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# Synthesis of Mono- and 1,3-Diaminocalix[4]arenes via Ullmann-Type Amination and Amidation of 1,3-Bistriflate Esters of Calix[4]arenes

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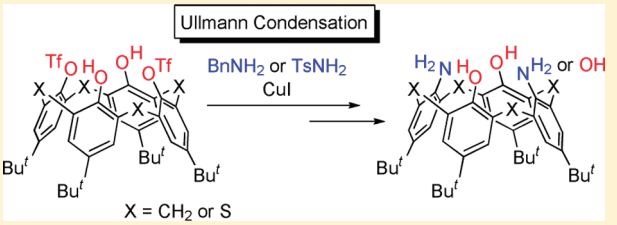
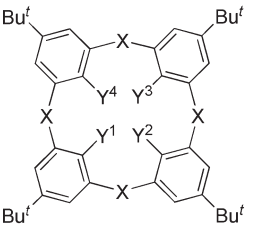
Supporting Information

**ABSTRACT:** Practical methods are described for the preparation of monoamines **4** and 1,3-diamines **5**, bearing one or two amino group(s) instead of the hydroxy group(s) at the 28-position or at both the 26- and 28-positions of *p-tert*-butylcalix[4]arene (**1a**) and *p-tert*-butylthiacalix[4]arene (**1b**), via the Ullmann-type amination or amidation. Thus, the copper-catalyzed or mediated amination of the 1,3-bistriflate ester (**2a**) of **1a** with benzylamine affords either mono(benzylamino) triflate **7a** or 1,3-bis(benzylamine) **8** in a high yield, depending on the reaction conditions. On the other hand, the 1,3-bistriflate ester (**2b**) of **1b** resists disubstitution and produces, under stoichiometric conditions, mono(benzylamino) triflate **7b**. The disubstitution of **2b** is achieved by amidation with tosylamide, giving 1,3-bis(tosylamide) **17b**. The hydrogenolysis of the benzylamino moiety of **7a**, followed by the hydrolysis of the Tf moiety, affords monoamine **4a**, while the hydrogenolysis of **8** affords 1,3-diamine **5a**. The amino moiety of **7b** can be deprotected under acidic conditions to give, after hydrolysis, monoamine **4b**. The hydrolysis of **17b** affords 1,3-diamine **5b**. The overall yields of compounds **4a**, **4b**, **5a**, and **5b** are 72%, 45%, 78%, and 24%, respectively, based on commercially available compounds **1** and are much higher than the ones previously reported in the literature.




## INTRODUCTION

Calix[4]arenes (e.g., **1**) play an important role in supramolecular chemistry as molecular scaffolds for elaborating sophisticated hosts.[1,2] A variety of functional groups have been regio- and stereospecifically introduced on the hydroxy groups of calix[4]arenes as recognition sites by linking moieties through etherification. However, the transformation results in locating the functional groups apart from the calix skeleton,[3] which makes it difficult for guests to be affected by the steric effects of the calix skeleton and/or to interact with substituents on it (e.g., with residual hydroxy groups or linking hetero atoms). This issue will be addressed by cleaving the aryl−oxygen bonds, thereby replacing the hydroxy groups with different functional groups. However, such a transformation is quite difficult for calix[4]arenes because of their steric and electronic environment near the narrow rims,[4] in addition to the poor nucleofugacity of the phenolic hydroxy group. Although the C−O bond cleavage of aryl triflates or other esters using a palladium or nickel catalyst, such as the Suzuki−Miyaura[5] and Migita−Kosugi−Stille couplings,[6] is one of the most reliable ways for replacing the phenolic hydroxy group, such reactions have been applied unsuccessfully to calix[4]arenes,[7] with the exception of a recent report by Georghiou and co-workers, who reported the Sonogashira coupling of 1,3-bistriflate ester **2a** to afford 1,3-dialkynylcalix[4]arenes.[4e] Out of many variants that bear functions other than the hydroxy group on their narrow rims, we are interested in aminocalix[4]arenes (e.g., **3**−**5**) for the following reasons: (1) The amino group serves as both a hydrogen bond donor and an acceptor and ligates to metal ions, similar to the hydroxy group. (2) Its high basicity and softness are expected to produce novel or improved properties as host molecules. (3) With its nitrogen atom, branched structures can be constructed.



| | X | $Y^1$ | $Y^2$ | $Y^3$ | $Y^4$ |
|---|---|---|---|---|---|
| **1a** | $CH_2$ | OH | OH | OH | OH |
| **1b** | S | OH | OH | OH | OH |
| **2a** | $CH_2$ | OTf | OH | OTf | OH |
| **2b** | S | OTf | OH | OTf | OH |
| **3** | S | $NH_2$ | $NH_2$ | $NH_2$ | $NH_2$ |
| **4a** | $CH_2$ | $NH_2$ | OH | OH | OH |
| **4b** | S | $NH_2$ | OH | OH | OH |
| **5a** | $CH_2$ | $NH_2$ | OH | $NH_2$ | OH |
| **5b** | S | $NH_2$ | OH | $NH_2$ | OH |
| **6** | SO | OMe | OMe | OMe | OMe |

(4) It can be diazotized, from which plenty of new compounds can be generated.[8] Recently, we succeeded in preparing the tetraaminated variant (**3**)[9] of thiacalixarene **1b** and later on, mono- (**4b**) and 1,3-diaminated ones **5b**[10] via a chelation-assisted nucleophilic aromatic substitution ($S_NAr$) of stereoisomers of tetra-O-methylated sulfinylcalixarene **6**[11] with lithium benzylamide. In solvent extraction experiments, tetraamine **3** selectively extracted gold and palladium,[12] whereas tetraol **1b** extracted a variety of metal ions ranging from soft to

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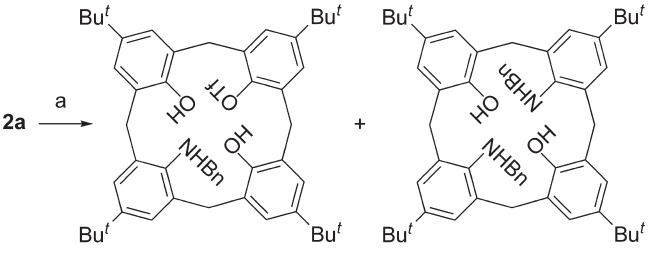
intermediate, depending on the soft/hard nature of the binding moieties. Biali and co-workers reported the synthesis of monoamine **4a** via the oxidation of **1a** to a spirodienone derivative, followed by the imination of the carbonyl group with hydrazine, and the subsequent rearomatization of the resulting Schiff base.[4c] Shinkai and co-workers succeeded in the synthesis of 1,3-diamine **5a** by the reaction of the 1,3-bis(diethylphosphate) of **1a** with potassium amide in liquid ammonia using HMPA as a cosolvent.[4b] However, these methods require many steps and/or produce low yields. In our previous communication,[13] we have reported an application of the Ullmann condensation to synthesize monoamines **4**. As a follow-up to the previous communication, here, we wish to describe in detail the first practical methods for preparing monoamines **4** and 1,3-diamines **5** via Ullmann-type reactions,[14] that is, the Ullmann condensation of 1,3-bistriflates **2** with benzylamine[15] and the Goldberg-modified Ullmann condensation of **2** with tosylamide.[16]

## RESULTS AND DISCUSSION

**Amination of 1,3-Bistriflates 2.** Our preliminary studies revealed that 1,3-bistriflate ester **2a**, upon treatment with benzylamine (2.0 molar equiv) in the presence of CuI (4.0 molar equiv) and $K_3PO_4$ (4.0 molar equiv) in toluene at 80 °C, gave benzylamino ester **7a** in 73% yield (Scheme 1 and entry 1 in Table 1), whereas a similar treatment of sulfur-bridged analogue **2b** afforded benzylamino ester **7b** up to 43% yield along with a number of byproducts (vide infra).[13] Therefore, we decided to explore the benzylamination of **2a**, starting from these reaction conditions. We have found that reducing the amount of CuI (1.2 molar equiv) gives not only benzylamino ester **7a** but also bis(benzylamine) **8**, the latter of which has not been obtained under the reaction conditions tested in the preliminary experiments (entry 2). In addition, the reaction proceeded even by using a catalytic amount (0.1 molar equiv) of CuI (entry 3); the product distribution between monoamine **7a** and diamine **8** shifted toward diamine **8**, indicating that a decreased amount of CuI favors the formation of diamine **8**. This suggests that the amination of benzylamino ester **7a** is impeded by an excess of CuI, with which **7a** forms an unfavorable complex for the subsequent amination (vide infra). Increasing the amount of benzylamine had no effect on the product distribution (entry 4). It has been reported that the addition of coordinative additives often accelerates catalytic Ullmann-type reactions.[14] We were pleased to know that the addition of ethylene glycol (EG)[17] facilitated the amination (entry 5). Increasing the molar equivalences of EG and benzylamine improved the yield of bis(benzylamine) **8** up to 80% at the expense of benzylamino ester **7a** (entries 6−8). On the other hand, benzylamino ester **7a** could also be selectively prepared under both stoichiometric and catalytic conditions by quenching the reaction immediately after the disappearance of the substrate spot in the TLC plate (entries 9−11). This indicates that bistriflate **2a** is aminated much faster than the resulting benzylamino ester **7a**. Interestingly, addition of bpy[18] afforded benzylamino ester **7a** in a shorter reaction period (entry 12). However, a long reaction with bpy did not produce bis(benzylamine) **8** in a satisfactory amount (entry 13), which could be attributed to the migrating tendency of the ester Tf moieties of calixarenes with the help of pyridine-type base.[19]

The amination of sulfur-bridge containing 1,3-bistriflate ester **2b** was more complex than the methylene-bridged counterpart **2a** (Scheme 2 and Table 2). Bistriflate **2b** was first aminated under the best conditions developed in the preliminary experiments,[13] using benzylamine (1.2 molar equiv), CuI (2.2 molar equiv),

**Scheme 1**[a]



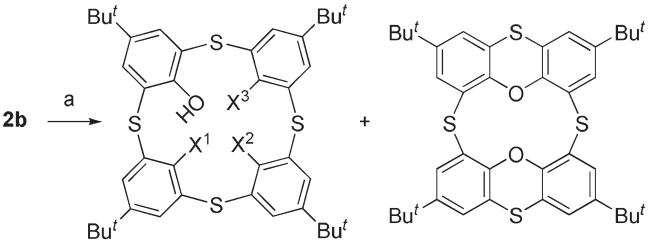

[a] Reagents and conditions: (a) $BnNH_2$, CuI, $K_3PO_4$, additive, toluene, 80 °C. See Table 1 for detail.

**Table 1. Amination of 1,3-Bistriflate 2a**[a]

| | | | | | yield (%)[c] | | |
|---|---|---|---|---|---|---|---|
| entry | $BnNH_2$[b] | CuI[b] | additive (equiv)[b] | time (h) | **7a** | **8** | **2a** |
| 1 | 2.0 | 4.0 | | 18 | 73 | n.d. | 23 |
| 2 | 2.4 | 1.2 | | 24 | 52 | 18 | n.d. |
| 3 | 2.4 | 0.1 | | 24 | 25 | 40 | n.d. |
| 4 | 4.0 | 0.1 | | 24 | 16 | 42 | n.d. |
| 5 | 2.4 | 0.1 | EG (1.0) | 24 | 13 | 66 | n.d. |
| 6 | 2.4 | 0.1 | EG (2.0) | 24 | 14 | 70 | n.d. |
| 7 | 4.0 | 0.1 | EG (2.0) | 24 | 11 | 74 | n.d. |
| 8 | 4.0 | 0.1 | EG (3.0) | 24 | 1 | 80 | n.d. |
| 9 | 2.4 | 1.2 | | 6 | 85 | n.d. | n.d. |
| 10 | 2.4 | 0.1 | EG (0.2) | 2 | 84 | n.d. | 2 |
| 11 | 2.4 | 0.1 | EG (1.0) | 10 min | 87 | n.d. | n.d. |
| 12 | 2.4 | 0.1 | bpy (1.0) | 1 | 86 | n.d. | n.d. |
| 13 | 2.4 | 0.1 | bpy (1.0) | 24 | 20 | 44 | n.d. |

[a] Reaction conditions: **2a** (1.10 mmol), $BnNH_2$, CuI, $K_3PO_4$ (4.0 molar equiv), additive, toluene (30 mL), 80 °C. [b] Molar equiv. [c] Isolated yield, n.d. = not detected.

