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Broad Functionalization of Deep-Cavity Cavitands by Directed *ortho* Metalation

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The *endo*- and *exo*-rim positions of deep-cavity cavitand **1** were functionalized by directed *ortho* metalation (D*o*M) procedures. A range of electrophilic quenchers led to hosts with ester, phenol and thioether functionality. In each case, a combination of host pre-organization and reaction control resulted in far fewer products than the theoretical sixty-nine. In addition to the nature of the lithiate, functionalization patterns were also dependent on the electrophile, with a general trend that the non-carbon electrophiles examined gave higher degrees of substitution.

Introduction

"Concavity" and "functionality" are two basic qualities that warrant consideration in designing enzyme mimics. Concavity is required for selectivity (the "specific sub-site" in the parlance of biochemists), while the functionality engenders catalysis (the "reaction sub-site"). Resorcinarene-based cavitands[1–3] are attractive tools in this context, as they possess a pre-organized cavity that can be tuned to selectively bind substrates,[4] and they possess suitable sites for the attachment of functional groups around their cavity. Combining these two facets have therefore led to some promising results.[5]

The commonly employed protocols for introducing functionalities to the concave surface of simple methylene-bridged cavitands involve halogen–metal exchange procedures[1c,6] or nucleophilic substitution on inherent halomethyl groups.[7] The deep-cavity cavitand **1** (Figure 1, a) reported from our laboratory functions as a versatile host for a variety of guests.[4f,8] To expand its scope to supramolecular catalysis, we are in search of ways to introduce suitable functionalities to its concave surface. Towards this, we recently reported two protocols, namely, directed *ortho* metalation (D*o*M)[9] and electrophilic substitution[10] to incorporate a range of functional groups to the rim of such cavitands. The former,[9] demonstrated that **1** possesses two kinds of weakly acidic rim positions: four positions pointing inward termed "*endo*" and four positions pointing with the cavity wall termed "*exo*" (Figure 1). We report here on the extension of this D*o*M strategy for functionalizing deep-cavity cavitands. These results illustrate the generality

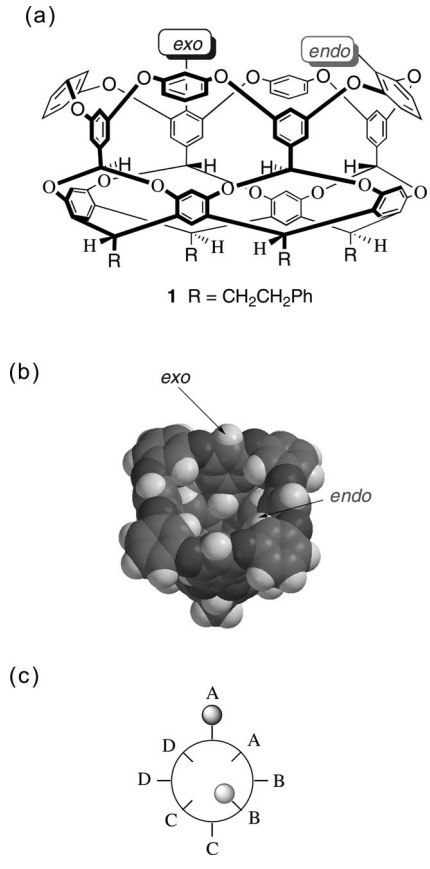

Figure 1. (a) Chemical structure and (b) space-filling model of cavitand **1**, showing the *endo* and *exo* positions. (c) Representation of a di-substituted cavitand to illustrate the nomenclature used (see text).

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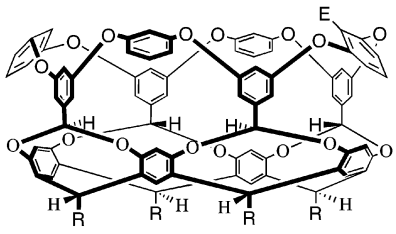
of the D*o*M strategy, and demonstrate how the procedure can lead to a wide variety of functionalized hosts with unprecedented substitution patterns.

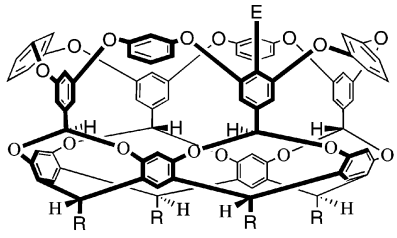
Results and Discussion

Cavitand **1** is available in three steps from commercially available materials, although we chose a four step process for economic reasons.[8a,8b] When **1** was treated with varying equivalents of butyllithium compounds and quenched with electrophiles, it afforded the corresponding functionalized cavitands. The following nomenclature is used to describe the various products (Figure 1, c). Looking down into the cavity, the *exo* positions are given priority and are labeled A–D in a clockwise manner. The *endo* positions are labeled similarly, starting at the position immediately clockwise to the *exo*-A position. The substitutions are given the lowest possible alphabetical designation. Thus, the di-substituted cavitand in Figure 1, c is termed A-*exo*, B-*endo*, whereas its enantiomer is named A-*exo*, C-*endo* (not shown).

