, 129.7, 129.0, 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 (MH^+).

Synthetic Procedures and Characterization Data for 32. *N′-(p-Cyanobenzenesulfonyl)-N″-(p-toluenesulfonyl)-[N,N-bis(3-aminopropyl)cyclohexylmethylamine (**31**, DJ001).* A mixture of 3.0 g (7.9 mmol) of *N*-(3-aminopropyl)-*N*-(3-*p*-toluenesulfonamidopropyl)-cyclohexylmethylamine,[11] 1.6 g (7.9 mmol) of *p*-cyanobenzenesulfonyl chloride, 51 mL of saturated aq. Na_2CO_3 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 103 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 again 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**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 8 Hz, 2 H, *o*-$ArSO_2$), 7.78 (d, 8 Hz, 2 H, *o*-Ts), 7.70 (d, 8 Hz, 2 H, *m*-$ArSO_2$), 7.29 (d, 8 Hz, 2 H, *m*-Ts), 3.04 (t, 6 Hz, 2 H, CH_2NHSO_2Ar), 2.96 (t, 6 Hz, 2 H, CH_2NHTs), 2.41 (s, 3

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H, CH_3), 2.38 (d, 7 Hz, 4 H, CH_2NCH_2Cy), 2.04 (d, 7 Hz, 2 H, CH_2Cy), 1.64 (m, 10 H, CCH_2C, Cy), 1.36 (m, 1 H, Cy), 1.12 (m, 2 H, Cy), 0.82 (m, 2 H, Cy). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 143.3, 136.8, 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-Cyanobenzenesulfonyl)-9-cyclohexylmethyl-3-methylene-5-(p-toluenesulfonyl)-1,5,9-triazacyclododecane (**32**, DJ002).* Using the improved Tsuji–Trost macrocyclization 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, $CDCl_3$) δ 7.92 (d, 8 Hz, 2 H, *o*-$ArSO_2$), 7.81 (d, 8 Hz, 2 H, *o*-Ts), 7.63 (d, 8 Hz, 2 H, *m*-$ArSO_2$), 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, H4/2), 3.36 (m, 2 H, H6/12), 2.99 (t, 6.3 Hz, 2 H, H12/6), 2.43 (s, 3 H, CH_3), 2.33 (m, 4 H, H8,10), 1.96 (d, 7 Hz, 2 H, CH_2Cy), 1.60 (m, 10 H, H7,10, Cy) 1.13 (m, 3 H, Cy), 0.73 (m, 2 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) 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, 45.3, 43.3, 35.8, 31.9, 27.7, 26.7, 26.0, 25.5, 23.8, 21.5. MS (ESI^+) m/z 599 (MH^+). Anal. calcd. for $C_{31}H_{42}N_4O_4S_2 \cdot HCl \cdot CH_3OH \cdot 0.5H_2O$: 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 macrocyclization procedure, 0.98 g (1.8 mmol) of **47**, which was prepared as described previously,[13] was converted to 0.51 g (47%) of pure 9-benzyl-1-(*p*-fluorobenzenesulfonyl)-3-methylene-5-(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane hydrochloride **48** (CK201·HCl). The chromatographed free base was converted to the HCl salt as described in the general macrocyclization procedure.

Synthetic Procedures and Characterization Data for 52. *N-(3-Hydroxypropyl)-N-(3-p-toluenesulfonamidopropyl)cyclohexylmethylamine (**51**, VGD041).* A mixture of 4.11 g (12.7 mmol) of *N*-(3-*p*-toluenesulfonamidopropyl)-cyclohexylmethylamine,[11] 1.48 g (14.0 mmol) of Na_2CO_3, 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) DCM/EtOH followed by neat EtOH to give 2.30 g (47%) of **51**, which was converted to **52** without further purification. ^1H NMR (500 MHz, $CDCl_3$) 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, CH_2OH), 2.96 (t, 6 Hz, 2 H, CH_2NHTs), 2.54 (t, 6 Hz, 2 H, CH_2NCH_2Cy), 2.42 (m, 5 H, CH_2N, CH_3), 2.11 (d, 7 Hz, 2 H, CH_2Cy), 1.67 (m, 8 H, CCH_2C, Cy), 1.44 (m, 1 H, Cy), 1.17 (m, 4 H, Cy), 0.82 (m, 2 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) 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, 26.1, 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 calcd. for $C_{20}H_{34}N_2O_3S$ (M^+) 382.2285, found 382.2273; calcd. for $C_{20}H_{34}N_2O_3SNa$ $(M + Na)^+$ 405.2182, found 405.2184.