**Scheme 2**[a]




| | $X^1$ | $X^2$ | $X^3$ | | $X^1$ | $X^2$ | $X^3$ |
|---|---|---|---|---|---|---|---|
| **7b** | NHBn | OH | OTf | **12** | OTf | OTf | OH |
| **9** | NHBn | OH | OH | **13** | H | OTf | OH |
| **10b** | $NH_2$ | OH | OTf | **14b** | OTf | OH | OH |
| **11** | $NH_2$ | OTf | OH | **1b** | OH | OH | OH |

[a] Reagents and conditions: (a) $BnNH_2$, CuI, $K_3PO_4$, additive, toluene, 80 °C. See Table 2 for details.


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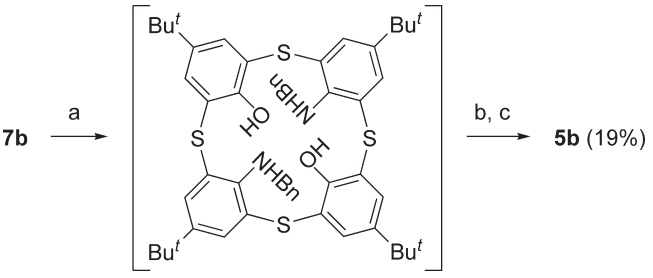
**Table 2. Amination of 1,3-Bistriflate 2b**[a]

| | | | | | yield (%)[c] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | $BnNH_2$[b] | CuI[b] | additive (equiv)[b] | time (h) | **7b** | *anti*-**7b** | **9** | **10b** | **11** | sub total | **12** | **13** | **14b** | **1b** | **15** | **2b** | total |
| 1[d] | 1.2 | 2.2 | | 10 | 39 | 6 | trace | 1 | 3 | 49 | 12 | 10 | 6 | n.d. | 5 | 1 | 83 |
| 2[d] | 1.2 | 1.2 | | 12 | 45 | 6 | trace | 1 | 1 | 53 | 14 | 9 | 8 | n.d. | 5 | 3 | 92 |
| 3 | 2.4 | 1.2 | | 6 | 43 | 4 | 16 | 3 | 1 | 67 | 4 | 7 | 10 | n.d. | 2 | trace | 90 |
| 4 | 4.0 | 1.2 | | 5 | 42 | 4 | 10 | trace | trace | 56 | 2 | 6 | 12 | n.d. | trace | 2 | 78 |
| 5 | 2.4 | 0.5 | | 5 | 26 | 2 | 9 | n.d. | n.d. | 37 | 7 | 3 | 34 | 18 | trace | n.d. | 99 |
| 6 | 2.4 | 0.5 | bpy (0.5) | 5 | 17[e] | n.d. | n.d. | n.d. | n.d. | 17[e] | 6[e] | n.d. | 64[e] | 11[e] | n.d. | n.d. | 98[e] |
| 7 | 2.4 | 0.5 | EG (0.5) | 3 | 23[e] | n.d. | 8[e] | n.d. | n.d. | 31[e] | 3[e] | n.d. | 46[e] | 20[e] | n.d. | n.d. | 100[e] |

[a] Reaction conditions: **2b** (1.02 mmol), $BnNH_2$, CuI, $K_3PO_4$ (4.0 molar equiv), additive, toluene (30 mL), 80 °C. [b] Molar equiv. [c] Isolated yield otherwise noted. [d] $K_3PO_4$ (2.0 molar equiv) was employed. [e] Determined by $^1H$ NMR analysis.

and $K_3PO_4$ (2.0 molar equiv) (entry 1). The reaction was quenched as soon as most of the substrate disappeared by monitoring on TLC, in order to minimize the loss of benzylamino ester **7b** by side reactions. Purification of the reaction mixture by crystallization, combined with chromatography (see the Experimental Section), allowed us to isolate benzylamino ester **7b** (39%), 1,2-bistriflate **12** (12%), and bis(phenoxathiine) **15**[20] (5%) in almost the same yields as reported before. The formation of 1,2-bistriflate **12** is attributed to the intramolecular rearrangement of 1,3-bistriflate **2b**, whereas bis(phenoxathiine) **15** by the Ullmann condensation (Ullmann biaryl ether synthesis).[14] It has been reported from our laboratory that the intramolecular rearrangement of **2b** with Hunig's base in DMSO at 60 °C proceeded quantitatively to afford **12**.[19] In addition to these compounds, we isolated and fully characterized monoaminated products *anti*-**7b**, **9**, **10b**, and **11**, reduced product **13**, monotriflate **14b**, as well as the recovery of substrate **2b**; the total yield of identified products amounted to 83%. Decreasing the amount of CuI to 1.2 molar equiv somewhat simplified the reaction system, as evidenced by TLC analysis, and improved the yield of benzylamino ester **7b** to 45% (entry 2). While keeping the amount of CuI at 1.2 molar equiv, increasing the amount of benzylamine to 2.4 molar equiv promoted detriflation (entry 3). However, a shortened reaction time was observed in this case. We believe that the amination was accelerated and could suppress other copper-mediated reactions (i.e., intramolecular etherification and reduction), as well as the intramolecular migration of a Tf moiety, to improve the subtotal yield of monoaminated products (67%). Further increase in the amount of benzylamine lowered the overall yield of products (entry 4), suggesting that an excess of benzylamine induces the production of unidentified compounds. The use of a catalytic amount of CuI (0.5 molar equiv), either by itself or in combination with EG or bpy, resulted in the preferential formation of monotriflate **14b** and tetraol **1b** (entries 5−7). Comparison of the subtotal yield of monoaminated compounds with the molar equivalence of CuI employed reveals that CuI serves as a stoichiometric reagent in the amination of bistriflate **2b**. As mentioned so far, it was difficult to selectively convert 1,3-bistriflate **2b** into benzylamino triflate **7b** because of the marked tendency of these thiacalix-based compounds to cause the migration and elimination of Tf moieties, in addition to the tendency of **2b** to undergo intramolecular cyclization and **7b** to undergo debenzylation. However, we could readily obtain deprotected amino triol **4b** in a synthetically useful yield by subjecting the crude reaction mixture to hydrolysis without purification (vide infra).

**Scheme 3**[a]




[a] Reagents and conditions: (a) $BnNH_2$ (1.2 molar equiv), CuI (2.2 molar equiv), $K_3PO_4$ (2.0 molar equiv), $H_2O$ (0.5 molar equiv), DMSO, 80 °C; (b) concd HCl, dioxane, 100 °C; (c) NaOH, $H_2O$, THF−EtOH, reflux.

To gain insights into the reaction mechanism, we attempted the amination of the 2,4-dimethoxy derivative (**16**) of 1,3-bistriflate **2b**, with the intention of preventing the intramolecular side reactions. The reaction carried out under the same conditions as employed in entry 3 with an exception of reaction time (24 h) resulted in the recovery of starting ester **16** (99%). This suggests that a hydroxy group adjacent to the TfO moiety that is to undergo the amination participates in the reaction. Similar treatment of monotriflate **14b**, as well as 1,2-bistriflate **12**, did not afford aminated products; monotriflate **14b** was recovered almost unchanged (92%), while 1,2-bistriflate **12** was detriflated to give monotriflate **14b** (60%) with the recovery of **12** (29%). This observation, in combination with the others made in the amidation of varying substrates (vide infra), may indicate that the amination, as well as the amidation, does not take place in mono- and bistriflated calixarenes that contain two underived phenolic hydroxy groups adjacently.

In the amination of bistriflate **2b**, the desired 1,3-bis(benzylamine) was not obtained. Then, we explored the possibility of further amination of benzylamino ester **7b** (Scheme 3). The treatment of **7b** with benzylamine (1.2 molar equiv) in DMSO in the presence of CuI (2.2 molar equiv) and $K_3PO_4$ (2.0 molar equiv) gave a complex mixture, in which deprotected diamine **5b** was detected by TLC analysis by the comparison of its elution behavior with that of an authentic sample. This implies the presence of 1,3-bis(benzylamine) and its monodebenzylated compound; however, they could not be isolated because of the complexity of the reaction mixture. Therefore, the mixture was directly subjected to debenzylation (vide infra) without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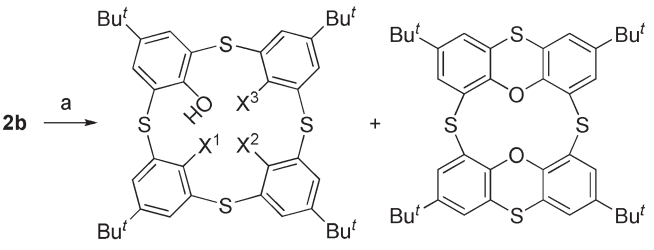
purification to obtain diamine **5b** (Scheme 3). It should be noted that the yield of **5b** varied with each run carried out under the same reaction conditions. We found that a trace amount of incidental water affected the reproducibility of the amination and that an active addition of water (0.5−1.0 molar equiv) repeatedly gave **5b** in 16−19% yields.[21]

**Amidation of 1,3-Bistriflates 2.** We reasoned that the displacement of the two TfO moieties of the 1,3-bistriflate ester (**2b**) of thiacalixarene **1b** might be realized if sulfonamides or carboxamides were employed as nucleophiles. These nucleophiles could avoid the formation of undesired copper complexes during the course of the second amidation step due to the weaker coordination ability of amide groups compared to the benzylamino group (vide infra). Another advantage of employing amides as nucleophiles was the improved stability of amide groups under the reaction conditions when compared to the benzyl amino group. In fact, the elimination of the benzyl moiety from benzylamino ester **7b** during the amination increases the complexity of the reaction system (vide supra). The reaction of bistriflate **2b** with tosylamide (2.4 molar equiv), carried out in the presence of CuI (2.2 molar equiv) and $K_3PO_4$ (4.0 molar equiv) in toluene at 80 °C for 24 h, resulted in the formation of 1,2-bistriflate **12** (22%) and monotriflate **14b** (41%) with the recovery of starting ester **2b** (30%) (Scheme 4 and entry 1 in Table 3). On the other hand, changing the solvent to DMSO gave a complex mixture, from which the desired bis(tosylamide) **17b** (20%), as well as tosylamino ester **18b** (3%), its regioisomer **19** (3%), and compound **20** (11%) generated by the detriflation of **18b**, could be isolated (entry 2). The comparison of the yield of diamide **17b** (20%) with the sum of the yields of monoamides **18b**, **19**, and **20**, which amounts to 17%, indicates that the displacement of the TfO moiety of tosylamino ester **18b** proceeds rather smoothly. The reaction mixture also contained bis(phenoxathiine) **15** (24%), together with the reduced product **13** (3%) and monotriflate **14b** (1%). The yield of bis(tosylamide) **17b** was improved to 30% when DMF was used as a solvent (entry 3). We then examined the amidation in DMF with varying amounts of tosylamide and CuI. Increasing the amount of tosylamide to 4.0 molar equiv improved the yield of tosylamino ester **18b** (15%) (entry 4), which was further increased to 19% when the amount of CuI was increased to 4.0 molar equiv (entry 5). Even after extending the reaction time to 48 h, however, the tosylamino ester **18b** could not be converted into bis(tosylamide) **17b** (entry 6). On the other hand, decreasing the amount of CuI to 1.0 molar equiv, with the intention of using CuI as a catalyst, resulted in increasing the yields of detriflated products **14b** (13%) and **20** (5%), in addition to producing thiacalixarene **1b** (12%), at the expense of the formation of bis(tosylamide) **17b** (13%) and tosylamino ester **18b** (3%) (entry 7). The addition of EG did not affect the product distribution (entry 8).

