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Improved Synthesis of Functional CTVs and Cryptophanes Using $Sc(OTf)_3$ as Catalyst

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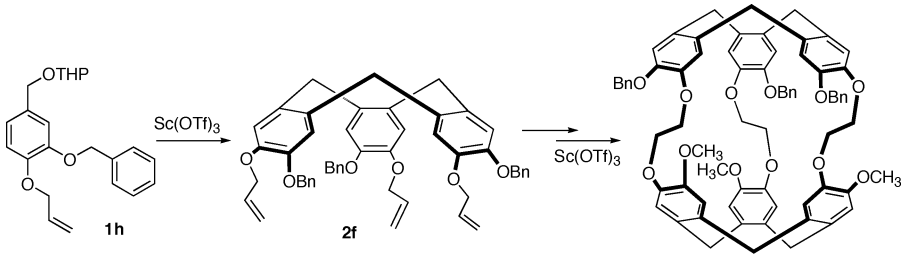
Received March 11, 2005



Functional cyclotriveratrylene (CTV) and cryptophane derivatives are synthesized in the presence of scandium triflate [$Sc(OTf)_3$]. This route allows the preparation of new derivatives that could not be prepared or easily obtained by using the previously reported experimental procedures. With a catalytic amount of scandium triflate (1% mol), CTVs were obtained with yields similar to or higher than those reported previously in reactions run under strong acidic conditions. Cryptophanes were also synthesized in fairly good yields by performing the ring-closure step in the presence of a stoichiometric amount of $Sc(OTf)_3$. Interestingly, this novel approach strongly reduces the formation of side products and gives rise to novel functionalized molecules for the construction of supramolecular host−guest systems.

Introduction

The cup-shape cyclotriveratrylene derivatives (CTV) are among the key structures, with, e.g., calixarenes and cavitands, which have been exploited for many years for the design of molecular hosts.[1] They still represent interesting starting compounds for the construction of new supramolecular architectures such as solid inclusion complexes,[2] chiral scaffolds for triple helix formation,[3] or more recently, coordination polymer networks[4] and self-assembled monolayers on gold surface.[5] A second but not least point of interest of the CTV derivatives is their use in the synthesis of cryptophane hosts.[6] Surprisingly, despite their increasing development, the current methods of preparation of CTVs still refer to old protocols, which usually require strong dehydrating reagents. These include perchloric acid in methanol,[7] phosphorus pentaoxide in diethyl ether,[8] sulfuric acid in acetic acid,[9] concentrated hydrochloric acid,[10] trifluoroacetic acid in chloroform,[11] and BF_3−etherate in benzene.[12] However, these conditions are often incompatible with the synthesis of new CTV derivatives bearing acid-sensitive functions, and it is therefore desirable to examine mild reagents which could provide new routes to functional CTVs. Recently, Raston et al. described the synthesis of a tri(*O*-allyl)-CTV obtained in good yield under mild conditions using an ionic liquid.[13] Their approach appears

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10.1021/jo050495g CCC: $30.25
Published on Web 07/06/2005

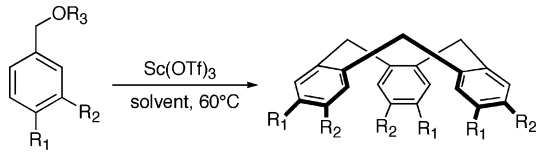
very promising even though ionic solvents are not still of common use in many laboratories and their price as solvent may be prohibitive for the production of large amounts of compounds. Moreover, for the same reason, the use of ionic liquids seems inappropriate for the synthesis of cryptophanes because dilute conditions are usually required. Konishi et al. reported an elegant synthesis of protected calixarenes obtained in good yields, using scandium triflate, $Sc(OTf)_3$, as Lewis acid.[14] This strong Lewis acid gained considerable interest for the last 15 years and was found to catalyze numerous organic reactions of prime importance like Friedel–Crafts alkylation reactions.[15] We recently reported the synthesis of monoprotected cryptophane[16] and hemicryptophane[17] obtained in fairly good yields using $Sc(OTf)_3$ as Lewis acid. These findings led us to investigate further scandium triflate as a potent reagent for the preparation of CTV and cryptophane derivatives. In this paper, we demonstrate the ability of $Sc(OTf)_3$ to promote the synthesis of CTVs with satisfactory yields. In addition, we show that the experimental procedure reported herein allows the formation of new compounds, which cannot be prepared, or properly purified, by using the previous methods. In a second part, we report that under dilute conditions, the reaction of a stoichiometric amount of $Sc(OTf)_3$ with the proper precursor leads to the formation of cryptophane derivatives. The yields obtained under these new conditions are in most cases similar, or even higher, than those reported in the literature for known compounds. Interestingly, we note that the simplicity of this approach, combined with a significant decrease of the side products of the reaction, and easier purification of the expected compounds, allow the synthesis of new cryptophanes, which cannot be prepared or easily purified by following the previous synthetic procedures.

Results and Discussion

Synthesis of CTVs. A series of differently substituted CTVs were prepared by treating the parent benzyl alcohols with $Sc(OTf)_3$ in catalytic amount (1% mol); the results are summarized in Table 1. Because only strongly activated benzyl alcohols provide the CTV derivatives, only O- or S-substituted phenyl compounds have been allowed to react with $Sc(OTf)_3$ in acetonitrile or in dichloromethane. In all cases, the procedure given in the Experimental Section provided CTVs with satisfactory yields. For instance, in acetonitrile compound **1a** gave rise to the corresponding CTV **2a** in 44% yield after purification. This result is better than those reported for the reactions run with 60% perchloric acid (35% yield)[12] or with trifluoroacetic acid in chloroform (19% yield),[18] but less than for the method using sulfuric acid in hot acetic acid (87% yield).[19] Interestingly, when one methyl group is replaced by an ethyl group (**1b**), compound **2b** is obtained with similar yield (48%) under the present experimental conditions, whereas it dropped to 10% when run in 65% $HClO_4$/methanol at 20 °C, due to an increase of its solubility in the medium.[20] In acetonitrile, benzyl alcohols **1c** and **1d** bearing *O*-allyl protective groups gave rise to the expected CTVs **2c** and **2d** in 50% and 43% yields, respectively (Table 1). By exchanging acetonitrile for dichloromethane, similar yields were obtained for compounds **2c** (55%) and **2d** (47%). Again, these results are better than those reported for **2c** prepared in $HCLO_4$/methanol solution.[21] Thus, this method provides a new efficient approach to easily synthesize CTV **2c**, which is an important intermediate in the synthesis of cryptophanes and related compounds.[6] These satisfactory results clearly demonstrate that $Sc(OTf)_3$ is an efficient catalysis for the improved synthesis of CTV derivatives and represent an important alternative to the former procedures requiring large amount of acids. Additionally, it is noteworthy that this new route strongly facilitates the purification steps by reducing significantly the formation of side products. Compounds **1e** and **1f** prepared, respectively, in five steps from vanillin and isovanillin using a Newman–Kwart reaction also provided the corresponding CTV **2e** in 48% and 31% yields, respectively.[22] In this case, the yields are lower than those reported by Garcia et al., who performed the ring closure reaction in formic acid (70% from **1e** and 60% from **1f**). However, as noted previously, the present procedure is still attractive as the purification step is facilitated.