*N,N′-Bis[(N-cyclohexylmethyl-N-3-hydroxypropyl)-3-aminopropyl]- N,N′-di(p-toluenesulfonyl)-2-methylene-1,3-diaminopropane (**52**, VGD043).* A mixture of 0.76 g (2.0 mmol) of **51**, 1.42 g (4.93 mmol) of 2-methylene-1,3-propanebis(*t*-butylcarbonate), 50 mg (0.12 mmol) of dppb, 57 mg (0.062 mmol) of tris(dibenzylideneacetone)-dipalladium(0), and 126 mL of anhydrous AN was stirred under nitrogen and boiled under reflux for 24 h, cooled to room temperature, and concentrated to dryness by rotary evaporation. A solution of the residue in 95 mL of DCM was washed with saturated aq. $NaHCO_3$ solution (2 × 30 mL) and 30 mL of saturated aq. NaCl solution, dried (Na_2SO_4), and concentrated to dryness by rotary evaporation. Column chromatography on silica gel, eluting with DCM/MeOH, gave 0.22 g (27%) of **52** as a light yellow, viscous oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 8 Hz, 4 H, *o*-Ts), 7.32 (d, 8 Hz, 4 H, *m*-Ts), 5.26 (s, 2 H, C=CH), 3.78 (m, 8 H, CH_2OH, $CH_2C{=}C$), 3.14 (m, 4 H, CH_2NTs), 2.63 (bs, 4 H, CH_2NCH_2Cy), 2.43 (s, 10 H, CH_3, CH_2NCH_2Cy), 2.22 (bs, 4 H, CH_2Cy), 1.71 (broad, 18 H, CCH_2C, Cy), 1.47 (bs, 2 H, Cy), 1.09 (m, 6 H, Cy), 0.86 (m, 4 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 140.3, 136.3, 129.9, 127.3, 116.3, 63.4, 61.7, 54.8, 52.0, 51.8, 47.6, 35.4, 31.8, 27.9, 26.6, 26.1, 25.1, 21.6. IR (neat, cm^{-1}): 2923 (m), 2850 (m), 1598 (w), 1449 (m), 1338 (m), 1159 (s), 1091 (m), 1036 (w), 918 (w), 816 (w), 735 (m), 710 (w), 693 (w), 656 (m). A solution of 84 mg of **52** free base in 10 mL of 2 N HCl in methanol/water was stirred at room temperature for 4 h and then concentrated to dryness by rotary evaporation. The residue was dried in vacuo and then triturated with anhydrous diethyl ether (5 × 20 mL) using sonication to give 76 mg of **52**·2HCl as a cream-colored solid. ^1H NMR (500 MHz, CD_3OD) δ 7.76 (d, 8 Hz, 4 H, *o*-Ts), 7.46 (d, 8 Hz, 4 H, *m*-Ts), 5.31 (s, 2 H, C=CH), 3.86 (s, 4 H, $C{=}CCH_2$), 3.73 (t, 6 Hz, 4 H, CH_2CH_2NTs), 3.24 (m, 14 H, CH_2NCH_2Cy, CH_2OH), 3.00 (m, 4 H, CH_2Cy), 2.46 (s, 6 H, CH_3), 2.02 (m, 4 H, CCH_2C), 1.92 (m, 4 H, CCH_2C), 1.74 (m, 12 H, Cy), 1.33 (m, 4 H, Cy), 1.22 (m, 2 H, Cy), 1.03 (m, 4 H, Cy). IR (neat, cm^{-1}): 3310 (w), 2925 (m), 2848 (w), 2585 (w), 2487 (w), 1600 (w), 1448 (m), 1331 (s), 1156 (s), 1089 (m), 1060 (m), 1035 (m), 921 (m), 816 (m), 804 (m), 738 (m), 710 (m), 692 (m). MS (ESI^+) m/z 817 (MH^+). Anal. calcd. for $C_{44}H_{72}N_4O_6S_2 \cdot 2HCl \cdot 0.5H_2O$: C, 58.78; H, 8.41; N, 6.23. Found: C, 58.62; H, 8.66; N, 6.03.