The conditions employed in entry 3 in Table 3 were extended to other amide reagents in order to explore the effect of nucleophiles on the formation of diamides. Various amide reagents successfully used in our study are shown in Scheme 5. *p*-Methoxybenzenesulfonamide, containing an electron-donating methoxy group, afforded the corresponding diamide **21** in the same yield (30%) as that of bis(tosylamide) **17b** (entry 3), whereas *p*-nitrobenzenesulfonamide bearing an electron-withdrawing nitro group afforded diamide **22** in a reduced yield (20%), presumably due to the decrease in nucleophilicity of the corresponding amidate. A similar tendency was observed for alkylsulfonamides; methanesulfonamide afforded diamide **23** (28%), while trifluoromethanesulfonamide did not yield diamide. Benzylamide and trifluoroacetamide, the amidate ions of which are more nucleophilic than those of sulfonamides, did not yield amidated products. A plausible explanation for this is that

**Scheme 4**[a]




| | $X^1$ | $X^2$ | $X^3$ |
|---|---|---|---|
| **17b** | NHTs | OH | NHTs |
| **18b** | NHTs | OH | OTf |
| **19** | NHTs | OTf | OH |
| **20** | NHTs | OH | OH |

| | $X^1$ | $X^2$ | $X^3$ |
|---|---|---|---|
| **12** | OTf | OTf | OH |
| **13** | H | OTf | OH |
| **14b** | OTf | OH | OH |

[a] Reagents and conditions: (a) $TsNH_2$, CuI, $K_3PO_4$, additive, solvent, 80 °C. See Table 3 for details.

**Table 3. Amidation of 1,3-Bistriflate 2b with Tosylamide**[a]

| | | | | | yield (%)[c] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | $TsNH_2$[b] | CuI[b] | additive (eq)[b] | solvent | **17b** | **18b** | **19** | **20** | **12** | **13** | **14b** | **15** | **2b** | total |
| 1 | 2.4 | 2.2 | | toluene | n.d. | n.d. | n.d. | n.d. | 22 | n.d. | 41 | trace | 30 | 93 |
| 2 | 2.4 | 2.2 | | DMSO | 20 | 3 | 3 | 11 | n.d. | 3 | 1 | 24 | n.d. | 65 |
| 3 | 2.4 | 2.2 | | DMF | 30 | 4 | 5 | 2 | n.d. | 2 | 3 | 36 | n.d. | 82 |
| 4 | 4.0 | 2.2 | | DMF | 29 | 15 | 6 | n.d. | n.d. | 4 | n.d. | 35 | n.d. | 89 |
| 5 | 4.0 | 4.0 | | DMF | 31 | 19 | 5 | n.d. | n.d. | 7 | 1 | 23 | n.d. | 86 |
| 6[d] | 4.0 | 4.0 | | DMF | 32 | 13 | 7 | n.d. | n.d. | 8 | 1 | 22 | n.d. | 83 |
| 7 | 2.4 | 1.0 | | DMF | 13 | 3 | 8 | 5 | trace | 4 | 13 | 19 | n.d. | 77[e] |
| 8 | 2.4 | 1.0 | EG (1.0) | DMF | 12 | 1 | 5 | 11 | trace | 4 | 7 | 22 | n.d. | 74[e] |

[a] Reaction conditions: **2b** (1.02 mmol), $TsNH_2$, CuI, $K_3PO_4$ (4.0 molar equiv), additive, solvent (30 mL), 80 °C, 24 h. [b] Molar equiv. [c] Isolated yield. [d] The reaction time was extended to 48 h. [e] **1b** (12%) was also isolated.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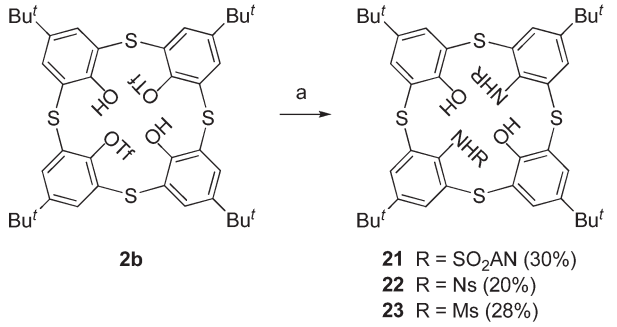
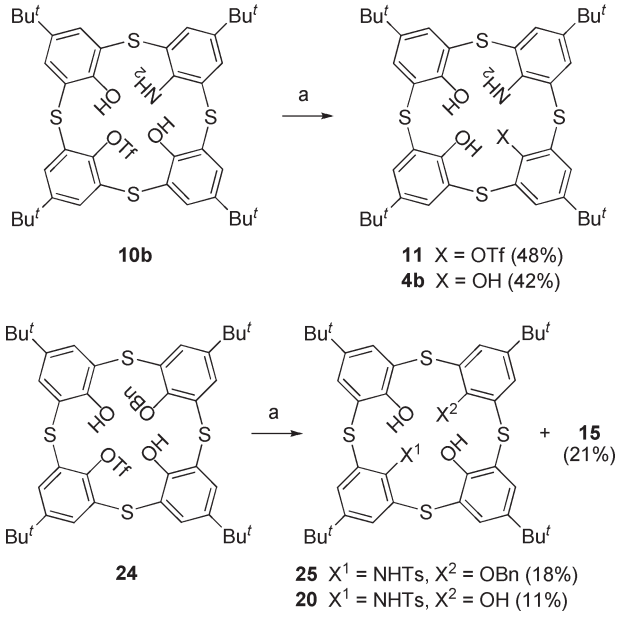
**Scheme 5**[a,b]




[a] Reagents and conditions: (a) $RNH_2$ (2.4 molar equiv), CuI (2.2 molar equiv), $K_3PO_4$ (4.0 molar equiv), DMF, 80 °C. [b] Abbreviations: AN = *p*-methoxyphenyl; Ns = *p*-nitrophenylsulfonyl.

**Scheme 6**[a]




[a] Reagents and conditions: (a) $TsNH_2$ (2.4 molar equiv), CuI (2.2 molar equiv), $K_3PO_4$ (4.0 molar equiv), DMF, 80 °C.

carboxamides are not acidic enough to be efficiently deprotonated under the reaction conditions.

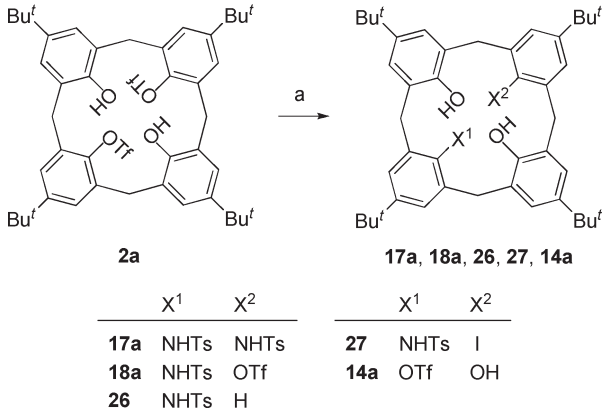
As in the case of amination, the reaction of the 2,4-dimethoxy derivative (**16**) of bistriflate **2b** with tosylamide, carried out under the standard conditions, recovered the starting ester, suggesting the participation of the hydroxy group in the amidation (vide supra). Under the same conditions, neither monotriflate **14b** nor 3-amino triflate **10b** produced amidated compounds; monotriflate **14b** was recovered almost unchanged, while 3-amino triflate **10b** underwent Tf migration, as well as detriflation, to afford 2-amino triflate **11** (48%) and amino triol **4b** (42%) (Scheme 6). These results, as discussed in the amination, suggest that two hydroxy groups, as well as a hydroxy and an amino group, residing adjacently on a substrate, disturb the displacement of a TfO moiety with a nitrogen nucleophile (vide supra). In fact, monotriflate **14b**, once the 3-hydroxy group was capped with a benzyl moiety, underwent the amidation to give the corresponding monoamide **25** (18%) and its debenzylated derivative **20** (11%) (Scheme 6).

**Table 4. Amidation of 1,3-Bistriflate 2a**[a]

| | | | | yield (%)[c] | | | | |
|---|---|---|---|---|---|---|---|---|
| entry | $TsNH_2$[b] | CuI[b] | additive (equiv)[b] | **17a** | **18a** | **26** | **27** | **14a** |
| 1 | 2.4 | 2.2 | | 33 | 16 | 16 | 9 | trace |
| 2 | 4.0 | 2.2 | | 38 | 19 | 10 | 13 | trace |
| 3 | 4.0 | 4.0 | | 45 | 12 | 11 | 4 | trace |
| 4 | 2.4 | 1.0 | | 30 | 14 | 10 | 10 | trace |
| 5 | 2.4 | 0.1 | | 3 | 53 | n.d. | n.d. | 23 |
| 6 | 2.4 | 0.1 | EG (1.0) | 2 | 50 | n.d. | n.d. | 20 |
| 7 | 2.4 | 0.1 | bpy (0.1) | 4 | 59 | n.d. | n.d. | 11 |

[a] Reaction conditions: **2a** (0.548 mmol), $TsNH_2$, CuI, $K_3PO_4$ (4.0 molar equiv), additive, DMF (15 mL), 80 °C, 24 h. [b] Molar equiv. [c] Isolated yield otherwise noted.

**Scheme 7**[a]




[a] Reagents and conditions: (a) $TsNH_2$, CuI, $K_3PO_4$, DMF, 80 °C. See Table 4 for details.

We found that methylene-bridged bistriflate **2a** was also diamidated (Scheme 7 and Table 4). Bistriflate **2a**, on treatment with tosylamide under the standard conditions, afforded the desired bis(tosylamide) **17a** (33%), along with tosylamino ester **18a** (16%), and its reduced and iodinated compounds **26** (16%) and **27** (9%) (entry 1).[22] The yield of **17a** was improved to 45% by increasing the molar equivalences of tosylamide and CuI (4.0 molar equiv each) (entry 3). On the other hand, decreasing the amount of CuI (0.1 molar equiv) resulted in the formation of detriflated compound **14a** (entry 5), as observed in the amidation of sulfur-bridged analogue **2b** with a reduced amount of CuI (1.0 molar equiv) (entry 7 in Table 3). In addition to this, it markedly changed the product ratio between bis(tosylamide) **17a** and tosylamino ester **18a** in favor of the latter; the comparison of the crop of **18a** (53%, 290 $\mu$mol) with the amount of CuI employed (54.8 $\mu$mol) indicates that the first amidation of bistriflate **2a** to **18a** proceeds catalytically. However, tosylamino ester **18a** could not be converted into bis(tosylamide) **17a** even after adding EG or bpy (entries 6 and 7).