To demonstrate the utility of this method to promote the formation of CTVs that could not be easily obtained

TABLE 1. Formation of CTVs 2a–f from the Corresponding Benzyl Alcohols 1a–h Using Catalytic Amounts of $Sc(OTf)_3$ (1% mol) in Acetonitrile or Dichloromethane at 60 °C Overnight



1a-h **2a-f**

compd	R_1	R_2	R_3	solvent	CTV	yield (%)
1a	OMe	OMe	H	CH_3CN	**2a**	44
1b	OEt	OMe	H	CH_3CN	**2b**	48
1c	*O*-allyl	OMe	H	CH_3CN	**2c**	50
1c	*O*-allyl	OMe	H	CH_2Cl_2	**2c**	55
1d	*O*-allyl	OEt	H	CH_3CN	**2d**	43
1d	*O*-allyl	OEt	H	CH_2Cl_2	**2d**	47
1e	OMe	SMe	H	CH_3CN	**2e**	48
1f	SMe	OMe	H	CH_3CN	**2e**	31
1g	*O*-allyl	OBn	H	CH_3CN	**2f**	37
1h	*O*-allyl	OBn	THP	CH_3CN	**2f**	33

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(20) Compound **2b** has been obtained in 51% yield in $HClO_4$/methanol solution by performing the reaction in a fridge in order to precipitate the product and to avoid partial decomposition (see ref 37). This procedure appears however very inconvenient and the use of scandium triflate as a catalyst is thus preferred for the synthesis of **2b**.
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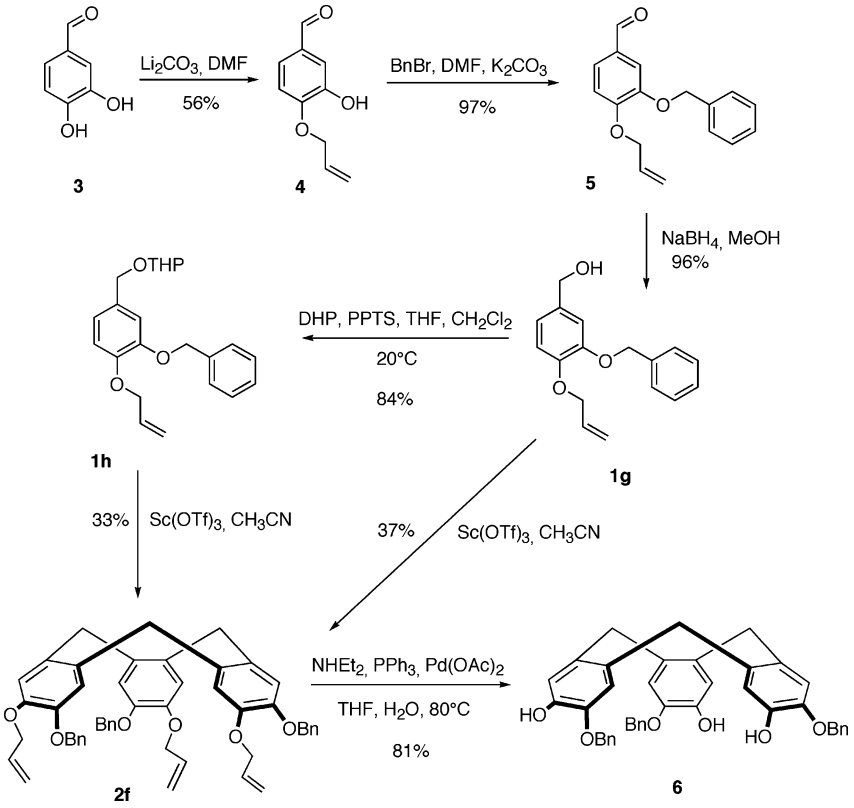
SCHEME 1



by following already known procedures, we performed the reaction of compound **1g** with $Sc(OTf)_3$. Benzyl alcohol **1g** was synthesized in three steps from 3,4-dihydroxybenzyl alcohol **3** (Scheme 1). Monoallylation was achieved according to a known method to give compound **4** in 56% yield.[23] Monoprotected derivative **4** was then reacted with benzyl bromide in acetone in the presence of potassium carbonate to give compound **5** in 97% yield. Reduction of **5** with $NaBH_4$ in methanol gave the benzyl alcohol derivative **1g** in 96% yield after purification. Attempts to prepare CTV **2f** from compound **1g** in $HClO_4$/methanol mixture failed. The presence of many side products did not allow purifying properly the small amount of CTV detected by ^1H NMR spectroscopy in the crude material. The situation is somewhat different when $Sc(OTf)_3$ in acetonitrile was used to promote the formation of compound **2f**, which was easily obtained in 37% yield after purification. Protected benzyl alcohols are usually required to purify properly some cryptophane precursors (see below). It was thus interesting to attempt the cyclization reaction with the *O*-THP-protected benzyl alcohol **1h**, which was prepared in 84% yield by treating **1g** with dihydropyran in the presence of PPTS. As expected, the reaction of **1h** with $Sc(OTf)_3$ in CH_2Cl_2 afforded CTV **2f** in 33% yield, a yield similar to that obtained from **1g**. This demonstrates that under these conditions the *O*-THP protection of the benzyl alcohol function does not affect significantly the yield of the cyclization reaction. CTV **2f** was fully characterized by usual spectroscopic techniques, and it represents an important building block for the elaboration of new derivatives, such as multiprotected cryptophanes. Indeed, both protecting groups can be selectively cleaved at different stage of the synthesis. For instance, reaction of **2f** with palladium catalyst afforded the trihydroxy CTV **6** in 81% yield (Scheme 1).[23]

Synthesis of Cryptophanes. The satisfactory results obtained with CTV derivatives prompted us to investigate scandium triflate as new potent reagent for the synthesis of cryptophane derivatives. Cryptophanes are molecular receptors usually synthesized in formic acid as solvent. This procedure gave satisfactory results, but this approach appeared inappropriate for the design of new molecules bearing protecting groups. Indeed, when we tried to perform in formic acid the synthesis of cryptophanes bearing several benzyl or allyl substituents, most of these attempts failed and a complex mixture of compounds was observed at the end of the reaction. An additional difficulty arose from the purification steps, which were particularly critical when only tiny amounts of cryptophanes were detected in the crude reaction mixtures. It thus became obvious that the use of $Sc(OTf)_3$ as a mild reagent might be an interesting option to synthesize cryptophane hosts. However, optimal reaction conditions require dilute solutions ($\sim 10^{-3}$ M) when the so-called *template method* is applied in order to avoid polymerization side reactions.[24] Consequently, catalytic amounts of $Sc(OTf)_3$ would be inappropriate to achieve the formation of cryptophanes in satisfactory yield, and we thus used $Sc(OTf)_3$ in stoichiometric amounts to perform these syntheses. We should mention that the use of larger amounts of reagents still presents interest as

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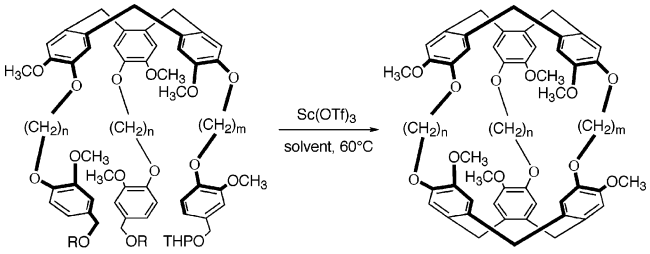
TABLE 2. Formation of Cryptophanes 8a–c from Their Precursors 7a–c Using a Stoichiometric Amount of $Sc(OTf)_3$ in Acetonitrile or Dichloromethane at 60 °C for 72 h



7a-c 8a-c

precursor	n	m	R	solvent	cryptophane	yield (%)
7a	2	2	OTHP	CH_3CN	**8a (A)**	36
7a	2	2	OTHP	CH_2Cl_2	**8a (A)**	51
7b	3	3	OTHP	CH_2Cl_2	**8b (E)**	28
7c	2	3	H	CH_2Cl_2	**8c (223)**	33

$Sc(OTf)_3$ can be easily recovered from the aqueous layer and reused for subsequent experiments.[25]

Substituted CTV precursors **7a–c** leading to the formation of known cryptophanes were reacted with $Sc(OTf)_3$, and results are summarized in Table 2. For instance, when precursor **7a**[23] was allowed to react with a stoichiometric amount of $Sc(OTf)_3$ in acetonitrile, the expected cryptophane-A **8a** was obtained in 36% yield. The yield increased to 51% when dichloromethane was used instead of acetonitrile. The present yields for **8a** are lower than those obtained by using formic acid (80% yield).[26] However, once again, this new procedure made easier the purification steps by column chromatography. Similar observations were made with precursors **7b** and **7c**. Compound **7b** afforded the expected *anti*-cryptophane-E **8b** in 28% yield,[27] and compound **7c** gave *anti*-cryptophane-223 **8c** in 33% yield.[28] These last two experiments gave yields similar to those reported in previous syntheses using formic acid.