Resynthesis of 54 (VGD020).[11] Using the improved Tsuji–Trost macrocyclization procedure, 0.21 g (0.38 mmol) of **53**, which was prepared as described previously,[11] was converted to 0.12 g (52%) of pure 9-cyclohexylmethyl-1-(*p*-methoxybenzenesulfonyl)-3-methylene-5-(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane **54** (VGD020).

Synthetic Procedures and Characterization Data for 56. A mixture of 0.93 g (2.9 mmol) of *N*-(3-*p*-toluenesulfonamidopropyl)benzylamine, 0.60 g (3.0 mmol) of *N*-tosylaziridine,[37] 29 mL of water, and 10 mL of $CHCl_3$ 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 $CHCl_3$ (2 × 25 mL). The combined organic solutions were concentrated by rotary evaporation, and the residue was dried in vacuo (50 °C), yielding 1.49 g (99%) of *N*-(3-*p*-toluenesulfonamidopropyl)-*N*-(2-*p*-toluenesulfonamidoethyl)benzylamine (**55**, ES26) as a light brown oil, which was sufficiently pure for use in the next step. Using the improved Tsuji–Trost macrocyclization 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-

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methylene-1,5-di(*p*-toluenesulfonyl)-1,5,8-triazacycloundecane (**56**) as a fine beige powder. A sample was converted to the HCl salt, which was found to be pure by combustion microanalysis after drying overnight in vacuo at 78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 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/H4), 3.82 (m, 2 H, H4/H2), 3.50 (s, 2 H, CH_2Ph), 3.15 (m, 4 H, H6/11), 2.59 (m, 2 H, H7), 2.44 (m, 8 H, H9, CH_3), 1.87 (m, 2 H, H10). ^{13}C NMR (125 MHz, $CDCl_3$) 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, 53.8, 53.3, 50.4, 48.2, 47.2, 26.8, 21.7. ES-US5·HCl: MS (ESI$^+$) *m/z* 568 (MH+). Anal. calcd. for $C_{30}H_{37}N_3O_4S_2$·HCl: C, 59.64; H, 6.34; N, 6.95. Found: C, 59.24; H, 6.74; N, 6.84.

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 *N,N′*-di(*p*-toluenesulfonyl)-2,6-bis(2-aminoethyl)pyridine (**57**),[38] 104 mg (0.36 mmol) of 2-methylene-1,3-propanediyl bis(*t*-butylcarbonate), 4 mg (0.11 mmol) of dppb, 2 mg (0.02 mmol) of anhydrous $NaHCO_3$, 8.5 mL of anhydrous AN, and 4 mg (4 μmol) of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was stirred under nitrogen and boiled under reflux for 24 h under nitrogen and then cooled to room temperature. The solvent was removed by rotary evaporation, and the residue was stirred with 6 mL of DCM for 30 min and then filtered. The filtrate was washed with saturated aq. sodium bicarbonate solution (2 × 2 mL) and saturated aq. sodium chloride solution (2 x 2 mL) and dried. The filtrate was concentrated by rotary evaporation to a viscous oil, which was triturated with 2 mL of ether and dried in vacuo to give 69 mg (87%) of a glassy solid, which was purified by column chromatography on silica, eluting with DCM followed by 99:1 (v/v) DCM/CH_3OH to give 44 mg (56%) of **58** as a white solid, mp 194−195 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 8 Hz, 4 H, *o*-Ts), 7.46 (t, 8 Hz, 1 H, H13), 7.33 (d, 8 Hz, 4 H, *m*-Ts), 6.90 (d, 10 Hz, 2 H, H12,14), 4.87 (s, 2 H, C═CH), 3.66 (t, 8 Hz, 4 H, H3,9), 3.34 (s, 4 H, H5,7), 3.05 (t, 8 Hz, 4 H, H2,10), 2.45 (s, 6 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 143.5, 137.8, 137.1, 135.5, 129.7, 127.5, 122.4, 52.6, 45.6, 37.3, 21.5. IR (neat, cm^{-1}): 2919 (w), 2851 (w), 1593 (w), 1574 (w), 1455 (w), 1334 (m), 1309 (m), 1149 (s), 1101 (m), 1087 (m), 915 (m), 813 (m), 760 (m), 687 (m), 580 (s), 549 (s). MS (ESI$^+$) *m/z* 526 (MH$^+$, 100%). Anal. calcd. for $C_{27}H_{31}N_3O_4S_2$: C, 61.69; H, 5.94; N, 7.99. Found: C, 61.48; H, 6.40; N, 7.99.