**Mechanistic Consideration.** Before discussing the reaction mechanisms of the amination and amidation carried out in this study, we would like to briefly mention the stereochemistry of the products. In calixarene chemistry, it is common knowledge that the two propyl groups on the phenolic oxygens of 1,3-di-O-alkylated calix[4]arenes are bulky enough to prevent the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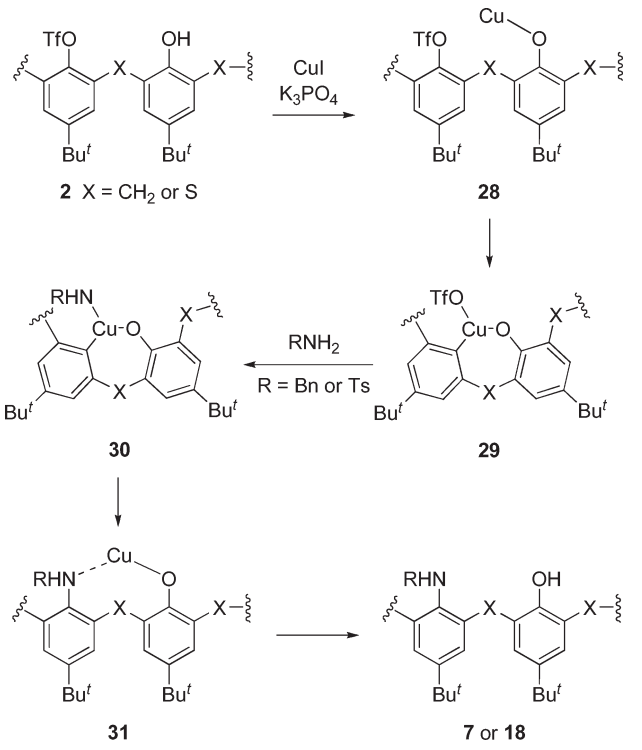
interconversion between their conformational isomers originating from the *syn* and *anti* arrangements of the two alkoxy groups with respect to the mean plane defined by the macrocycle.[23] On the basis of this fact, it is readily conceivable that benzylamino ester **7a**, bis(benzylamine) **8**, bis(tosylamide) **17a**, and tosylamino ester **18a** should have stereoisomers among the products derived from methylene-bridged bistriflate **2a**. In the $^1$H NMR spectrum of a methylene-bridged calix[4]arene, the chemical shift difference ($\Delta\delta$) between a pair of geminal methylene protons is known to vary depending on its stereostructure.[24] Above all, the cone isomer of a compound can be readily differentiated from other isomers as its $\Delta\delta$ values for all the methylene protons lie within 0.9−0.5 ppm in nonpolar solvents. The $\Delta\delta$ values of all the methylene protons of the above-mentioned compounds in $CDCl_3$ fall within the range of 0.76−0.49 ppm, indicating that they adopt cone conformation (that is, they are *syn* stereoisomers).[25] This means that bistriflate **2a**, adopting *syn* form,[7a] was stereospecifically converted into these compounds by the Ullmann-type reactions. On the other hand, it is difficult to determine the stereochemistry of thiacalix[4]arenes because of the lack of NMR structural information from the bridging moieties. However, based on X-ray crystallography, benzylamino ester **7b** and bis(tosylamide) **17b**, as well as staring bistriflate **2b**, could be designated as *syn* stereoisomers (see the Supporting Information). The $^1$H NMR spectrum of *anti*-**7b** exhibited three singlets with the integrated intensity values of 9H, 9H, and 18H, respectively, for the *tert*-butyl protons, one singlet for the methylene protons (2H), one multiplet (5H) for the aryl protons of the benzyl moiety, two doublets (2H each) and two singlets (2H each) for the aryl protons of the calixarene skeleton, and one broad signal for the amino proton; the magnetic equivalence suggests a $C_s$-symmetric structure in which the benzylamino and TfO moieties are in the $\sigma$-plane, that is, *syn*- or *anti*-1,3-disubstituted compound. This observation, combined with the fact that the spectrum is different from that of authentic **7b** of *syn* form, allowed us to assign *anti*-**7a**. The stereochemistry of 1,2-bistriflate **12** was already established as *syn*.[19] We could not determine the stereochemistry of other thiacalixarene derivatives, but it did not hinder our goals of obtaining deprotected amines **4b** and **5b**.

Scheme 8 illustrates a feasible mechanism for the amination and amidation. Bistriflate **2** reacts with CuI with the aid of $K_3PO_4$ to produce copper phenoxide **28**, the formation of which will assist the otherwise difficult oxidative addition of an Ar−OTf bond of the calix class compound.[14,26] This also explains the inability of the 2,4-dimethoxy derivative (**16**) of 1,3-bistriflate **2b** to undergo neither amination nor amidation (vide supra). The TfO moiety of the resulting putative metallacycle **29** is replaced with a benzylamide or tosylamidate ion to produce a new metallacycle **30**, which undergoes reductive elimination of the Ar−N bond to give copper chelate **31**. This mechanism can also explain the difference in reactivity between methylene-bridged bistriflate **2a** and the sulfur-bridged one **2b**. As mentioned above, monotriflate **14b** and 3-amino triflate **10b** did not undergo amination and/or amidation. This suggests that once two adjacent hydroxy groups in compound **14b** (hydroxy and amino group in compound **10b**) chelate to a copper ion tightly, the resulting species has difficultly forming such a copper phenoxide as **28** with another copper ion, using the residual hydroxy group adjacent to the TfO moiety. This would be the case with benzylamino esters **7**, as well as tosylamino esters **18**. This means that the displacement of the second TfO moiety of

**Scheme 8**




bistriflate **2** with a nitrogen nucleophile is disturbed by the formation of such an undesired copper chelate; in other words, the displacement of the second TfO moiety does not take place unless copper chelate **31** formed in the first displacement reaction dissociates in situ to give benzylamino ester **7**, as well as tosylamino ester **18**. This is consistent with the observation that decreasing the amount of CuI and/or adding a coordinative additive facilitated the formation of diamine **8** in the amination of methylene-bridged calixarene **2a**. It is readily conceivable that the dissociation of the copper chelate **31** formed from thiacalixarene **2b** is more difficult than that of **31** formed from calixarene **2a** because the former copper chelate should adopt a stable five-membered bischelate structure by the additional coordination of the sulfur atom interposed between the amino or amide group and an adjacent hydroxy group. Such a five-membered bischelate structure is often found in metal complexes of thiacalixarene **1b**.[27] In the case of the amidation of **2b**, the initially introduced amide group that has a weaker coordination ability than the amino group will be able to dissociate from copper chelate **31** with the assistance of the polar aprotic solvent, which appears to be responsible for the realization of the second amidation. However, in the amidation of methylene-bridged calixarene **2a**, an excess amount of CuI favored diamide **17a**. Although the reason is not clear at present, considering the fact that the monoamidation of **2a** proceeds catalytically, high loading of CuI seems to have diminished a certain difficulty that arose in the second amidation, against the likelihood that high loading will retard the second amidation by stabilizing copper chelate **31**.

The *syn*-stereospecificity of the amination and amidation agrees with this reaction mechanism as the TfO and RNH ligands in metallacycles **29** and **30**, as well as those in the corresponding metallacycles in the second TfO displacement, are apparently bulky enough to prevent the *syn-anti* isomerization via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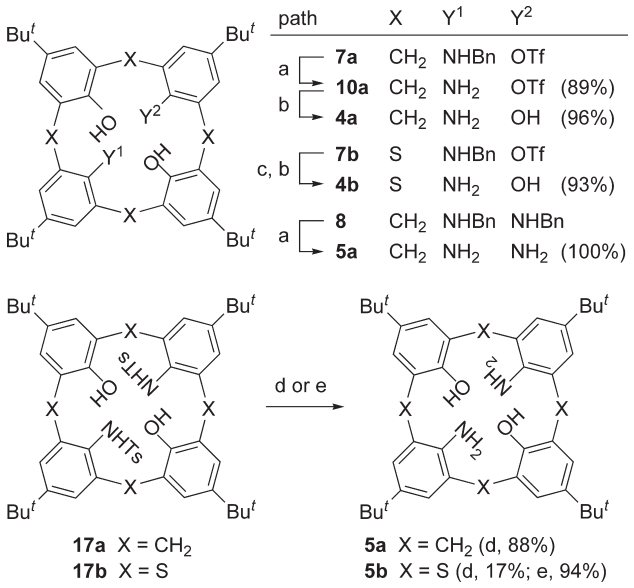
**Scheme 9**[a]




[a] Reagents and conditions: (a) $H_2$, Pd/C, EtOH, 60 °C; (b) NaOH, $H_2O$, THF−EtOH, reflux; (c) concd HCl, AcOH, reflux; (d) $SmI_2$, $H_2O$, pyrrolidine, THF, rt; (e) concd $H_2SO_4$, $H_2O$, AcOH, reflux.

the oxygen-through-the-annulus rotation.[23] The exceptional formation of *anti*-**7b** can be rationalized by the detriflation of benzylamino ester **7b** to trisphenol **9**, followed by the triflation of **9** at the resulting hydroxy group from the side opposite to the benzylamino moiety with respect to the mean plane defined by the macrocycle. Alternatively, it might proceed via the initial isomerization of bistriflate **2b** to the *anti* isomer by the detriflation−triflation sequence, followed by benzylamination.

**Deprotection of Benzylamines 7 and 8 and Tosylamides 17 to Mono- and Diamines 4 and 5.** In our previous communication,[13] we reported that the benzyl moiety of benzylamino ester **7a**, as well as that of **7b**, could be removed by a three-step process,[9,10] that is, the initial bromination of a benzylamino-substituted calixarene with NBS and BPO, followed by spontaneous dehydrobromination to the corresponding imine, and subsequent acid hydrolysis to give the desired deprotected amine. However, the yields of amino esters **10a** and **10b** were moderate (69% and 50%, respectively). We have found that a simple hydrogenolysis of **7a** affords **10a** with improved yield (89%) (Scheme 9). The alkaline hydrolysis of the resulting amino ester **10a** furnished amino triol **4a**. Bis(benzylamine) **8** could also be deprotected by hydrogenolysis to afford diamine **5a** quantitatively. On the other hand, the benzyl moiety of sulfur-bridged benzylamino ester **7b** was found to be removed by simply refluxing in concd HCl and acetic acid (Scheme 9). As the acid treatment was accompanied by the formation of a small amount of detriflated amine **4b**, the crude mixture was subjected to alkaline hydrolysis without purification to give **4b** in 93% yield. This process could be advantageously utilized to merge mono-aminated compounds generated by the amination of bistriflate **2b** as **4b** (vide supra). Thus, bistriflate **2b** was benzylaminated under the same conditions as those employed in entry 3 in Table 2 to afford amino triol **4b** in 53% yield. In contrast, methylene-bridged benzylamino ester **7a** resisted acid hydrolysis. The cleavage of an N−C linkage should happen via the protonation of the benzylamino group. Although the reason for the difference in reactivity between the calix- and thiacalixarenes is not clear at present, we believe that the epithio linkage may assist the protonation of the amino group in the case of **7b**, forming a hydrogen bond between NH and S.[9]

The hydrolysis of tosylamides generally requires a strong acid. We have found that $H_2SO_4$ is efficient for the deprotection of bis(tosylamide) **17b**. Upon refluxing with $H_2SO_4$ in acetic acid, diamine **5b** was obtained in 94% yield (Scheme 9). On the other hand, methylene-bridged counterpart **17a** resisted hydrolysis under the conditions and the starting material was recovered almost unchanged (86%). We then explored the possibility to reductively remove the tosyl moieties of **17a**. It is known that $SmI_2$ is one of the most efficient reductants for tosyl amides and the reduction is generally carried out in refluxing THF in the presence of DMPU or HMPA.[28] Recently, Ankner and Hilmersson reported that the combination of $SmI_2$ with an amine and water is powerful in reducing tosyl amides at room temperature.[28b] This method could be successfully applied to bis(tosylamide) **17a**, giving diamine **5a** in 88% yield (Scheme 9), whereas a similar treatment of sulfur-bridged counterpart **17b** gave diamine **5b** in a poor yield (17%).

## EXPERIMENTAL SECTION

**General.** Melting points were taken with a micro melting point apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were measured with tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. Silica gel (63−200 $\mu$m) was used for column chromatography and TLC. Water- and air-sensitive reactions were routinely carried out under nitrogen. Toluene was distilled from sodium diphenyl ketyl. DMF, DMSO, benzylamine, and EG were distilled from calcium hydride. Acetone was distilled from $CaSO_4$. Bistriflate **2a** was prepared according to the literature procedure.[7a]

**5 11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl Bis(trifluoromethanesulfonate) (2b).** To an ice-cold solution of thiacalixarene **1b** (10.0 g, 13.9 mmol) and pyridine ($d$ = 0.983; 6.7 mL, 83.3 mmol) in dichloromethane (160 mL) was added dropwise trifluoromethanesulfonic anhydride ($d$ = 1.719; 6.8 mL, 41.4 mmol) with stirring. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with 2 M HCl (200 mL) and the resulting mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from methanol−dichloromethane to give 1,3-bistriflate **2b** (10.1 g). On the other hand, the mother liquid was evaporated and the residue was purified by column chromatography with hexane−chloroform (1:1) as an eluent to give an additional crop of **2b** (1.56 g) for a total yield of 11.7 g (85%) as a colorless powder: mp 296.0−298.0 °C dec; IR (KBr) 3460, 2966, 1427, 1211, 1138, 1065 cm$^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.92 (s, 18H), 1.34 (s, 18H), 6.12 (s, 2H), 7.16 (s, 4H), 7.74 (s, 4H); $^{13}C$ NMR (100 MHz) $\delta$ 30.7, 31.4, 34.3, 34.5, 121.0, 128.8, 133.4, 134.9, 143.8, 147.7, 151.5, 155.4; MS (FAB) $m/z$ 984 $M^+$. Anal. Calcd for $C_{42}H_{46}F_6O_8S_6$: C, 51.20; H, 4.71; S, 19.53. Found: C, 51.01; H, 4.71; S, 19.82.