We then explored further the advantages of $Sc(OTf)_3$ reagent over the usual procedures using strong acidic conditions by performing the synthesis of cryptophane **15** from the substituted cyclotriphenolene **14**. Compound **14** was prepared in four steps from CTV **9** using a novel and efficient synthetic approach described in Scheme 2. Deprotection of CTV **2c** with a palladium catalyst following a known procedure gave compound **9**,[29] which was then allowed to react with triflic anhydride in pyridine to afford **10** in 85% yield. The reduction step was achieved with a palladium catalyst, and compound **11** was obtained in 71% yield.[30] Compound **11** is very useful and has been involved in the studies of the optical properties of CTVs or in the synthesis of *anti*-cryptophane-C **15a**. To our knowledge, two different approaches have been proposed to prepare **11**. In a first approach, the phenol groups in **9** could be removed by hydrogenolysis of the tris(2-phenyl-1-tetrazolyl) derivative to give **11** in 90% yield.[31] A second route used Raney-Ni desulfuration of **2e**.[22] Both methods gave satisfactory results, but the present novel procedure is more appropriate to give sizable amounts of compound **11**. Removal of the three methyl groups in **11** was easily achieved using BBr_3 in dichloromethane to give the cyclotriphenolene **12** in 66% yield.[32] The cryptophane precursor **14** was obtained in 70% yield from **12**, and protected benzyl alcohol **13** in the presence of cesium carbonate in DMF. Compound **14** was then allowed to react with $Sc(OTf)_3$ for 72 h to give *anti*-cryptophane-C **15a** and *syn*-cryptophane-D **15b** in 50% and 8% yields, respectively. Compound **15a** is known for its interesting binding properties toward chiral halogenomethanes.[33]

The syntheses of **15a** and **15b** have been previously reported with 25% and 5% yields, respectively.[34] The results presented herein enlighten the simplicity of both the method and the purification procedure that make this approach very attractive for the design and purification of cryptophanes **15a**,**b**. These CTVs and cryptophane derivatives were characterized by usual analytical techniques. To our knowledge, cryptophane-D **15b** is the only *syn*-isomer with OCH_2CH_2O bridges, which has been unambiguously isolated and characterized; its 500 MHz ^1H NMR spectrum is given in Figure 1. Thus, the obtaining of sizable amounts of **15b** is crucial for further spectroscopic investigations including the studies of encapsulation processes within the molecular cavity of the host. For instance, cryptophane-D **15b** is suitable for complexation of xenon guest, which is accessible through NMR experiments using laser-polarized ^{129}Xe.[35]

In an attempt to further improve the capability of $Sc(OTf)_3$ in the formation of cryptophanes, we synthesize the new cryptophane **17** bearing three benzyl protecting groups (Scheme 3). Cryptophane precursor **16** was obtained in 88% yield from CTV **6** and compound **13** in the presence of cesium carbonate. Attempts to obtain **17** from **16** dissolved in a mixture of formic acid and chloroform at 55 °C were unsuccessful. Although **17** was clearly detected in tiny amount in the crude reaction mixture, the purification by column chromatography was inefficient as several side-products were eluted with the desired cryptophane. When compound **16**, was allowed to react with $Sc(OTf)_3$ in CH_2Cl_2, the expected cryptophane **17** was isolated as the *anti*-isomer in 42% yield.

Figure 2 shows the 500 MHz ^1H NMR spectrum of cryptophane **17**. We observed a signal at 3.4 ppm, corresponding to the three methoxy groups, high-field shifted by 0.4 ppm with respect to the usual chemical shift observed for methoxy groups in cryptophane-A **8a**, a consequence of the shielding effect of the benzyl moieties on the facing CTV unit. Once again, the forma-

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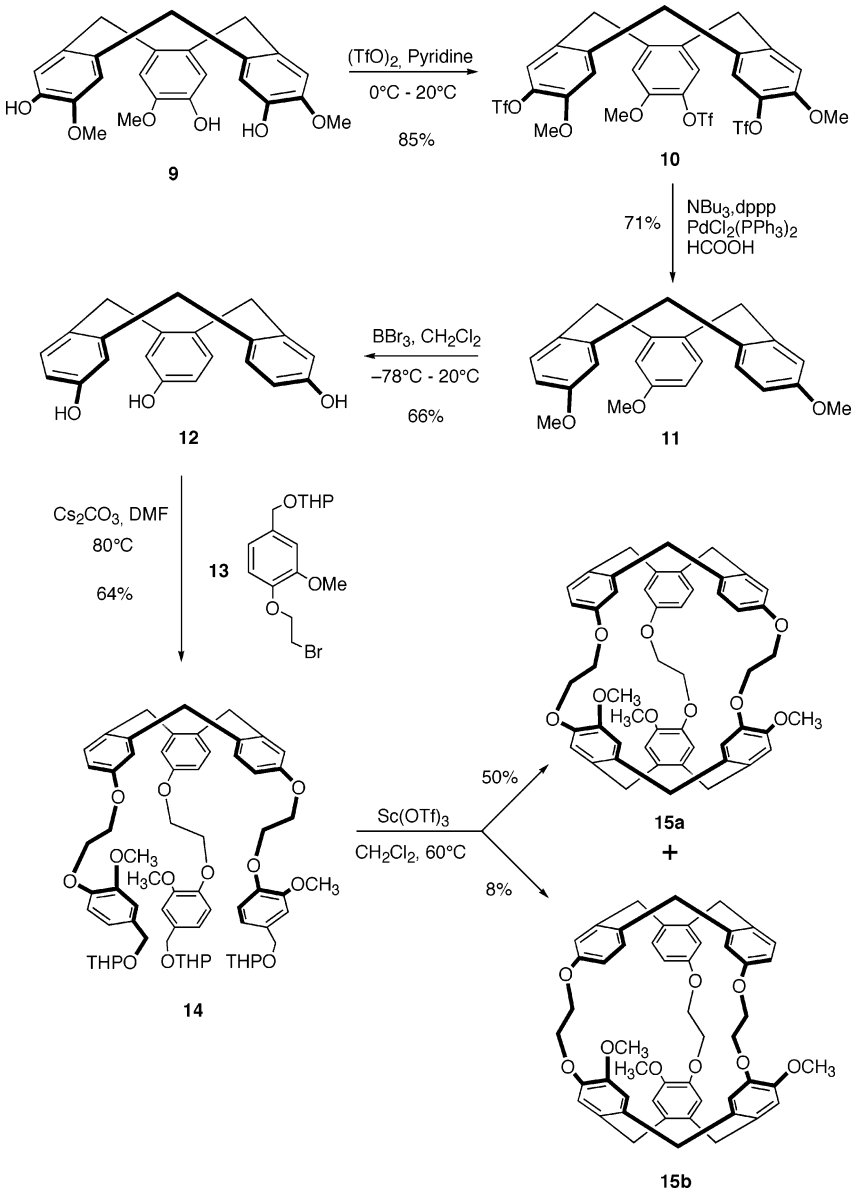
SCHEME 2



tion of this new cryptophane exemplifies the synthetic possibilities of $Sc(OTf)_3$ in the design of more complex cryptophane derivatives, which cannot be easily obtained or even purified using previously reported procedures. Furthermore, such multiprotected molecules are key compounds for achieving the optical resolution of new cryptophanes[36] and the construction of new supramolecular structures.