Synthetic Procedures and Characterization Data for 60. *N,N′-Di(p-toluenesulfonyl)-2,6-bis(aminomethyl)-pyridine (**59**, LAL009).* A mixture of 2.00 g (14.8 mmol) of pyridine-2,6-dicarboxaldehyde, 4.52 g (26.4 mmol) of *p*-toluenesulfonamide, 1.5 mL of triethylamine, and 60 mL of 1,2-dichloroethane was stirred under nitrogen at 0 °C as 11.2 g (52.8 mmol) of sodium triacetoxyborohydride was added in portions. The resulting suspension was stirred for 30 min at 0 °C and then at room temperature for 25 h. An additional 5.3 g (25 mmol) of sodium triacetoxyborohydride and 7 mL of AcOH were added, and the suspension was stirred for 24 h at room temperature. The reaction mixture was diluted with 120 mL of EtOAc, 60 mL of distilled water was added, and stirring was continued for 30 min. After further dilution with 120 mL of EtOAc, the pH of the aqueous layer was adjusted to 7 with saturated aq. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic solutions were washed with saturated aq. $NaHCO_3$ solution (2 × 100 mL) and then with saturated aq. NaCl solution (2 × 200 mL), dried (Na_2SO_4), and concentrated by rotatory evaporation. Purification by column chromatography on neutral alumina, eluting with 3:7 (v/v) $CHCl_3$/EtOAc, gave 3.42 g (52%) of **59** as a white solid, mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 9.2 Hz, 4 H, *o*-Ts), 7.51 (t, 7.4 Hz, 1 H, *p*-Py), 7.22 (d, 7.9 Hz, 4 H, *m*-Ts), 7.03 (d, 7.5 Hz, 2 H, *m*-Py), 5.66 (s, 2 H, NH), 4.17 (d, 5.8 Hz, 4 H, CH_2), 2.39 (s, 6 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 143.5, 137.5, 136.7, 129.7, 127.2, 120.6, 47.4, 21.5. IR (neat, cm^{-1}): 1596 (m), 1461 (w), 1350 (s), 1323 (s), 1155 (s), 1168 (s), 1151 (s), 1087 (s), 1048 (w), 909 (w), 886 (w), 832 (w), 811 (s), 805 (m), 784 (m), 748 (w), 662 (s). MS (ESI+) *m/z* 469 (MH$^+$ + Na, 100%), 446 (MH$^+$, 28%). Anal. calcd. for $C_{21}H_{23}N_3O_4S_2$: C, 56.61; H, 5.20; N, 9.43. Found: C, 57.01; H, 5.60; N, 9.83.