**Typical Procedure for the Amination of 1,3-Bistriflate 2a (Entry 8 in Table 1).** To a suspension of bistriflate **2a** (1.00 g, 1.10 mmol), CuI (21.5 mg, 0.113 mmol), and $K_3PO_4$ (930 mg, 4.38 mmol) in toluene (30 mL) were added benzylamine ($d$ = 0.981; 479 $\mu$L, 4.39 mmol) and EG ($d$ = 1.11; 183 $\mu$L, 3.27 mmol), and the mixture was stirred at 80 °C for 24 h. After cooling, most of the solvent was evaporated and the residue was dissolved by the addition of saturated aqueous $NH_4Cl$ and chloroform. After the two layers were separated, the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aqueous layer was extracted with chloroform, and the combined organic layer was washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with chloroform−hexane (3:1) as an eluent to give bis(benzylamine) **8** (728 mg, 80%) and benzylamino ester **7a** (13.1 mg, 1%).

The same reaction, carried out at 80 °C for 10 min by using reduced amounts of benzylamine (287 μL, 2.63 mmol) and EG (61.1 μL, 1.09 mmol), gave benzylamino ester **7a** (827 mg, 87%), after chromatographic purification with chloroform−hexane (2:1) as an eluent (entry 11).

**27-Benzylamino-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxypentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl Trifluoromethanesulfonate (7a):** colorless powder, mp 120.0−122.0 °C; IR (KBr) 3584, 3526, 3329, 2955, 1462, 1396, 1362, 1207, 1138, 1072 cm$^{-1}$; $^1$H NMR (400 MHz) δ 0.89 (s, 9H), 1.06 (s, 9H), 1.27 (s, 18H), 3.45 (d, 2H, *J* = 13.9 Hz), 3.48 (d, 2H, *J* = 13.9 Hz), 3.94 (d, 2H, *J* = 13.9 Hz), 4.13 (s, 2H), 4.24 (d, 2H, *J* = 13.9 Hz), 6.81 (s, 2H), 6.93 (s, 2H), 7.05 (d, 2H, *J* = 2.4 Hz), 7.14 (d, 2H, *J* = 2.4 Hz), 7.29−7.38 (m, 5H); $^{13}$C NMR (100 MHz) δ 30.7, 31.0, 31.6, 32.8, 33.9, 34.0, 34.0, 34.8, 56.3, 125.3, 125.7, 125.7, 127.3, 127.3, 127.6, 127.7, 127.8, 128.7, 133.1, 134.6, 138.4, 138.9, 141.5 142.5, 147.7, 150.2, 150.8; MS (FAB) *m*/*z* 869 M$^+$. Anal. Calcd for $C_{52}H_{62}F_3NO_5S$: C, 71.78; H, 7.18; N, 1.61. Found: C, 71.68; H, 7.15; N, 1.48.

**26,28-Bis(benzylamino)-5,11,17,23-tetra-*tert*-butylpentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (8):** colorless powder, mp 254.0−256.0 °C; IR (KBr) 3267, 2963, 1594, 1480, 1452, 1308, 1208, 872, 696 cm$^{-1}$; $^1$H NMR (500 MHz) δ 1.18 (s, 18H), 1.19 (s, 18H), 3.30 (d, 4H, *J* = 13.3 Hz), 3.96 (d, 4H, *J* = 13.3 Hz), 4.04 (s, 4H), 6.93 (s, 4H), 7.03 (s, 4H), 7.31−7.39 (m, 10H), 10.75 (s, 4H); $^{13}$C NMR (100 MHz) δ 31.6, 31.9, 34.1, 34.5, 35.0, 56.9, 125.5, 126.2, 128.0, 128.2, 129.0, 129.5, 137.4, 137.8, 138.3, 141.9, 148.5, 150.7; MS (FAB) *m*/*z* 827 (M + H)$^+$; HRMS (ESI) calcd for $C_{58}H_{70}N_2NaO_2$ (M + Na)$^+$ 849.5335, found 849.5330.

**Typical Procedure for the Amination of 1,3-Bistriflate 2b (Entry 3 in Table 2).** To a suspension of bistriflate **2b** (1.00 g, 1.02 mmol), CuI (234 mg, 1.23 mmol), and $K_3PO_4$ (863 mg, 4.07 mmol) in toluene (30 mL) was added benzylamine (*d* = 0.981; 266 μL, 2.44 mmol), and the mixture was stirred at 80 °C for 6 h and worked up as before. The resulting mixture was crystallized from methanol−dichloromethane, and the precipitate was collected by filtration and chromatographed on a silica gel column with hexane−chloroform (1:1) as an eluent to give benzylamino ester **7b** (315 mg, 33%) and its detriflated compound **9** (135 mg, 16%). The filtrate contained a number of compounds, which could not be separated by column chromatography. Therefore, one-fifth portion of the filtrate was purified by TLC with hexane−chloroform (1:1) as a developer, which isolated *anti*-**7b** (6.7 mg, 4%), 1,2-bis(triflate) **12** (7.8 mg, 4%), reduced product **13** (11.6 mg, 7%), monotriflate **14b** (16.6 mg, 10%), bis(phenoxathiine) **15** (2.4 mg, 2%), and an additional crop of **7b** (20 mg, 43% in total); yields (%) are given as 5-fold values of the crops. Also obtained was a mixture of debenzylated product **10b** (6.0 mg, 3%) and its regioisomer **11** (2.3 mg, 1%), which could be separated into each component by TLC with hexane−ethyl acetate (6:1) as a developer.

**27-Benzylamino-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl trifluoromethanesulfonate (7b):** colorless powder, mp 241.0−243.0 °C; IR (KBr) 3425, 3283, 2963, 1450, 1427, 1207, 1134 cm$^{-1}$; $^1$H NMR (400 MHz) δ 0.71 (s, 9H), 1.13 (s, 9H), 1.30 (s, 18H), 4.42 (s, 2H), 6.93 (s, 2H), 7.32−7.47 (m, 5H), 7.51 (s, 2H), 7.66 (s, 4H); $^{13}$C NMR (100 MHz) δ 30.4, 30.9, 31.4, 34.1, 34.2, 34.3, 57.5, 121.4, 121.4, 127.5, 128.6, 128.6, 129.4, 130.0, 132.3, 134.7, 134.9, 136.1, 138.1, 143.0, 146.9, 148.5, 149.4, 151.2, 156.3; MS (FAB) *m*/*z* 941 M$^+$. Anal. Calcd for $C_{48}H_{54}F_3NO_5S_5$: C, 61.18; H, 5.78; N, 1.49; S, 17.01. Found: C, 61.42; H, 5.77; N, 1.48; S, 16.80.

**27-Benzylamino-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl trifluoromethanesulfonate (*anti*-7b):** colorless powder, mp 237.0−239.0 °C; IR (KBr) 3442, 2964, 2360, 1457, 1412, 1212, 1126, 868, 668 cm$^{-1}$; $^1$H NMR (400 MHz) δ 1.02 (s, 9H), 1.27 (s, 9H), 1.28 (s, 18H), 4.20 (s, 2H), 7.29−7.38 (m, 5H), 7.47 (d, 2H, *J* = 2.4 Hz), 7.49 (d, 2H, *J* = 2.4 Hz), 7.50 (s, 2H), 7.64 (s, 2H), 7.82 (br, 1H); $^{13}$C NMR (100 MHz) δ 30.7, 30.2, 31.3, 34.2, 34.5, 34.6, 57.1, 120.0, 122.0, 127.8, 128.6, 128.8, 129.1, 129.1, 131.1, 131.8, 133.5, 135.8, 137.8, 143.0, 147.1, 148.8, 149.8, 151.8, 154.5; MS (FAB) *m*/*z* 941 M$^+$; HRMS (ESI) calcd for $C_{48}H_{54}F_3NNaO_5S_5$ (M + Na)$^+$ 964.2455, found 964.2450.

**28-Benzylamino-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27-triol (9):** colorless powder, mp 287.2−288.0 °C; IR (KBr) 3239, 2963, 2905, 2867, 1456, 1260, 1245, 890, 746 cm$^{-1}$; $^1$H NMR (400 MHz) δ 1.21 (s, 27H), 1.23 (s, 9H), 4.48 (s, 2H), 7.40−7.43 (m, 1H), 7.46−7.50 (m, 2H), 7.57 (d, 2H, *J* = 2.5 Hz), 7.61 (s, 2H), 7.63−7.68 (m, 2H), 7.65 (d, 2H, *J* = 2.5 Hz), 7.73 (s, 2H); $^{13}$C NMR (100 MHz) δ 31.0, 31.3, 31.3, 34.1, 34.2, 34.5, 57.7, 120.6, 120.9, 121.0, 128.1, 128.8, 129.2, 130.9, 136.1, 136.1, 136.2, 136.8, 136.9, 143.5, 144.0, 148.1, 150.2, 156.3, 157.3; MS (FAB) *m*/*z* 810 (M + H)$^+$; HRMS (ESI) calcd for $C_{47}H_{56}NO_3S_4$ (M + H)$^+$ 810.3143, found 810.3138.

**27-Amino-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-2,-8,14,20-tetrathiapentacyclo-[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl trifluoromethanesulfonate (10b):** colorless powder, mp 252.0−254.0 °C; IR (KBr) 3472, 2963, 1454, 1427, 1204, 1138 cm$^{-1}$; $^1$H NMR (400 MHz) δ 0.72 (s, 9H), 1.09 (s, 9H), 1.32 (s, 18H), 6.95 (s, 2H), 7.38 (s, 2H), 7.67 (d, 2H, *J* = 2.5 Hz), 7.68 (d, 2H, *J* = 2.5 Hz); $^{13}$C NMR (100 MHz) δ 30.5, 31.0, 31.4, 34.0, 34.2, 34.2, 120.3, 121.0, 121.5, 121.6, 129.9, 132.1, 134.1, 134.5, 135.2, 143.3, 144.4, 147.1, 131.1, 155.3; MS (FAB) *m*/*z* 851 M$^+$. Anal. Calcd for $C_{41}H_{48}F_3NO_5S_5$: C, 57.79; H, 5.68; N, 1.64. Found: C, 57.68; H, 5.57; N, 1.57.

**26-Amino-5,11,17,23-tetra-*tert*-butyl-27,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl trifluoromethanesulfonate (11):** colorless powder, mp 244.0−246.0 °C; IR (KBr) 3466, 3427, 3356, 2965, 2870, 1611, 1456, 1425, 1211, 1133, 867 cm$^{-1}$; $^1$H NMR (400 MHz) δ 0.88 (s, 9H), 1.12 (s, 9H), 1.26 (s, 9H), 1.30 (s, 9H), 7.15 (d, 1H, *J* = 2.4 Hz), 7.27 (d, 1H, *J* = 2.4 Hz), 7.41 (d, 1H, *J* = 2.4 Hz), 7.46 (d, 1H, *J* = 2.4 Hz), 7.62 (d, 1H, *J* = 2.3 Hz), 7.65 (d, 1H, *J* = 2.3 Hz), 7.68 (d, 1H, *J* = 2.4 Hz), 7.70 (d, 1H, *J* = 2.4 Hz); $^{13}$C NMR (100 MHz) δ 30.6, 31.1, 31.4, 34.0, 34.1, 34.3, 34.4, 119.7, 120.1, 120.6, 120.6, 120.7, 121.0, 128.5, 129.9, 133.3, 133.9, 134.7, 135.1, 135.1, 135.7, 135.8, 135.9, 141.6, 144.0, 147.8, 147.8, 151.9, 155.4, 155.5; MS (FAB) *m*/*z* 852 (M + H)$^+$; HRMS (ESI) calcd for $C_{41}H_{48}F_3NNaO_5S_5$ (M + Na)$^+$ 874.1986, found 874.1980.