Conclusion

Scandium triflate $Sc(OTf)_3$ was used for the preparation of various CTVs and cryptophanes. We showed that $Sc(OTf)_3$ used in catalytic amounts (1% mol) promoted the formation of CTVs **2a**−**g** in moderate yields (30−55%). These values are similar to those reported in previous works using strong acids such as perchloric or formic acids. Interestingly, we noted that using this catalyst strongly reduced the formation of side-products and thus made the purification steps easier. On the other hand, the mild conditions reported herein allowed the synthesis of new functionalized CTV derivatives such as **2g** bearing both allyl and benzyl moieties as protecting groups. We also reported the synthesis of new CTV derivatives **6** and **10** in good yields, which are important precursors for the preparation of new functional CTVs or cryptophanes. In a second part, we showed that $Sc(OTf)_3$ used in stoichiometric amount in diluted solution, provided the expected cryptophanes from their respective precursors. In most cases the yields obtained are similar to those reported for other methods. Several parameters such as solvent, temperature, and dilution may influence the formation of the cryptophanes, and some experimental conditions could be optimized. However, the yields reported herein and the procedure given in the Experimental Section lead to very satisfactory results. The following criteria can be retained to underline the advantages of $Sc(OTf)_3$ in the synthesis of CTVs

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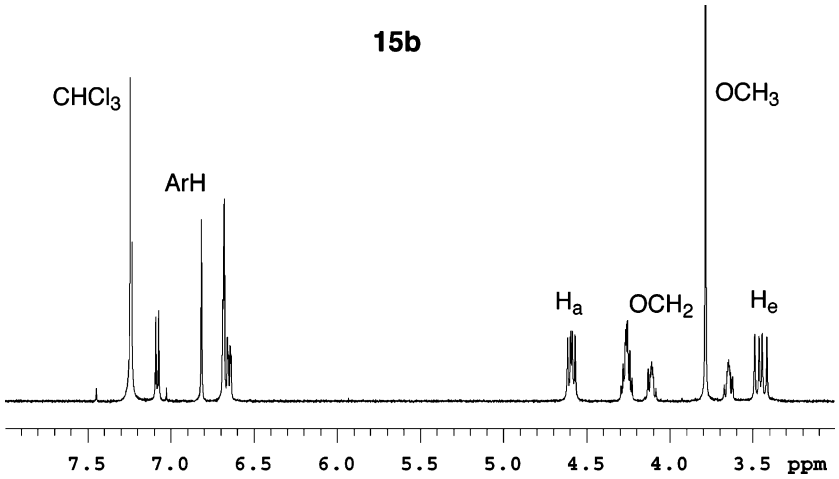


FIGURE 1. 500 MHz ^{1}H NMR spectrum of *syn*-cryptophane-D **15b** ($CDCl_3$).

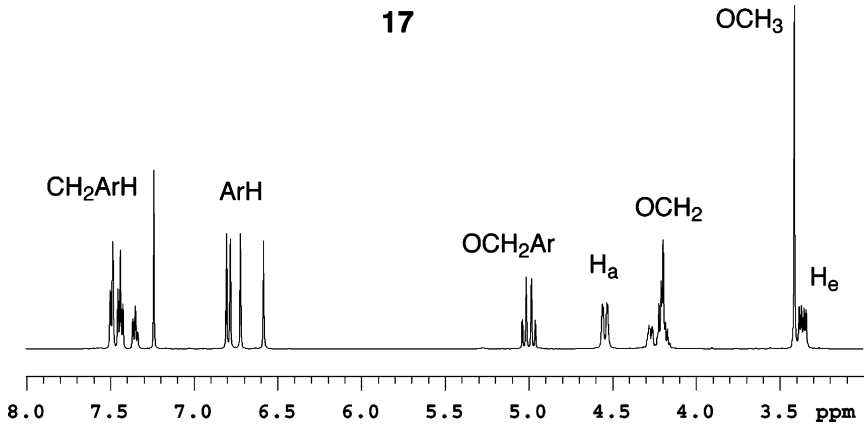
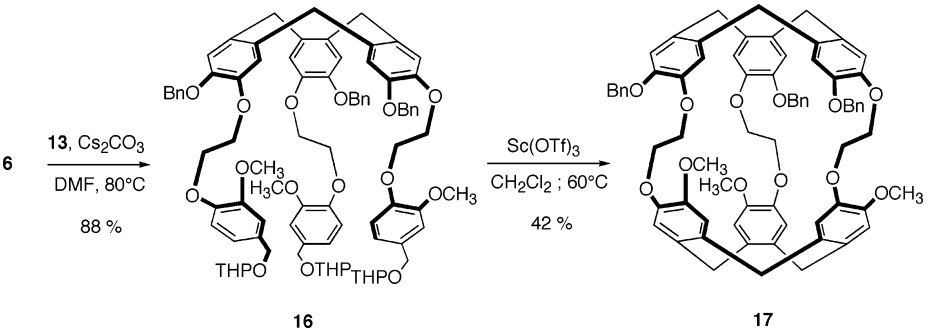


FIGURE 2. 500 MHz ^{1}H NMR spectrum of *anti*-cryptophane **17** ($CDCl_3$).

SCHEME 3



and cryptophanes: $Sc(OTf)_3$ is an environmentally safe Lewis acid and reduces the amount of solvents in the preparation of cryptophane by the template method (both catalyst and solvent can be easily recovered and reused). Importantly, the use of $Sc(OTf)_3$ catalyst, strongly reduces the formation of side-products and facilitates the purification steps. This was exemplified by the formation and the purification of *syn*-cryptophane-D **15b** prepared in moderate yield from compound **14**. Furthermore, $Sc(OTf)_3$ allowed the formation of new cryptophanes, which could not be easily prepared or purified by the previous procedures. For instance, cryptophane **17** was isolated in fairly good yield, but could not be obtained when formic acid was used as solvent. $Sc(OTf)_3$ appears therefore as a very promising reagent for the formation of more complex cryptophanes derivatives such as multiprotected cryptophanes and will probably contribute significantly to the design of new original molecules.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 499.83 and 125.7 MHz, respectively. Chemical shifts are in δ values from Me_4Si (^{1}H, ^{13}C). Multiplicities are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; $H_{a,e}$, H axial, equatorial. High-resolution mass analyses were recorded using LSIMS. Column chromatographic separations were carried out over silica gel 60 (0.040−0.063 mm). Analytical thin-layer chromatography (TLC) was performed on silica

gel TLC plates with F-254 indicator. Melting points were measured using differential scanning calorimeter. Solvents were distilled prior to use: DMF from CaH_2, CH_2Cl_2 from $CaCl_2$, THF from Na/benzophenone and NEt_3 from KOH. All other commercially available compounds were used without further purification.

3,4-Dimethoxybenzyl alcohol **1a** was commercially available. Benzyl alcohol **1b** was commercially available or was easily prepared from vanillyl alcohol.[37] Benzyl alcohols **1c**,[31] **1d**,[37] and **1e**,**f**[22] were prepared as described. Compounds **4**,[23] **7a**,[23] **9**,[29] **12**,[32] and **13**[23] were synthesized according to known procedures.