*5,17-Dimethylene-3,7,15,19-tetrakis(p-toluenesulfonyl)-3,7,15,19,25,26-hexaazatricyclo[19.3.1.1^{9,13}]hexacosa-1-(25),9(26),10,12,21,23-hexaene (**60**, LAL012).* Using the improved Tsuji−Trost macrocyclization procedure, 0.50 g (1.13 mmol) of intermediate **59** was converted to **60**, which was purified by column chromatography on silica gel, eluting with 9:1 (v/v) chloroform/ethyl acetate, giving 0.28 g (50%) of a white solid, mp 213−215 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) 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, ArCH_2N), 3.70 (s, 8 H, C═CCH_2N), 2.43 (s, 12 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) 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), 992 (w), 968(m), 926 (w), 906 (w), 805 (m), 784 (m), 763 (w), 752 (m), 732 (w), 709 (m), 727 (w), 695 (w), 649 (s), 613 (s), 596 (m). MS (ESI+) *m/z* 1016 (M−1 + Na$^+$). Anal. calcd. for $C_{50}H_{54}N_6O_8S_4$: C, 60.34; H, 5.47; N, 8.44. Found: C, 60.48; H, 5.66; N, 8.53.

Synthetic Procedures and Characterization Data for 62. *2-Carboethoxymethylene-1,3-propanediyl bis(t-butylcarbonate) (**61**).*[26] A solution of 2.5 g (11 mmol) of triethyl phosphonoacetate in 150 mL of anhydrous THF was stirred under nitrogen as 0.81 g (20 mmol) of a 60% dispersion of NaH in mineral oil was added. The mixture was stirred for 15 min at room temperature and then boiled under reflux for 15 min. 2-Oxo-1,3-propane bis(*t*-butylcarbonate)[26] (3.2 g, 11 mmol) 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 aq. 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 80:20 (v/v) hexane/ethyl acetate to give 2.8 g (75%) of **61** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1 H, C═CH), 5.26 (s, 2 H, C═CCH_2), 4.74 (s, 2 H, C═CCH_2), 4.18 (q, 5 Hz, 2 H, OCH_2), 1.50 (s, 18 H, *t*-Bu, 1.29 (t, 5 Hz, 3 H, CH_2CH_3). ^{13}C NMR (400 MHz, $CDCl_3$/TMS) δ 167.2, 154.9, 147.6, 117.1, 82.1, 67.1, 65.0, 59.6, 27.6, 14.4.

*9-Cyclohexylmethyl-3-(carboethoxymethylene)-1-(p-methoxybenzenesulfonyl)-5-(p-toluenesulfonyl)-1,5,9-triazacyclododecane (**62**, RA014).* Using the improved Tsuji−Trost macrocyclization procedure, *N′*-(*p*-methoxybenzenesulfonyl)-

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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) hexane/ethyl 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 1.4:1 mixture of stereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 9 Hz, 2.8 H, *o*-$ArSO_2$, major), 7.70 (d, J = 9 Hz, 2 H, *o*-$ArSO_2$, minor), 7.67 (d, 8 Hz, 2 H, *o*-Ts, minor), 7.61 (d, 8 Hz, 2.8 H, *o*-Ts, major), 7.31 (d, 8 Hz, 2 H, *m*-Ts, minor), 7.26 (d, 8 Hz, 2.8 H, *m*-Ts, major), 6.98 (d, 9 Hz, 2.8 H, *m*-$ArSO_2$, major), 6.93 (d, 9 Hz, 2 H, *m*-$ArSO_2$, minor), 5.29 (s, 2.4 H, C═CH, both), 4.17 (m, 4 H, CH_2CH_3, both), 3.87 (s, 4.2 H, OCH_3, major), 3.84 (s, 3 H, OCH_3, minor), 3.0−3.4 (m, br, 19.2 H, H2,4,8,10, both), 2.42 (s, 3 H, $ArCH_3$, minor), 2.40 (s, 4.2 H, $ArCH_3$, major), 2.20 (m, 4.8 H, H6/12, both), 1.92 (m, 4.8 H, H12/6, both), 1.80 (m, 7.2 H, Cy, both) 1.60 (m, 16.8 H, H7,11, Cy, both), 1.29 (m, 7.2 H, CH_2CH_3, both), 1.09 (m, 7.2 H, Cy, both), 0.69 (m, 4.8 H, Cy, both). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.1, 163.0, 162.8, 143.6, 143.2, 135.9, 135.3, 132.7, 132.6, 131.2, 131.1, 130.6, 130.0, 129.7, 129.6, 129.5, 129.4, 127.5, 127.3, 114.2, 114.1, 60.8, 60.6, 55.61, 55.59, 53.4, 52.5, 49.6, 49.0, 45.6, 35.8, 33.2, 32.1, 28.2, 27.5, 26.7, 26.1, 21.6, 21.5, 14.2. IR (neat, cm^{-1}): 2927.6 (w), 2835.8 (w), 2803.9 (w), 1739.1 (m), 1593.0 (m), 1574.9 (w), 1492.9 (w), 1445.6 (w), 1411.8 (w), 1346.4 (s), 1339.2 (s), 1304.4 (m), 1285.9 (w), 1253.8 (w), 1164.6 (s), 1138.9. MS (ESI$^+$) *m*/*z* 676 (MH^+). Anal. calcd. for $C_{34}H_{49}N_3O_7S_2$: C, 60.42; H, 7.31; N, 6.22. Found: C, 60.25; H, 7.49; N, 6.29.