Compounds **12**,[19] **13**,[20] **14b**,[20] and **15**[20] are know compounds. The NMR spectra of the samples are essentially identical with those reported in the literature.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dimethoxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl Bis(trifluoromethanesulfonate) (16).** A mixture of 1,3-bistriflate **2b** (1.00 g, 1.02 mmol), iodomethane (*d* = 2.287; 1.26 mL, 20.3 mmol), and $Cs_2CO_3$ (3.30 g, 10.1 mmol) in acetone (30 mL) was refluxed for 4 h. After most of the solvent was evaporated, the residue was dissolved by the addition of 2 M HCl and chloroform. After the two layers were separated, the aqueous layer was extracted with chloroform,

and the combined organic layer was washed successively with 2 M $Na_2SO_3$ and water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with hexane−chloroform (1:1) as an eluent to give dimethyl ether **16** (896 mg, 87%) as a colorless powder, mp 290.0−292.0 °C; IR (KBr) 2966, 1423, 1204, 1138, 999 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.01 (br s, 18H), 1.35 (s, 18H), 3.86 (br s, 6H), 7.23 (br s, 4H), 7.77 (br s, 4H); $^{13}C$ NMR (100 MHz) $\delta$ 30.8, 31.2, 34.3, 34.5, 59.2, 114.9, 117.5, 120.0, 122.6, 129.1, 134.0, 134.3, 147.5, 150.3; MS (FAB) $m/z$ 1012 $M^+$. Anal. Calcd for $C_{44}H_{50}F_6O_8S_6$: C, 52.16; H, 4.97. Found: C, 52.33; H, 4.99.

**Amination of Benzylamino Ester 7b and Subsequent Deprotection to 26,28-Diamino-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (5b).** To a suspension of benzylamino ester **7b** (49.7 mg, 52.7 $\mu$mol), CuI (22.1 mg, 0.116 mmol), and $K_3PO_4$ (22.0 mg, 0.104 mmol) in DMSO (3.0 mL) were added benzylamine ($d$ = 0.981; 6.9 $\mu$L, 63 $\mu$mol) and water (0.5 $\mu$L, 28 $\mu$mol), and the mixture was stirred at 80 °C for 24 h. After cooling, the solvent was evaporated and the residue was dissolved by the addition of saturated aqueous $NH_4Cl$ and chloroform. After the two layers were separated, the water layer was extracted with chloroform, and the combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was treated with concd HCl (3.0 mL) in dioxane (3.0 mL) at 80 °C for 24 h. After cooling, the mixture was neutralized with 2 M NaOH and extracted with chloroform. The extract was washed with water and evaporated to leave a residue, which was dissolved by the addition of THF (3.0 mL) and ethanol (1.5 mL). To the solution were added water (1.5 mL) and NaOH (293 mg, 7.33 mmol), and the mixture was refluxed for 24 h. After cooling, the mixture was poured into 2 M HCl (15 mL) and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by TLC with chloroform−ethyl acetate (30:1) as an eluent to give diamine **5b** (7.2 mg, 19%) as a colorless powder, mp 290.0−292.0 °C; IR (KBr) 3445, 3395, 3360, 2963, 1454, 1269, 1242 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.13 (s, 18H), 1.25 (s, 18H), 7.49 (s, 4H), 7.61 (s, 4H); $^{13}C$ NMR (100 MHz) $\delta$ 31.1, 31.4, 34.0, 34.1, 121.6, 123.9, 134.8, 135.4, 142.9, 145.3, 146.4, 157.2; MS (FAB) $m/z$ 719 $(M + H)^+$; HRMS (ESI) $m/z$ calcd for $C_{40}H_{50}N_2NaO_2S_4$ $(M + Na)^+$ 741.2647, found 741.2644.

**27-Benzyloxy-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl Trifluoromethanesulfonate (24).** A mixture of monotriflate **14b** (200 mg, 0.234 mmol), $Na_2CO_3$ (249 mg, 2.35 mmol), (bromomethyl)benzene ($d$ = 1.44; 279 $\mu$L, 2.35 mmol), and acetone (10 mL) was refluxed for 6 h. After cooling, the mixture was quenched with 2 M HCl (10 mL) and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column with hexane−chloroform (1:1) as an eluent to give benzyl ether **24** (167 mg, 76%) as a colorless powder, mp 238.2−239.6 °C; IR (KBr) 3394, 2964, 1451, 1424, 1206, 1138, 1067, 911, 875 $cm^{-1}$; $^1H$ NMR (500 MHz) $\delta$ 0.58 (s, 9H), 1.13 (s, 9H), 1.31 (s, 18H), 5.26 (s, 2H), 6.75 (s, 2H), 7.40−7.47 (m, 3H), 7.49 (s, 2H), 7.55 (s, 2H), 7.55−7.58 (m, 2H), 7.62 (d, 2H, $J$ = 2.4 Hz), 7.70 (d, 2H, $J$ = 2.4 Hz); $^{13}C$ NMR (125 MHz) $\delta$ 30.4, 30.9, 31.4, 33.9, 34.2, 34.6, 81.3, 120.1, 120.2, 122.6, 127.7, 129.0, 129.1, 129.2, 130.8, 131.3, 133.3, 134.4, 135.5, 136.1, 142.8, 147.0, 149.7, 150.2, 156.0, 156.0; MS (FAB) $m/z$ 943 $(M + H)^+$. Anal. Calcd for $C_{48}H_{53}F_3O_6S_5$: C, 61.12; H, 5.66. Found: C, 60.91; H, 5.63.

**Typical Procedure for the Amidation of 1,3-Bistriflate 2b (Entry 3 in Table 3).** A suspension of bistriflate **2b** (1.00 g, 1.02 mmol), tosylamide (417 mg, 2.44 mmol), CuI (426 mg, 2.24 mmol), and $K_3PO_4$ (862 mg, 4.06 mmol) in DMF (30 mL) was stirred at 80 °C for 24 h. After cooling, the mixture was poured into saturated aqueous $NH_4Cl$ and extracted with chloroform. The extract was washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated to leave a residue, which was suspended in hot methanol. The insoluble part was collected by filtration and chromatographed on a silica gel column with chloroform−ethyl acetate (1:0 to 10:1) as an eluent to give bis(tosylamide) **17b** (301 mg, 29%), bis(phenoxathiine) **15** (236 mg, 34%), tosylamino ester **18b** (19.2 mg, 2.0%), its regioisomer **19** (4.9 mg, 0.5%), and detriflated tosylamide **20** (20 mg, 2%). On the other hand, one-fifth portion of the filtrate was purified by TLC with hexane−ethyl acetate (4:1) as a developer to give reduced product **13** (3.2 mg, 2%), monotriflate **14b** (5.2 mg, 3%), and additional crops of **17b** (1.8 mg, 30% in total), **15** (3.2 mg, 36% in total), **18b** (5.1 mg, 4% in total), and **19** (9.6 mg, 5% in total).

***N*,*N*′-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl)bis(*p*-toluenesulfonamide) (17b):** colorless powder, mp 326.1−327.8 °C; IR (KBr) 3346, 3258, 2964, 1448, 1168, 1090, 676 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.88 (s, 18H), 1.26 (s, 18H), 2.46 (s, 6H), 7.20 (s, 4H), 7.29 (d, 4H, $J$ = 8.2 Hz), 7.42 (s, 2H), 7.57 (s, 4H), 7.58 (d, 4H, $J$ = 8.2 Hz), 8.22 (s, 2H); $^{13}C$ NMR (100 MHz) $\delta$ 21.9, 30.7, 31.5, 34.3, 34.5, 121.9, 128.1, 130.0, 133.5, 133.7, 134.1, 135.7, 136.9, 143.8, 144.3, 150.9, 155.3; MS (FAB) $m/z$ 1027 $(M + H)^+$; HRMS (ESI) calcd for $C_{54}H_{62}N_2NaO_6S_6$ $(M + Na)^+$ 1049.2830, found 1049.2824.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathia-27-(*p*-toluenesulfonylamino)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),-21,23-dodecaene-25-yl trifluoromethanesulfonate (18b):** colorless powder, mp 283.5−285.2 °C; IR (KBr) 3386, 3262, 2965, 1420, 1207, 1169, 1128, 866, 685, 618 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.75 (s, 9H), 0.95 (s, 9H), 1.31 (s, 18H), 2.45 (s, 3H), 6.69 (br s, 2H), 6.93 (s, 2H), 7.24 (s, 2H), 7.25−7.29 (m, 2H), 7.53 (d, 2H, $J$ = 8.3 Hz), 7.65 (d, 2H, $J$ = 2.5 Hz), 7.67 (d, 2H, $J$ = 2.5 Hz), 8.04 (br s, 1H); $^{13}C$ NMR (100 MHz) $\delta$ 21.7, 30.5, 30.7, 31.4, 31.2, 34.3, 34.4, 120.9, 122.6, 128.0, 129.2, 129.8, 132.4, 133.3, 133.6, 134.3, 134.5, 135.5, 136.8, 143.7, 144.2, 147.0, 150.9, 151.2, 155.1. Anal. Calcd for $C_{48}H_{54}F_3NO_7S_6$: C, 57.29; H, 5.41; N, 1.39. Found: C, 57.32; H, 5.40; N, 1.35.

**5,11,17,23-Tetra-*tert*-butyl-27,28-dihydroxy-2,8,14,20-tetrathia-26-(*p*-toluenesulfonylamino)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),-21,23-dodecaene-25-yl trifluoromethanesulfonate (19):** colorless powder, mp 263.0−265.0 °C; IR (KBr) 3377, 2964, 1449, 1430, 1207, 1168, 860, 676, 616 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.01 (s, 9H), 1.10 (s, 9H), 1.19 (s, 9H), 1.21 (s, 9H), 2.45(s, 3H), 7.28 (m, 2H), 7.32 (d, 1H, $J$ = 2.3 Hz), 7.36 (d, 1H, $J$ = 2.3 Hz), 7.48 (d, 1H, $J$ = 2.5 Hz), 7.51 (d, 1H, $J$ = 2.5 Hz), 7.52 (d, 1H, $J$ = 2.5 Hz), 7.54 (m, 3H), 7.55 (d, 2H, $J$ = 6.1 Hz), 7.73 (s, 1H), 8.09 (s, 1H), 8.17 (s, 1H); $^{13}C$ NMR (100 MHz) $\delta$ 21.7, 30.8, 30.9, 31.2, 31.3, 34.2, 34.5, 34.7, 117.1, 119.8, 120.0, 120.1, 121.9, 128.1, 129.6, 129.8, 131.1, 133.7, 134.2, 134.3, 135.2, 135.2, 135.4, 135.6, 135.6, 135.8, 135.9, 136.6, 143.8, 143.9, 144.1, 148.4, 150.9, 152.0, 155.4, 155.8; MS (FAB) $m/z$ 1006 $M^+$; HRMS (ESI) calcd for $C_{48}H_{54}F_3NNaO_7S_6$ $(M + Na)^+$ 1028.2074, found 1028.2069.