(4-Allyloxy-3-benzyloxyphenyl)methanol (1g). Sodium borohydride (1.62 g, 0.043 mol) was added in small portions to an ice-cooled solution of **5** (8.17 g, 0.031 mol) in methanol (50 mL). After complete addition, the solution was stirred at room temperature for 5 h. Then, most of the solvent was removed by rotary evaporation under reduced pressure. Water (100 mL) was added, and the solution was slowly acidified with a concd HCl solution at 0 °C. The white precipitate was then extracted twice with ethyl acetate. The combined organic layers were then washed with brine and dried over sodium sulfate. Evaporation of the solvent gave a residue, which was purified by column chromatography (AcOEt). The combined fractions were evaporated under reduced pressure to give **1g** as a white crystalline compound (7.9 g, 94%): mp (DSC) 61 °C; TLC R_f 0.83 (AcOEt); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.435 (m, 2H, Ar), 7.35 (m, 2H, Ar), 7.28 (m, 1H, Ar), 6.95 (s, 1H, Ar), 6.865 (m, 2H, Ar), 6.05 (m, 1H), 5.395 (m, 1H), 5.34 (m, 1H), 5.13 (m, 2H), 4.60 (m, 2H, OCH_2), 4.55 (d, 2H, OCH_2, ^3J = 6.0 Hz), 1.58 (t, 1H, OH, ^3J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 148.69, 148.09, 137.10, 134.07, 133.38, 128.39 (2C), 127.69, 127.18 (2C), 119.94, 117.45, 114.23, 113.64, 70.90, 69.97, 64.91. Anal. Calcd for $C_{17}H_{18}O_3$ (270.327): C, 75.53; H, 6.71. Found: C, 75.54; H, 6.84.

2-(4-Allyloxy-3-benzyloxybenzyloxy)tetrahydropyran (1h). A solution of PPTS (0.64 g, 0.026 mol) dissolved in CH_2Cl_2 (10 mL) was added in one portion to a stirred solution of **1g** (6.9 g, 0.026 mol) and DHP (3.22 g, 0.038 mol) in THF (100 mL) at room temperature. The solution was stirred overnight at room temperature. The solvent was then evaporated under reduced pressure, and the residue was extracted with diethyl ether. The organic layer was washed twice with brine and then dried over sodium sulfate. The solvent was evaporated under reduced pressure to leave a residue, which was purified by chromatography (Et_2O/pentane: 50/50). Evaporation of the solvent gave white crystals of compound **1h** (7.74 g, 84%): mp (DSC) 46.5 °C; TLC R_f 0.83 (Et_2O/pentane 50/50); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.43 (m, 2H, Ar), 7.34 (m, 2H, Ar), 7.27 (m, 1H, Ar), 6.94 (s, 1H, Ar), 6.86 (m, 2H, Ar), 6.05 (m, 1H), 5.39 (m, 1H), 5.25 (m, 1H), 5.14 (m, 2H, OCH_2), 4.65 (d, 1H, ^2J = 11.5 Hz), 4.60 (m, 3H), 4.375 (d, 1H, ^2J = 11.5 Hz), 3.85 (m, 1H), 3.49 (m, 1H), 1.86−1.74 (m, 1H), 1.72−1.63 (m, 1H), 1.62−1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 148.66, 148.25, 137.29, 133.53, 131.31, 128.38 (2C), 127.65, 127.19 (2C), 121.03, 117.38, 114.76, 114.25, 97.39, 71.08, 70.07, 68.48, 62.10, 31.52, 25.42, 19.35. Anal. Calcd for $C_{22}H_{26}O_4$ (254.445): C, 74.55; H, 7.39. Found: C, 74.65; H, 7.45.

General Method for the Synthesis of CTV Derivatives with Sc(OTf)$_3$. Method A. 2,3,7,8,12,13-Hexamethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2a. A solution of scandium triflate (0.128 g, 0.3 mmol) and 3,4-dimethoxybenzyl alcohol **1a** (5.0 g, 30 mmol) in acetonitrile (30 mL) was stirred at 60 °C for 18 h under argon. Acetonitrile was removed by rotary evaporation and the residue extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to leave a yellow residue. Addition of AcOEt allows the precipitation of **2a**, which was collected on a frit and washed with a small amount of AcOEt and diethyl ether. The solid was then recrystallized from CH_2Cl_2/pentane mixture to give **2a** as a white solid (2.0 g, 44%): mp (DSC) 230.5 °C (lit.[12] 232 °C).

2,7,12,-Triethoxy-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2b. According to method A, 4-ethoxy-3-methoxybenzyl alcohol **1b** (2.0 g, 11.8 mmol) and scandium triflate (0.051 g, 0.12 mmol) in acetonitrile gave compound **2b** (0.92 g, 48%) after purification by column chromatography (AcOEt/CH_2Cl_2: 80/20): mp (DSC) 172 °C (lit.[37] 172 °C).

2,7,12-Triallyloxy-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2c. (a) Procedure Using Acetonitrile as Solvent. According to general procedure A, 4-allyloxy-3-methoxybenzyl alcohol **1c** (20.0 g, 104.0 mmol) and scandium triflate (0.45 g, 1.04 mmol) in acetonitrile (50 mL) gave compound **2c** (9.0 g, 50%) after purification by column chromatography (CH_2Cl_2/Et_2O: 95:5). **(b) Procedure Using Dichloromethane as Solvent.** According to general procedure A, **1c** (5.0 g, 25.8 mmol) and scandium triflate (0.127 g, 0.26 mmol) in dichloromethane (50 mL) gave compound **2c** (2.5 g, 55%) after purification by column chromatography (CH_2Cl_2/Et_2O: 95/5): mp (DSC) 168 °C (lit.[21] 172 °C).

2,7,12-Triallyloxy-3,8,13-triethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2d. (a) Procedure Using Acetonitrile as Solvent. According to method A, 4-allyloxy-3-ethoxybenzyl alcohol **1d** (2.0 g, 9.15 mmol) and scandium triflate (0.047 g, 0.1 mmol) in acetonitrile (20 mL) gave compound **2d** (0.8 g, 43%) after purification by column chromatography (CH_2Cl_2/Et_2O: 95/5): mp (DSC) 116 °C (lit.[37] 116 °C); ^{1}H NMR ($CDCl_3$, 20 °C) δ 6.83 (s, 3H, Ar), 6.79 (s, 3H, Ar), 6.03 (m, 3H, Ar), 5.35 (m, 3H), 5.21 (m, 3H), 4.69 (d, 3H, H_a, ^2J = 14.0 Hz), 4.54 (m, 6H), 4.03 (m, 6H, OCH_2), 3.47 (d, 3H, H_e, ^2J = 14.0 Hz), 1.38 (t, 9H, CH_3, ^2J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 147.64 (3C), 147.30 (3C), 134.02 (3C), 132.61 (3C), 132.09 (3C), 117.03 (3C), 116.58 (3C), 114.94 (3C), 70.49 (3C, OCH_2), 64.84 (3C, OCH_2), 36.43 (3C, $C_{a,e}$), 14.92 (3C, CH_3). Anal. Calcd for $C_{36}H_{42}O_6$ (570.724): C, 75.76; H, 7.41. Found: C, 75.48; H, 7.52. **(b) Procedure Using Dichloromethane as Solvent.** According to method A, **1d** (2.0 g, 9.15 mmol) and scandium triflate (0.048 g, 0.11 mmol) in CH_2Cl_2 (20 mL) gave compound **2d** (0.86 g, 47%) after purification by column chromatography (CH_2Cl_2/Et_2O: 95/5).

2,7,12,-Trimethoxy-3,8,13-trimethylthio-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2e. (a) From 1e. According to method A, 4-methoxy-3-methylthiobenzyl alcohol **1e** (2.2 g, 12.0 mmol) and scandium triflate (0.052 g, 0.12 mmol) in acetonitrile (40 mL) gave compound **2e** (0.95 g, 48%) after purification by column chromatography (CH_2Cl_2/hexane: 99/1): mp (DSC) 242 °C (lit.[22] 238 °C). **(b) From 1f.** According to general procedure A, 3-methoxy-4-methylthiobenzyl alcohol **1f** (1.0 g, 5.4 mmol) and scandium triflate (0.023 g, 0.05 mmol) in acetonitrile gave compound **2e** (0.28 g, 31%) after purification by column chromatography (CH_2Cl_2/hexane: 99/1).