Synthetic Procedures and Characterization Data for 64. *2-Isopropylidene-1,3-propanediyl bis(t-butylcarbonate) (**63**, TL001).* A mixture of 12.1 g (60.5 mmol) of diethyl 2-isopropylidenemalonate,[39] 3.45 g (90.8 mmol) of $LiAlH_4$, and 450 mL of benzene was stirred under nitrogen and boiled under reflux for 6 h and then stirred at 0 °C as 13.5 mL of deionized water followed by 3.5 mL of 6 N aq. NaOH solution were added dropwise. The mixture was warmed to room temperature, stirred for 3 h, and then filtered. The residue was washed with 1 L of benzene, and then, the combined filtrates were concentrated to dryness by rotatory evaporation. The residue was dried in vacuo and then stirred with 200 mL of diethyl ether, 24.6 g (113 mmol) of di-*t*-butyl dicarbonate, and 0.55 g (4.5 mmol) of 4-*N*,*N*-dimethylaminopyridine. The resulting solution was stirred for 24 h and then washed with saturated aq. $CuSO_4$ (3 × 20 mL), saturated aq. $NaHCO_3$ (3 × 25 mL), and saturated aq. NaCl (3 × 25 mL) solutions. The solution was dried and concentrated to dryness by rotatory evaporation. The residue was dried in vacuo and purified by column chromatography on silica gel, eluting with 15:85 (v/v) ethyl acetate/hexane, followed by bulb-to-bulb distillation in vacuo. This gave 2.2 g (8%) of **63** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 4 H, CH_2), 1.83 (s, 6 H, C═CCH_3), 1.47 (s, 18 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 142.3, 122.6, 81.9, 64.7, 27.8, 20.8. IR (neat, cm^{-1}): 2979 (w), 1733 (s), 1456 (w), 1393 (w), 1367 (m), 1269 (m), 1247(s), 1153 (s), 1079 (m), 1035 (w), 927 (w), 854 (m), 792 (m), 764 (w). Anal. calcd. for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.36; H, 8.71.