***N*-(5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-2,8,14,20-tetrathiapentacyclo-19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl-*p*-toluenesulfonamide (20):** colorless powder, mp 316.0−318.0 °C; IR (KBr) 3320, 2963, 1451, 1167, 1091, 886 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.15 (s, 9H), 1.20 (s, 18H), 1.22 (s, 9H), 2.45 (s, 3H), 7.30 (d, 2H, $J$ = 8.1 Hz), 7.55 (d, 2H, $J$ = 2.5 Hz), 7.62 (m, 6H), 7.64 (s, 2H), 9.03 (s, 1H), 9.20 (s, 2H), 9.73 (s, 1H); $^{13}C$ NMR (100 MHz) $\delta$ 21.7, 30.8, 31.2, 31.3, 34.1, 34.2, 34.6, 119.1, 120.5, 121.5, 128.1, 129.8, 133.5, 135.4, 135.6, 136.0, 136.1, 136.4, 137.8, 144.3, 144.3, 144.4, 151.8, 155.9, 156.0; MS (FAB) $m/z$ 874 $(M + H)^+$; HRMS (ESI) calcd for $C_{47}H_{55}NNaO_5S_5$ $(M + Na)^+$ 896.2581, found 896.2576.

The following compounds were also obtained by this procedure with a different substrate or amide reagents.

***N,N′*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl)bis(*p*-methoxybenzenesulfonamide) (21):** colorless powder, mp 335.0−337.0 °C; IR (KBr) 3350, 3262, 2964, 1597, 1497, 1437, 1261, 1161, 1094, 1026, 679 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.89 (s, 18H), 1.26 (s, 18H), 3.89 (s, 6H), 6.96 (d, 4H, $J$ = 8.9 Hz), 7.21 (s, 4H), 7.47 (s, 2H), 7.57 (s, 4H), 7.64 (d, 4H, $J$ = 8.9 Hz), 8.23 (s, 2H); $^{13}$C NMR (100 MHz) $\delta$ 30.8, 31.5, 34.3, 34.5, 55.8, 114.5, 121.9, 130.3, 133.5, 133.8, 134.2, 137.0, 143.8, 150.9, 155.3, 163.6; HRMS (ESI) calcd for $C_{54}H_{62}N_2NaO_8S_6$ (M + Na)$^+$ 1081.2728, found 1081.2723.

***N,N′*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl)bis(*p*-nitrobenzenesulfonamide) (22):** colorless powder, mp 342.0−343.0 °C; IR (KBr) 3370, 3249, 2964, 1533, 1348, 1173, 1089, 854, 739 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.90 (s, 18H), 1.26 (s, 18H), 7.21 (s, 4H), 7.38 (s, 2H), 7.57 (s, 4H), 7.89 (d, 4H, $J$ = 8.9 Hz), 8.35 (d, 4H, $J$ = 8.9 Hz), 8.48 (s, 2H); $^{13}$C NMR (100 MHz) $\delta$ 30.7, 31.5, 34.4, 34.6, 121.6, 124.6, 129.5, 133.6, 134.0, 134.4, 136.0, 144.0, 144.5, 150.6, 151.8, 154.8; HRMS (ESI) calcd for $C_{52}H_{56}N_4NaO_{10}S_6$ (M + Na)$^+$ 1111.2218, found 1111.2213.

***N,N′*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl)bis(methanesulfonamide) (23):** colorless powder, mp 313.0−316.0 °C; IR (KBr) 3360, 3254, 2963, 1448, 1337, 1161, 970, 880 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.95 (s, 18H), 1.31 (s, 18H), 3.24 (s, 6H), 7.34 (s, 4H), 7.59 (s, 2H), 7.69 (s, 4H), 8.47 (s, 2H); $^{13}$C NMR (100 MHz) $\delta$ 30.8, 31.5, 34.4, 34.6, 40.8, 121.7, 132.9, 134.3, 134.5, 137.3, 144.4, 151.3, 155.2; MS (FAB) $m/z$ 875 (M + H)$^+$; HRMS (ESI) calcd for $C_{42}H_{54}N_2NaO_6S_6$ (M + Na)$^+$ 897.2204, found 897.2198.

***N*-(27-Benzyloxy-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl)-*p*-toluenesulfonamide (25):.** colorless powder, mp 257.0−259.0 °C; IR (KBr) 3385, 2963, 1449, 1261, 1167, 1090, 882 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.77 (s, 9H), 1.09 (s, 9H), 1.26 (s, 18H), 2.43 (s, 3H), 5.28 (s, 2H), 7.01 (s, 2H), 7.24 (d, 2H, $J$ = 8.6 Hz), 7.45 (s, 2H), 7.48−7.57 (m, 5H), 7.58 (d, 2H, $J$ = 2.5 Hz), 7.59 (d, 2H, $J$ = 2.5 Hz), 7.69 (s, 1H), 7.71 (d, 2H, $J$ = 8.6 Hz), 7.86 (s, 2H); $^{13}$C NMR (100 MHz) $\delta$ 21.9, 30.7, 31.1, 31.5, 34.2, 34.3, 34.6, 120.1, 123.1, 128.0, 128.2, 129.1, 129.2, 129.5, 129.7, 132.5, 134.0, 135.1, 135.2, 135.3, 136.0, 136.3, 136.5, 143.0, 143.7, 149.6, 150.1, 156.3, 156.8; MS (FAB) $m/z$ 964 (M + H)$^+$; HRMS (ESI) calcd for $C_{54}H_{61}NNaO_5S_5$ (M + Na)$^+$ 986.3051, found 986.3045.

**Typical Procedure for the Amidation of 1,3-Bistriflate 2a (Entry 3 in Table 4).** A suspension of bistriflate **2a** (501 mg, 0.549 mmol), tosylamide (376 mg, 2.20 mmol), CuI (418 mg, 2.19 mmol), and $K_3PO_4$ (465 mg, 2.19 mmol) in DMF (15 mL) was stirred at 80 °C for 24 h. After cooling, the mixture was poured into saturated aqueous $NH_4Cl$ and extracted with chloroform. The extract was washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated to leave a residue, one-tenth portion of which was purified by TLC with hexane−ethyl acetate (4:1) as a developer to give bis(tosylamide) **17a** (23.7 mg, 45%), tosylamino ester **18a** (6.2 mg, 12%), reduced amide **26** (4.7 mg, 11%), and iodinated amide **27** (2.1 mg, 4%).

Bis(tosylamide) **17a** could be isolated on a preparative scale by column chromatography. Thus, the same reaction was carried out in 2-fold scale, using bistriflate **2a** (1.00 g, 1.10 mmol). After workup, the mixture was suspended in hot methanol and the insoluble part was collected by filtration and chromatographed on a silica gel column with hexane−ethyl acetate (4:1) as an eluent to give bis(tosylamide) **17a** (479 mg, 46%).

***N,N′*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxypentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diyl)bis(*p*-toluenesulfonamide) (17a):** colorless powder, mp 337.0−339.0 °C; IR (KBr) 3104, 2956, 1598, 1449, 1165, 1092 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 1.10 (s, 18H), 1.17 (s, 18H), 2.47 (s, 6H), 3.16 (d, 4H, $J$ = 14.1 Hz), 3.91 (d, 4H, $J$ = 14.1 Hz), 6.92 (s, 4H), 6.98 (s, 4H), 7.31 (d, 4H, $J$ = 8.2 Hz), 7.64 (d, 4H, $J$ = 8.2 Hz), 8.62 (s, 2H), 9.42 (s, 2H); $^{13}$C NMR (125 MHz) $\delta$ 21.7, 30.9, 31.5, 33.8, 33.9, 34.3, 125.4, 126.2, 126.5, 127.1, 127.9, 129.8, 135.1, 138.4, 143.4, 144.5, 148.5, 150.7; MS (FAB) $m/z$ 955 (M + H)$^+$; HRMS (ESI) calcd for $C_{58}H_{70}N_2NaO_6S_2$ (M + Na)$^+$ 977.4573, found 977.4568.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-27-(*p*-toluenesulfonylamino)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl trifluoromethanesulfonate (18a):** colorless powder, mp 147.0−148.0 °C; IR (KBr) 3261, 2963, 1486, 1208, 1166, 875 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.81 (s, 9H), 0.96 (s, 9H), 1.29 (s, 18H), 2.45 (s, 3H), 3.07 (d, 2H, $J$ = 14.5 Hz), 3.47 (d, 2H, $J$ = 14.1 Hz), 3.80 (d, 2H, $J$ = 14.5 Hz), 4.20 (d, 2H, $J$ = 14.1 Hz), 5.26 (s, 2H), 6.70 (s, 2H), 6.79 (s, 2H), 7.04 (d, 2H, $J$ = 2.0 Hz), 7.11 (d, 2H, $J$ = 2.0 Hz), 7.25 (d, 2H, $J$ = 7.9 Hz), 7.55 (d, 2H, $J$ = 7.9 Hz), 7.76 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 21.8, 30.7, 30.9, 31.7, 31.8, 32.0, 33.9, 34.1, 34.2, 34.2, 125.6, 125.6, 125.9, 127.2, 127.6, 127.9, 128.0, 128.0, 129.8, 132.6, 135.6, 137.4, 141.4, 143.6, 144.4, 149.6, 150.5, 150.7; MS (FAB) $m/z$ 934 (M + H)$^+$; HRMS (ESI) calcd for $C_{52}H_{62}F_3NNaO_7S_2$ (M + Na)$^+$ 956.3817, found 956.3812.

***N*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxypentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl)-*p*-toluenesulfonamide (26):** colorless powder, mp 228.0−230.0 °C; IR (KBr) 3483, 2962, 1486, 1158 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 1.64 (s, 9H), 1.22 (s, 9H), 1.25 (s, 18H), 2.44 (s, 3H), 3.23 (d, 2H, $J$ = 14.3 Hz), 3.65 (d, 2H, $J$ = 14.3 Hz), 3.82 (d, 2H, $J$ = 14.3 Hz), 3.95 (d, 2H, $J$ = 14.3 Hz), 5.60 (s, 2H), 6.93 (br, 1H), 7.00 (d, 2H, $J$ = 2.3 Hz), 7.02 (d, 2H, $J$ = 2.3 Hz), 7.05 (br s, 2H), 7.06 (s, 2H), 7.25 (d, 2H, $J$ = 8.1 Hz), 7.54 (d, 2H, $J$ = 8.1 Hz), 7.86 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 21.7, 31.0, 31.3, 31.5, 34.0, 34.3, 34.5, 34.7, 37.9, 123.8, 124.9, 125.6, 126.0, 126.3, 127.1, 127.3, 127.8, 128.3, 129.7, 135.9, 138.8, 140.8, 143.5, 144.2, 149.4, 151.2, 151.6; MS (FAB) $m/z$ 786 (M + H)$^+$; HRMS (ESI) calcd for $C_{51}H_{63}NNaO_4S$ (M + Na)$^+$ 808.4375, found 808.4370.

***N*-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-27-iodopentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl)-*p*-toluenesulfonamide (27):** colorless powder, mp 256.0−258.0 °C; IR (KBr) 3516, 2963, 1487, 1364, 1168, 874, 816 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 0.73 (s, 9H), 0.96 (s, 9H), 1.32 (s, 18H), 2.44 (s, 3H), 3.02 (d, 2H, $J$ = 14.5 Hz), 3.72 (d, 2H, $J$ = 14.1 Hz), 3.79 (d, 2H, $J$ = 14.5 Hz), 4.39 (d, 2H, $J$ = 14.1 Hz), 5.19 (s, 2H), 6.56 (s, 2H), 6.78 (s, 2H), 7.03 (d, 2H, $J$ = 2.4 Hz), 7.11 (d, 2H, $J$ = 2.4 Hz), 7.24 (d, 2H, $J$ = 8.0 Hz), 7.53 (d, 2H, $J$ = 8.3 Hz), 7.63 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 21.7, 30.5, 30.8, 31.7, 33.6, 33.8, 34.0, 34.1, 41.2, 104.0, 125.2, 125.7, 126.1, 126.1, 127.8, 127.9, 128.1, 128.6, 129.7, 135.9, 137.6, 142.9, 142.9, 144.0, 150.0, 150.2, 150.3; MS (FAB) $m/z$ 912 (M + H)$^+$; HRMS (ESI) calcd for $C_{51}H_{62}INNaO_4S$ (M + Na)$^+$ 934.3342, found 934.3336.