2,7,12-Triallyloxy-3,8,13-tribenzyloxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene 2f. (a) From 1g. Scandium triflate (0.016 g, 0.037 mmol) was added in one portion to a stirred solution of benzyl alcohol **1g** (0.93 g, 3.45 mmol) in acetonitrile (20 mL). The solution was stirred at 60 °C for 18 h under argon. The solvent was then removed under reduced pressure and the remaining residue extracted twice with dichloromethane. The combined organic layers were then washed with brine and dried over sodium sulfate. Filtration and removal of the solvent by rotary evaporation afforded a residue, which was then purified by column chromatography (CH_2Cl_2/pentane: 50/50, then gradient 60/40, 70/30, 80/20). Removal of the solvent gave compound **2f** as a white crystalline solid (0.32 g, 37%): mp (DSC) 122 °C; TLC R_f 0.94 (CH_2Cl_2/Et_2O: 95/5); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.40 (m, 6H, Ar), 7.33 (m, 6H, Ar), 7.27 (m, 3H, Ar), 6.83 (s, 3H, Ar), 6.73 (s, 3H, Ar), 6.03 (m, 1H), 5.23 (m, 3H), 5.07 (s, 6H, OCH_2), 4.65 (d,

(37) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299−1308.

3H, H_a, ^2J = 14.0 Hz), 4.47 (m, 6H, OCH_2), 3.425 (d, 3H, H_e, ^2J = 14.0 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 147.69, 147.56, 137.55, 133.82, 132.68, 132.41, 128.49 (2C), 127.75, 127.06 (2C), 117.25, 116.92, 116.47, 71.74, 70.34, 36.45. Anal. Calcd for $C_{51}H_{48}O_6$ (756, 9366): C, 80.93; H, 6.39. Found: C, 80.93; H, 6.67. **(b) From 1h.** Scandium triflate (0.025 g, 0.056 mmol) dissolved in acetonitrile (5 mL) was added in one portion to a stirred solution of **1h** (2.0 g, 0.0056 mol) in acetonitrile (25 mL). The solution was stirred at 60 °C for 48 h under argon. Acetonitrile was then removed in a vacuum to give a residue, which was extracted twice with dichloromethane. The combined organic layers were then washed with water and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (CH_2Cl_2). Crystallization from CH_2Cl_2/pentane mixture gave white crystals, which were collected on a frit and washed with a mixture of diethyl ether and pentane (0.47 g, 33%).

4-Allyloxy-3-benzyloxybenzaldehyde 5. Benzyl bromide (6.34 g, 0.037 mol) was added in one portion to a stirred mixture of potassium carbonate (5.11 g, 0.037 mol) and compound **4** (6.0 g, 0.034 mol) in DMF (70 mL). The mixture was stirred overnight at 80 °C under argon and then poured into water. The product was then extracted three times with ethyl acetate. The combined organic layers were then washed five times with brine to remove DMF and then dried over sodium sulfate. Evaporation of the solvent under reduce pressure gave a residue, which was purified by column chromatography (AcOEt/pentane: 50/50). Evaporation of the solvent afforded compound **5** as a slight yellow crystalline compound (8.72 g, 97%): mp (DSC) 49 °C; TLC R_f 0.88 (AcOEt/pentane: 50/50); ^{1}H NMR ($CDCl_3$, 20 °C) δ 9.80 (s, 1H, CHO), 7.45 (d, 1H, Ar, ^4J = 2.0 Hz), 7.44 (m, 2H, Ar), 7.42 (dd, 1H, Ar, ^4J = 2.0 Hz, ^3J = 8.0 Hz), 7.36 (m, 2H, Ar), 7.30 (m, 1H, Ar), 6.98 (d, 1H, Ar, ^3J = 8.0 Hz), 6.06 (m, 1H), 5.44 (m, 1H), 5.31 (m, 1H), 5.18 (s, 2H, OCH_2), 4.69 (m, 2H, OCH_2); ^{13}C NMR ($CDCl_3$, 20 °C) δ 154.06, 148.90, 136.43, 132.32, 130.06, 128.48 (2C), 127.92, 127.23 (2C), 126.54, 118.07, 112.44, 112.07, 70.80, 69.57. Anal. Calcd for $C_{17}H_{16}O_3$ (268,3116): C, 76.10; H, 6.0. Found: C, 76.10; H, 6.07.

3,8,13-Tribenzyloxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]-cyclononene-2,7,12-triol 6. Compound **2f** (0.175 g, 0.23 mmol), PPh_3 (0.010 g, 0.38 mmol), THF (4 mL), diethylamine (1.6 mL), palladium acetate (0.005 g, 0.022 mmol), and water (0.8 mL) were mixed in a 25 mL flask. The mixture was stirred at 80 °C for 4 h 30 under argon. The solvent was then removed under reduced pressure and the residue extracted three times with AcOEt. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent afforded a residue, which was purified by column chromatography (CH_2Cl_2/EtOH: 99/1). Evaporation of the solvent gave **6** as a white crystalline compound (0.120 g, 81%): mp (DSC) 144.5 °C (first polymorph crystalline structure); TLC R_f 0.71 (CH_2Cl_2/ethanol: 99/1); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.40−7.33 (m, 15H, Ar), 6.85 (s, 3H, Ar), 6.82 (s, 3H, Ar), 5.42 (s, 3H, OH), 6.02 (m, 6H, OCH_2), 4.77 (d, 3H, H_a, ^2J = 14.0 Hz), 3.45 (d, 3H, H_e, ^2J = 14.0 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 144.66 (3 C), 144.59 (3 C), 136.60 (3 C), 133.07 (3 C), 131.21 (3 C), 128.74 (3 C), 128.37 (6 C), 127.88 (6 C), 115.74 (3 C), 114.12 (3 C), 71.53 (3 C), 36.36 (3 C); HRMS calcd for $C_{42}H_{36}O_6$ ($M^{\bullet+}$) 636.2512, found 636.2514. Anal. Calcd for $C_{42}H_{36}O_6$, 0.5 H_2O (645.7504): C, 78.06; H, 5.78. Found: C, 78.12; H, 5.66.

Compound 7b. This compound was prepared according to a known procedure from 2-[4-(3-iodopropoxy)-3-methoxybenzyloxy]tetrahydropyran (2.51 g, 6.17 mmol),[28] CTV **9** (0.7 g, 1.71 mmol), and cesium carbonate (3.35 g, 10.3 mmol) in DMF (30 mL). Purification by column chromatography gave **7b** as a glassy solid (1.6 g, 75%): ^{1}H NMR ($CDCl_3$, 20 °C) δ 6.91 (s, 3H, Ar), 6.88 (s, 3H, Ar), 6.86−6.82 (m, 9H, Ar), 4.71 (d, 3H, H_a, ^2J = 14.0 Hz), 4.69 (d, 3H, ^2J = 11.5 Hz), 4.65 (m, 3H), 4.41 (d, 3H, ^2J = 11.5 Hz), 4.26−4.12 (m, 12H, OCH_2), 3.90 (m, 3H), 3.82 (s, 9H, OCH_3), 3.71 (s, 9H, OCH_3), 3.53 (m, 3H), 3.49 (d, 3H, H_e, ^2J = 14.0 Hz), 2.78 (q, 3H, CH_2, ^3J = 7.0 Hz), 2.66 (q, 3H, CH_2, ^3J = 7.0 Hz), 1.90−1.80 (m, 3H), 1.74−1.67 (m, 3H), 1.64−1.48 (m, 12H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 149.31 (3C), 148.13 (3C), 147.76 (3C), 146.83 (3C), 132.12 (3C), 131.77 (3C), 130.98 (3C), 120.51 (3C), 115.09 (3C), 113.55 (3C), 112.86 (3C), 111.70 (3C), 97.46 (3C), 68.69 (3C, OCH_2), 65.84 (3C, OCH_2), 65.58 (3C, OCH_2), 62.24 (3C, OCH_2), 56.01 (3C, OCH_3), 55.78 (3C, OCH_3), 36.35 (3C), 30.55 (3C), 29.06 (3C), 19.43 (3C); HRMS calcd for $C_{72}H_{90}O_{18}$ ($M^{\bullet+}$) 1242.6127, found 1242.6131.