*N,N-Bis[N′-(3-methyl-1,3-butadien-2-yl)-3-p-toluenesulfonamidopropyl]cyclohexylmethylamine (**64**, TL002).* Using the improved Tsuji−Trost macrocyclization procedure, 80 mg (0.14 mmol) of *N*′-(*p*-methoxybenzenesulfonyl)-*N*″-(*p*-toluenesulfonyl)[*N*,*N*-bis(3-aminopropyl)]-cyclohexylmethylamine (**53**)[11] and 0.20 g (0.69 mmol) of **63** were converted to **64**, which was isolated by column chromatography on neutral alumina, eluting with 4:1 hexane/ethyl acetate to give 66.1 mg (88%) of **64** as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 9 Hz, 2 H, *o*-$ArSO_2$), 7.69 (d, 8 Hz, 2 H, *o*-Ts), 7.30 (d, 8 Hz, 2 H, *m*-Ts), 6.97 (d, 9 Hz, 2 H, *m*-$ArSO_2$), 5.26 (s, 2 H, C═CH), 5.24 (s, 2 H, C═CH), 5.15 (s, 2 H, C═CH), 5.07 (s, 2 H, C═CH), 3.92 (s, 3 H, OCH_3), 3.87 (m, 4 H, C═CCH_2NSO_2), 3.02 (m, 4 H, $CH_2CH_2NSO_2$), 2.42 (s, 3 H, $ArCH_3$), 2.17 (t, 7 Hz, 4 H, CH_2NCH_2Cy), 1.95 (d, 7.1 Hz, 2 H, CH_2Cy), 1.91 (s, 6 H, C═CCH_3), 1.64 (m, 10 H, CCH_2C, Cy), 1.19 (m, 3 H, Cy), 0.72 (m, 2 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) δ 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. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd. for $C_{39}H_{58}N_3O_5S_2$ 712.3818; found 712.3788.

Synthetic Procedures and Characterization Data for 66. *2-Benzylidene-1,3-propanediyl bis(t-butylcarbonate) (**65**, TL004).* A mixture of 1.50 g (9.14 mmol) of 2-benzylidenepropane-1,3-diol,[40] 0.11 g (0.91 mmol) of 4-*N*,*N*-dimethylaminopyridine, 4.18 g (19.2 mmol) of di-*t*-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 × 20 mL), saturated aq. $NaHCO_3$ (3 × 20 mL), and saturated aq. NaCl (3 × 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, $CDCl_3$) δ 7.34 (m, 2 H, *o*-Ph), 7.27 (m, 3 H, *m*,*p*-Ph), 6.85 (s, 1 H, C═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, $CDCl_3$) δ 153.3, 153.2, 135.3, 134.9, 130.5, 128.8, 128.4, 127.8, 82.3, 68.6, 62.9, 27.76, 27.74. IR (neat cm^{-1}) 2979 (w), 1736 (s), 1457 (w), 1394 (w), 1367 (m), 1270 (s), 1246 (s), 1151 (s), 1083 (m), 1035 (w), 925 (w), 896 (m), 855 (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. calcd. for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.82; H, 7.66.

*9-Benzyl-3-benzylidene-1,5-di(p-toluenesulfonyl)-1,5,9-triazacyclododecane (**66**, TL005).* Using the improved Tsuji−Trost macrocyclization procedure, 0.15 g (0.29 mmol) of *N*′,*N*″-di(*p*-toluenesulfonyl)-*N*,*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, $CDCl_3$) δ 7.73 (d, 8 Hz, 2 H, *o*-Ts), 7.55 (d, 8 Hz, 2 H, *o*-Ts), 7.29 (m, 4 H, *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═CH), 4.27 (s, 2 H, CH_2C═C), 3.86 (s, 2 H, CH_2C═C), 3.49 (m, 2 H, H6/12), 3.40 (s, 2 H, CH_2Ph), 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, $CDCl_3$) δ 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),

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814 (w), 746 (m) 724 (m), 699 (s), 657 (m). MS (ESI^+) *m/z* 658 (MH^+). Anal. calcd. for $C_{37}H_{44}O_4S_2$·HCl: C, 64.00; H, 6.39; N, 6.05. Found: C, 64.26; H, 6.66; N, 5.67.

■ ASSOCIATED CONTENT

Supporting Information

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

^1H and ^{13}C NMR spectra of new compounds **12**, **29**, **30**, **32**, **51**, **52**, **56**, **58**, **59**, **60**, **62**, **63**, **64**, **65**, and **66**; and ^1H NMR spectra of resynthesized compounds **2**, **4**, **6**, **8**, **10**, **28**, **48**, and **54** (PDF)

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Notes

The authors declare no competing financial interest.

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