Monotriflate **14a** is a known compound. The NMR spectra of the sample are identical with those reported in the literature.[7a]

**27-Amino-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxypentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25-yl Trifluoromethanesulfonate (10a).** To a solution of benzylamino ester **7a** (201 mg, 0.231 mmol) in degassed ethanol (10 mL) was added palladium on carbon (5 w/w %, 20.0 mg), and the mixture was stirred at 60 °C under a

hydrogen atmosphere for 24 h. After the catalyst was filtered off, the filtrate was evaporated to leave a residue, which was crystallized from methanol−dichloromethane to give amino ester **10a** (100 mg). The mother liquid was evaporated and the residue was purified by TLC with hexane−ethyl acetate (4:1) as an eluent to give an additional crop of **10a** (59.6 mg) for a total yield of 160 mg (89%) as crystals, mp 141.0−143.0 °C; IR (KBr) 3522, 3418, 2963, 1485, 1420, 1396, 1362, 1208, 1138, 1072 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 0.88 (br s, 9H), 1.05 (s, 9H), 1.33 (s, 18H), 3.51 (d, 2H, $J$ = 14.7 Hz), 3.55 (d, 2H, $J$ = 14.8 Hz), 4.01 (br d, 2H, $J$ = 14.0 Hz), 4.24 (d, 2H, $J$ = 14.2 Hz), 6.79 (br s, 2H), 6.90 (s, 2H), 7.13 (d, 2H, $J$ = 2.3 Hz), 7.17 (d, 2H, $J$ = 2.3 Hz); $^{13}C$ NMR (100 MHz) $\delta$ 30.7, 31.1, 31.6, 33.1, 33.9, 34.0, 34.0, 35.1, 113.9, 117.1, 120.3, 125.5, 125.5, 125.8, 127.3, 127.7, 128.3, 131.0, 133.0, 142.3, 143.0, 150.0, 150.6; MS (FAB) $m/z$ 780 $(M + H)^+$. Anal. Calcd for $C_{45}H_{56}F_3NO_5S$: C, 69.29; H, 7.24; N, 1.80. Found: C, 69.40; H, 7.17; N, 1.75.

**28-Amino-5,11,17,23-tetra-*tert*-butylpentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27-triol (4a).** Amino ester **10a** (150 mg, 0.192 mmol) was boiled with 2 M NaOH (5.0 mL) in a mixture of THF (3.0 mL) and ethanol (3.0 mL) for 4 h. After cooling, the mixture was quenched with 2 M HCl (20 mL) and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. Crystallization of the residue from methanol−dichloromethane gave amino triol **4a** (120 mg, 96%) as crystals, mp 306.0−307.0 °C (lit.[4c] mp 296−297 °C); IR (KBr) 3342, 3221, 2960, 1482, 1363, 1305, 1202, 871, 782 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.19 (s, 9H), 1.21 (s, 18H), 1.23 (s, 9H), 3.48 (br, 4H), 4.23 (br, 4H), 7.00 (d, 2H, $J$ = 2.5 Hz), 7.06 (s, 2H), 7.07 (d, 2H, $J$ = 2.5 Hz), 7.08 (s, 2H); $^{13}C$ NMR (100 MHz) $\delta$ 31.2, 31.4, 33.1, 33.9, 34.0, 34.2, 34.7, 125.6, 125.7, 125.7, 125.8, 127.6, 128.3, 128.3, 131.8, 135.2, 143.3, 143.7, 147.6, 147.9, 148.4. The NMR spectra are essentially identical with those reported in the literature.[4c]

**28-Amino-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27-triol (4b).** Benzylamino ester **7b** (201 mg, 0.213 mmol) was boiled with concd HCl (6 mL) in acetic acid (10 mL) for 3 d. After cooling, most of the acetic acid was evaporated and the residue was suspended by the addition of water. The suspension was neutralized with 2 M NaOH and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to leave a residue, which was dissolved by the addition of THF (6.0 mL) and ethanol (3.0 mL). To the solution was added a solution of NaOH (860 mg, 21.5 mmol) in water (3.0 mL), and the mixture was refluxed for 12 h. After cooling, the mixture was acidified with 2 M HCl and the resulting mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with chloroform−ethyl acetate (20:1) as an eluent to give amino triol **4b** (143 mg, 93%) as a colorless powder, mp 282.0−284.0 °C dec; IR (KBr) 3356, 3302, 2963, 1458, 1265, 1242 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.20 (s, 9H), 1.23 (s, 9H), 1.23 (s, 18H), 7.60 (d, 2H, $J$ = 2.5 Hz), 7.63 (s, 2H), 7.65 (s, 2H), 7.66 (d, 2H, $J$ = 2.5 Hz); $^{13}C$ NMR (100 MHz) $\delta$ 31.1, 31.3, 31.3, 34.1, 34.2, 34.3, 120.8, 121.0, 121.4, 126.0, 135.9, 136.2, 136.2, 143.9, 144.3, 145.5, 147.1, 153.4, 156.3, 156.8; MS (FAB) $m/z$ 719 $M^+$. Anal. Calcd for $C_{40}H_{49}NO_3S_4$: C, 66.72; H, 6.86; N, 1.95. Found: C, 66.70; H, 6.80; N, 1.78.

Compound **4b** was obtained in an improved yield based on bistriflate **2b** by subjecting the crude reaction mixture of the amination to this deprotection process. Thus, the amination of **2b** (1.00 g, 1.02 mmol) was carried out under the same conditions as mentioned in the typical procedure (vide supra) and the worked-up mixture was boiled with concd HCl (30 mL) in acetic acid (50 mL) for 3 d. After the workup, the mixture was dissolved by the addition of THF (30 mL) and ethanol (15 mL), and boiled with a solution of NaOH (3.00 g, 75.0 mmol) in water (15 mL) for 12 h. After the workup, the mixture was purified by column chromatography with chloroform−hexane (3:1) as an eluent to give **4b** (385 mg, 53%).

**Debenzylation of Bis(benzylamine) 8 to 26,28-Diamino-5,11,17,23-tetra-*tert*-butylpentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (5a).** The procedure employed for the preparation of compound **10a** was applied. Thus, bis(benzylamine) **8** (201 mg, 0.243 mmol) was treated with palladium on carbon (5 w/w %, 21.0 mg) in ethanol (10 mL) under a hydrogen atmosphere at 60 °C for 16 h. Crystallization of the worked-up mixture from methanol−dichloromethane gave diamine **5a** (123 mg). An additional crop of **5a** (33.7 mg) was obtained by the TLC of the mother liquid with hexane−ethyl acetate (2:1) as an eluent for a total yield of 157 mg (100%) as a colorless powder, mp 269.0−270.0 °C (lit.[4b] mp 277.5−278.5 °C); IR (KBr) 3342, 2961, 1482, 1363, 1203, 870 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.20 (s, 18H), 1.21 (s, 18H), 3.88 (br, 8H), 7.02 (s, 4H), 7.06 (s, 4H); $^{13}C$ NMR (100 MHz) $\delta$ 31.4, 31.7, 34.0, 34.3, 35.1, 125.5, 128.4, 133.5, 135.8, 142.2, 147.2, 150.3. The $^1H$ NMR spectrum is essentially identical with that reported in the literature.[4b]

**Reduction of Bis(tosylamide) 17a to Diamine 5a.** A mixture of bis(tosylamide) **17a** (50.3 mg, 52.7 $\mu$mol), 0.1 M $SmI_2$ in THF (15.7 mL, 1.57 mmol), pyrrolidine ($d$ = 0.866; 258 $\mu$L, 3.14 mmol), and water (84.8 $\mu$L, 4.71 mmol) was stirred at room temperature for 12 h. The mixture was quenched by the addition of 2 M HCl (10 mL) and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to leave a residue, which was purified by TLC with hexane−ethyl acetate (2:1) as an eluent to give diamine **5a** (30.0 mg, 88%).

**Hydrolysis of Bis(tosylamide) 17b to Diamine 5b.** Bis(tosylamide) **17b** (50.5 mg, 49.1 $\mu$mol) was boiled with concd $H_2SO_4$ (1.0 mL) and water (0.2 mL) in acetic acid (6.0 mL) for 8 h. To the cooled mixture was added water (6 mL) and the mixture was neutralized in an ice bath by adding dropwise satuared aqueous NaOH. The mixture was extracted with chloroform, and the extract was dried over $MgSO_4$ and evaporated. The residue was purified by TLC with hexane−ethyl acetate (4:1) as an eluent to give diamine **5b** (33.0 mg, 94%).

**Reduction of Bis(tosylamide) 17b to Diamine 5b.** The procedure employed for the reduction of bis(tosylamide) **17a** was applied. Thus, a mixture of bis(tosylamide) **17b** (50.2 mg, 48.9 $\mu$mol), 0.1 M $SmI_2$ in THF (14.6 mL, 1.46 mmol), pyrrolidine ($d$ = 0.866; 240 $\mu$L, 2.92 mmol), and water (78.6 $\mu$L, 4.38 mmol) was stirred at room temperature for 8 h. After the workup, the crude product was purified by TLC with hexane−ethyl acetate (4:1) as an eluent to give diamine **5b** (6.0 mg, 17%).

**X-ray Crystallographic Analyses of Compounds 2b, 7b, and 17b.** Single-crystal X-ray diffraction data were collected with a CCD diffractometer using Mo Kα radiation ($\lambda$ = 0.71073 Å), employing a monochromator and a fine-focus rotating anode as radiation source. Data integration and reduction were performed with SAINT and XPREP software and the absorption correction was performed by the semiempirical method with SADABS.[29] The structure was solved by the direct method using SHELXS-97 and refined by using least-squares methods on $F^2$ with SHELXL-97.[30] X-ray analysis was undertaken using the free GUI software of Yadokari-XG 2009.[31]

**Data for compound 2b:** $C_{42.5}H_{48}F_6O_{8.5}S_6$, fw =1001.17, monoclinic, $P2_1/c$, $a$ = 20.749(4) Å, $b$ = 20.042(4) Å, $c$ = 11.915(2) Å, $\beta$ = 95.042(2)°, $V$ = 4935.6(15) $Å^3$, $Z$ = 4, $T$ = 100(2) K, 27403 reflections measured, 11120 independent reflections, 7930 reflections were observed ($I > 2\sigma(I)$), $R_1$ = 0.0690, $wR_2$ = 0.1682 (observed), $R_1$ = 0.984, $wR_2$ = 0.1902 (all data).

**Data for compound 7b:** $C_{48}H_{54}F_3NO_5S_5$, fw = 942.22, triclinic, $P\bar{1}$, $a$ = 10.3827(17) Å, $b$ = 13.578(2) Å, $c$ = 18.340(3) Å, α = 86.422(2)°, $\beta$ = 87.024(2)°, $\gamma$ = 74.012(2)°, $V$ = 2479.0(7) $Å^3$, $Z$ = 2, $T$ = 173(2) K, 27260 reflections measured, 10968 independent reflections, 7928 reflections were observed ($I > 2\sigma(I)$), $R_1$ = 0.0601, $wR_2$ = 0.1452 (observed), $R_1$ = 0.0877, $wR_2$ = 0.1685 (all data).

**Data for compound 17b:** $C_{60}H_{76}N_2O_6S_6$, fw =1113.59, monoclinic, $C2/c$, $a$ = 14.710(3) Å, $b$ = 23.366(3) Å, $c$ = 18.063(4) Å, $\beta$ = 106.207(2)°, $V$ = 5962.0(17) Å$^3$, $Z$ = 4, $T$ = 173(2) K, 33189 reflections measured, 6800 independent reflections, 5945 reflections were observed ($I > 2\sigma(I)$), $R_1$ = 0.0414, $wR_2$ = 0.1125 (observed), $R_1$ = 0.0483, $wR_2$ = 0.1196 (all data).

## ■ ASSOCIATED CONTENT

**Supporting Information.** CIF files for compounds **2b**, **7b**, and **17b** and NMR spectral charts for the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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