[4-[2-(12-[2-(4-hydroxymethyl-2-methoxyphenoxy)-ethoxy]-3,8,13-trimethoxy-7-[3-[2-methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]propoxy]-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2-yloxy)ethoxy]-3-methoxyphenyl]methanol (7c). This compound was prepared according to a known procedure from 7,12-bis[2-(4-hydroxymethyl-2-methoxyphenoxy)ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononen-2-ol (0.5 g, 0.65 mmol),[38] 2-[4-(3-iodopropoxy)-3-methoxybenzyloxy]tetrahydropyran (0.33 g, 0.81 mmol),[28] and cesium carbonate (0.32 g, 0.98 mmol) in DMF (30 mL). Purification by column chromatography (AcOEt/EtOH: 98/2) gave compound **7c** as a glassy solid (0.48 g, 70%): TLC R_f 0.31 (AcOEt/EtOH: 98:2); ^{1}H NMR ($CDCl_3$, 20 °C) δ 6.985 (s, 1H, Ar), 6.98 (s, 1H, Ar), 6.92 (s, 1H, Ar), 6.90−6.84 (m, 8H, Ar), 6.81−6.77 (m, 4H, Ar), 4.71 (d, 2H, H_a, ^2J = 14.0 Hz), 4.709 (d, 1H, H_a, ^2J = 14.0 Hz), 4.685 (d, 1H, ^2J = 11.5 Hz), 4.652 (m, 1H), 4.585 (d, 4H, OCH_2, ^3J = 6.0 Hz), 4.411 (d, 1H, ^2J = 11.5 Hz), 4.40−4.30 (m, 8H, OCH_2), 4.26−4.14 (m, 4H, OCH_2), 3.90 (m, 1H), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.52 (m, 1H), 3.505 (d, 2H, H_e, ^2J = 14.0 Hz), 3.50 (d, 1H, H_e, ^2J = 14.0 Hz), 2.285 (q, 1H, CH_2, ^3J = 6.0 Hz), 2.27 (q, 1H, CH_2, ^3J = 6.0 Hz), 1.88−1.78 (m, 1H), 1.73 (t, 1H, OH, ^3J = 6.0 Hz), 1.72 (t, 1H, OH, ^3J = 6.0 Hz), 1.76−1.68 (m, 1H), 1.64−1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 149.82 (2C), 149.51, 148.59 (2C), 148.28, 147.89, 147.59 (2C), 147.02, 146.89 (2C), 134.68 (2C), 133.14 (2C), 132.23, 132.01, 131.89 (2C), 131.19, 120.56, 119.37 (2C), 116.97 (2C), 115.46, 114.19 (2C), 114.02 (2C), 113.83, 113.22, 111.96, 111.13 (2C), 97.57, 68.74 (1C, OCH_2), 68.32 (2C, OCH_2), 67.96 (2C, OCH_2), 66.08 (1C, OCH_2), 65.79 (1C, OCH_2), 65.14 (1C, OCH_2), 62.26 (1C, OCH_2), 56.17 (3C, OCH_3), 55.88 (1C, OCH_3), 55.78 (2C, OCH_3), 36.38 (3C, $C_{a,e}$), 30.59, 29.22 (1C, CH_2), 25.45, 19.46; HRMS calcd for $C_{60}H_{70}O_{16}$ ($M^{\bullet+}$) 1046.4664, found 1046.4663.

General Method for the Synthesis of Cryptophanes Using Sc(OTf)$_3$. Method B. *anti*-Cryptophane-A 8a. A solution of cryptophane precursor **7a** (0.5 g, 0.42 mmol) in CH_2Cl_2 (130 mL) was added at 60 °C over a period of 25−30 h to a stirred suspension of scandium triflate (0.180 g, 0.42 mmol) in CH_2Cl_2 (30 mL). After complete addition, the solution was stirred at 60 °C for 48 h. The solution was then poured into water and the organic layer extracted once with water and dried over sodium sulfate. The solvent was removed under vacuum to give a residue, which was purified by column chromatography (CH_2Cl_2/acetone: 90/10). Evaporation of the solvent afforded compound **8a** (0.18 g, 51%). The 500 MHz ^{1}H NMR spectrum is identical to that previously reported.[36]

***anti*-Cryptophane-E 8b.** According to method B, cryptophane precursor **7b** (0.5 g, 0.4 mmol) and scandium triflate (0.174 g, 0.4 mmol) in CH_2Cl_2 (160 mL) gave derivative **8b** (0.105 g, 28%) after purification by column chromatography (CH_2Cl_2/acetone: 90/10). The 500 MHz ^{1}H NMR spectrum is identical to that previously reported.[26]

***anti*-Cryptophane-223 8c.** According to method B, cryptophane precursor **7c** (0.39 g, 0.37 mmol) and scandium triflate (0.161 g, 0.37 mmol) in CH_2Cl_2 (160 mL) gave compound **8c** (0.11 g, 33%) after purification by column chromatography (CH_2Cl_2/acetone: 90:10). The 500 MHz ^{1}H NMR spectrum is identical to that previously reported.[28]

Compound 10. A solution of triflic anhydride (1.5 mL) was slowly added under argon to an ice-cooled solution of **9** (1.0 g,

(38) Darzac, M.; Brotin, T.; Rousset-Arzel, L.; Bouchu, D.; Dutasta, J. P. *New J. Chem.* **2004**, *28*, 502−512.

2.45 mmol) in a mixture of pyridine (8 mL) and CH_2Cl_2 (15 mL). After addition, the solution was allowed to warm to room temperature and stirred for 18 h. Water was then added, and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and dried other sodium sulfate. Filtration and evaporation of the solvent afforded a residue, which was purified by column chromatography (CH_2Cl_2). Evaporation of the solvent gave compound **10** as a slight yellow solid (1.5 g, 85%): mp (DSC) 210 °C; TLC R_f 0.93 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.17 (s, 3H, Ar), 6.89 (s, 3H, Ar), 4.73 (d, 3H, H_a, ^2J = 15.0 Hz), 3.86 (s, 9H, OCH_3), 3.64 (d, 3H, H^e, ^2J = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 150.66 (3C), 140.88 (3C), 137.90 (3C), 131.67 (3C), 124.29 (3C), 119.28 (q, 3C, CF_3, $^1J_{CF}$ = 321.6 Hz), 115.01 (3C), 56.81 (3C, OCH_3), 36.70 (3C, $C_{a,e}$); HRMS calcd for $C_{27}H_{21}O_{12}S_3F_9$ ($M^{\bullet+}$) 804.0051, found 804.0051. Anal. Calcd for $C_{27}H_{21}O_{12}S_3F_9 \cdot CH_2Cl_2$ (889.566): C, 37.80; H, 2.60; S, 10.81. Found: C, 37.57; H, 2.51; S, 10.81.

Compound 11. Compound **10** (1.45 g, 1.79 mmol), dppp (0.33 g, 0.8 mmol), tributylamine (7.18 g, 1.55 mmol), dichlorobis(triphenylphosphine)palladium (0.391 g, 0.56 mmol), formic acid (0.94 mL), and DMF (9.5 mL) were mixed in a 25 mL three-neck flask. The solution was heated at 100 °C for 18 h under argon. Then, water was added, and the product was extracted with CH_2Cl_2. The organic layer was washed several times with water and dried over sodium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (CH_2Cl_2/pentane: 70/30). Evaporation of the solvent gave compound **11** as a white solid (0.460 g, 71%). The ^{1}H NMR spectrum is identical to that previously reported.[31]

Compound 14. Compound **13** (0.91 g, 2.63 mmol) was added to a solution of CTV **12** (0.209 g, 0.73 mmol) and cesium carbonate (0.95 g, 2.92 mmol) in DMF (15 mL). The mixture was stirred at 80 °C for 18 h under argon. The mixture was then poured into water and extracted twice with chloroform. The combined organic layers were dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum gave a very insoluble solid, which was washed on a frit with diethyl ether to afford **14** (0.57 g, 70%) as a white solid: mp (DSC) 111 °C; ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.24 (d, 3H, Ar, ^3J = 8.0 Hz), 6.91 (d, 3H, Ar, ^4J = 2.0 Hz), 6.90−6.86 (m, 9H, Ar), 6.64 (dd, 3H, Ar, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 4.73 (d, 3H, H_a, ^2J = 13.5 Hz), 4.70 (d, 3H, ^2J = 12.0 Hz), 4.65 (m, 3H), 4.42 (d, 3H, ^2J = 12.0 Hz), 4.31−4.22 (m, 12 H, OCH_2), 3.91 (m, 3H), 3.83 (s, 9H, OCH_3), 3.61 (d, 3H, H_e, ^2J = 12.0 Hz), 3.53 (m, 3H), 1.88−1.79 (m, 3H), 1.75−1.68 (m, 3H), 1.64−1.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 157.26 (3C), 149.57 (3C), 147.50 (3C), 141.01 (3C), 131.78 (3C), 131.63 (3C), 131.00 (3C), 120.45 (3C), 116.09 (3C), 113.78 (3C), 112.84 (3C), 111.89 (3C), 68.68 (3C, OCH_2), 67.62 (3C, OCH_2), 66.23 (3C, OCH_2), 62.25 (3C, OCH_2), 55.85 (3C, OCH_3), 36.48 (3C, $C_{a,e}$), 30.56 (3C), 25.41 (3C), 19.45 (3C); HRMS calcd for $C_{66}H_{78}O_{15}$ ($M^{\bullet+}$) 1110.5441, found 1110.5449. Anal. Calcd for $C_{66}H_{78}O_{15}$ (1111.333): C, 71.33; H, 7.07. Found: C, 71.06; H, 7.18.

Cryptophanes 15a and 15b. According to method B, cryptophane precursor **14** (0.413 g, 0.37 mmol) and scandium triflate (0.160 g, 0.37 mmol) in acetonitrile (160 mL) gave a mixture of cryptophanes **15a** (0.13 g, 50%) and **15b** (0.021 g, 8%) after purification by column chromatography (CH_2Cl_2/acetone: 90/10). Spectral data of compound **15a** and **15b** are identical to those previously reported.[34] Additional information for compound **15a**: ^{13}C NMR ($CDCl_3$, 20 °C) δ 156.55 (3C), 148.54 (3C), 147.34 (3C), 141.06 (3C), 132.84 (3C), 132.18 (3C), 131.75 (3C), 130.83 (3C), 119.40 (3C), 116.76 (3C), 114.91 (3C), 111.78 (3C), 66.90 (3C, OCH_2), 65.43 (3C, OCH_2), 56.54 (3C, OCH_3), 36.24 (3C, $C_{a,e}$), 36.02 (3C, $C_{a,e}$); additional information for compound **15b**: ^{13}C NMR ($CDCl_3$, 20 °C) δ 157.14 (3C), 150.01 (3C), 140.83 (3C), 134.70 (3C), 132.29 (3C), 131.92 (3C), 130.80 (3C), 121.20 (3C), 119.03 (3C), 114.10 (3C), 113.34 (3C), 71.46 (3C, OCH_2), 66.05 (3C, OCH_2), 56.13 (3C, OCH_3), 36.29 (3C, $C_{a,e}$), 36.03 (3C, $C_{a,e}$).

Compound 16. Compound **13** (0.4 g, 1.15 mmol) was added in one portion to a stirred solution of CTV **6** (0.205 g, 0.32 mmol) and cesium carbonate (0.415 g, 1.28 mmol) in DMF (9 mL). The mixture was stirred at 80 °C for 18 h under argon and then poured into water and extracted three times with AcOEt. The combined organic layers were washed five times with water to remove the remaining DMF and then dried over sodium sulfate. Filtration and evaporation of the solvent gave a yellow residue, which was purified by column chromatography (AcOEt/pentane: 50/50, then AcOEt/pentane: 70/30). Evaporation of the solvent under vacuum afforded **16** as a yellow oil (0.39 g, 85%): TLC R_f 0.55 (AcOEt/pentane: 50/50); ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.34−7.32 (m, 6H, Ar), 7.30−7.22 (m, 9H, Ar), 6.88−6.78 (m, 12H, Ar), 6.81−6.79 (m, 3H, Ar), 5.01 (s, 6H), 4.69−4.64 (m, 9H, CH_2 + H_a), 4.40 (d, 3H, ^2J = 11.5 Hz), 4.36−4.22 (m, 12 H, OCH_2), 3.90 (m, 1H), 3.77 (s, 9H, OCH_3), 3.52 (m, 1H), 3.45 (d, 3H, H_e, ^2J = 14.0 Hz), 1.88−1.78 (m, 3H), 1.74−1.66 (m, 3H), 1.64−1.46 (m, 12 H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 149.60 (3C), 147.89 (3C), 147.78 (3C), 147.73 (3C), 137.52 (3C), 132.92 (3C), 132.81 (3C), 131.56 (3C), 128.38 (6C), 127.62 (3C), 127.22 (6C), 120.51 (3C), 117.30 (3C), 117.22 (3C), 113.83 (3C), 112.0 (3C), 97.52 (3C), 71.81 (3C), 68.68 (3C), 68.49 (3C), 67.94 (3C), 62.22 (3C), 55.80 (3C), 36.37 (3C), 30.57 (3C), 25.44 (3C), 19.44 (3C); ESI MS *m/z* $[M + H]^+$ 1123.3.

Cryptophane 17. According to method B, a solution of cryptophane precursor **16** (0.45 g, 0.32 mmol) in CH_2Cl_2 (130 mL) was added at 60 °C over a period of 25−30 h to a stirred suspension of scandium triflate (0.136 g, 0.32 mmol) in CH_2Cl_2 (30 mL). After complete addition, the solution was stirred at 60 °C for 48 h. The solution was then poured into water and the organic layer extracted once with water and dried over sodium sulfate. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (CH_2Cl_2/acetone: 98/2). Evaporation of the solvent afforded compound **17** as a white solid (0.15 g, 42%), which was then washed on a frit with small amounts of diethyl ether and pentane: mp (DSC) dec above 310 °C; ^{1}H NMR ($CDCl_3$, 20 °C) δ 7.49 (m, 6H, Ar), 7.44 (m, 6H, Ar), 7.35 (m, 3H, Ar), 6.81 (s, 3H, Ar), 6.78 (s, 3H, Ar), 6.72 (s, 3H, Ar), 6.58 (s, 3H, Ar), 5.02 (d, 3H, OCH_2, ^2J = 11.5 Hz), 4.98 (d, 3H, OCH_2, ^2J = 11.5 Hz), 4.55 (d, 6H, H_a, ^2J = 13.5 Hz), 4.30−4.16 (m, 12 H, OCH_2), 3.41 (s, 9H, OCH_3), 3.37 (d, 3H, H_e, ^2J = 13.5 Hz), 3.36 (d, 3H, H_e, ^2J = 13.5 Hz); ^{13}C NMR ($CDCl_3$, 20 °C) δ 149.71 (3C), 149.14 (3C), 147.79 (3C), 146.64 (3C), 137.28 (3C), 134.31 (3C), 134.07 (3C), 132.78 (3C), 131.60 (3C), 128.55 (6C), 127.86 (3C), 126.96 (6C), 122.103 (3C), 120.63 (3C), 117.71 (3C), 114.30 (3C), 71.71 (3C), 69.63 (3C), 69.31 (3C), 55.81 (3C), 36.13 (6C); HRMS calcd for $C_{72}H_{66}O_{12}$ ($M^{\bullet+}$) 1122.4554, found 1122.4549.

JO050495G