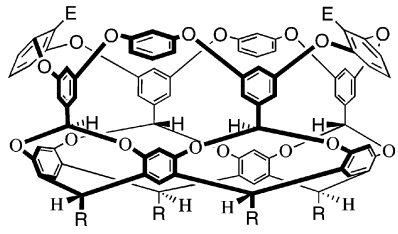
The first electrophile examined was methyl chloroformate, a quencher that converts the lithiates generated from **1** into their corresponding methyl esters; ester groups subsequently provide access to carboxylic acids, functionality that is repeatedly utilized by nature in enzyme catalysis. When 2.2 equiv. of *n*BuLi was used as a base, in addition to the starting material, the mono-*endo* ester **2** and



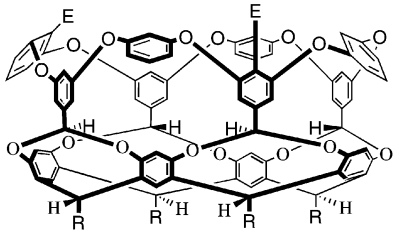
2 E = CO_2Me
11 E = OH



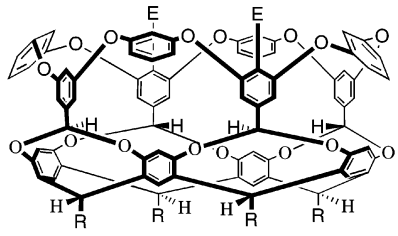
3 E = CO_2Me
12 E = OH



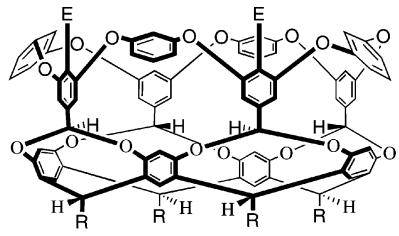
4 E = CO_2Me
18 E = SMe



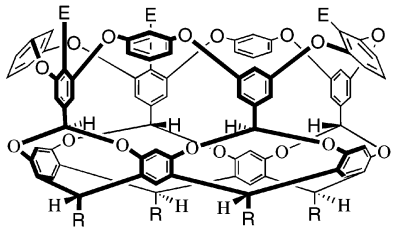
5 E = CO_2Me
19 E = SMe



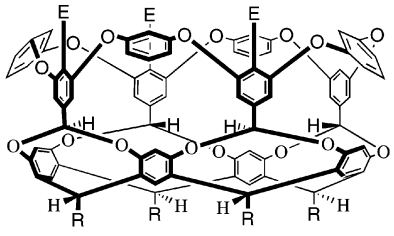
6 E = CO_2Me
13 E = OH
20 E = SMe



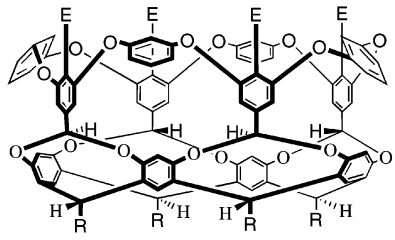
7 E = CO_2Me
14 E = OH



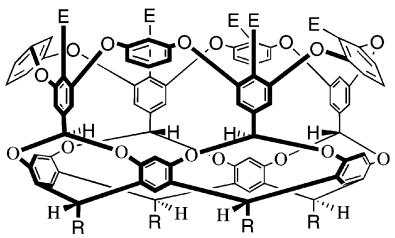
8 E = CO_2Me
21 E = SMe



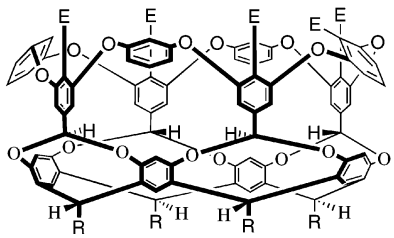
9 E = CO_2Me
15 E = OH
22 E = SMe



10 E = CO_2Me
16 E = OH
25 E = SMe



23 E = SMe



17 E = OH
24 E = SMe

Figure 2. Chemical structures of products arising from this study.

the mono-*exo* ester **3** were obtained (Table 1 and Figure 2). With 5.5 equiv. of *n*BuLi, the A/C-*endo* diester **4**, the chiral A-*exo*, B-*endo* diester **5** (and its enantiomer) and the two (inseparable) A/C- and A/B-*exo* diesters **6** and **7** were also isolated. Using 10 equiv. of base did not change the nature of the products, but did influence their yields. Switching the base to *s*BuLi resulted in a different functionalization pattern. For example, 5.5 equiv. afforded the A/B-*exo*, C-*endo* triester **8**, the A/B/C-*exo* triester **9** and the tetra-*exo* ester **10**. Using 10 equiv. gave the same three products, but increased the yield of the tetra-ester **10** to a remarkable 70%. The use of *t*BuLi gave little in the way of mono-substitution; with 5.5 equiv. di-, tri-, and tetra esters were formed, whilst 10 equiv. produced tri- and tetra-esters. To sum up, paralleling dimethylformamide,[9] methyl chloroformate gave a range of ten esters, from mono- through to tetra-substitutions, with *n*BuLi giving mono- and di-substitution, *s*BuLi giving tri- and tetra-, and *t*BuLi giving di-, tri-, and tetra-substitution.

Table 1. Range and yield of products arising from treatment of **1** with different butyllithium compounds and quenching with $ClCO_2Me$.[a]

Base	Equiv.	Range and yield (%) of products								
		1	**2**	**3**	**4**	**5**[b]	**6/7**[c]	**8**	**9**	**10**
*n*BuLi	2.2	28	29	28	–	–	–	–	–	–
	5.5	12	12	22	8	14	23	–	–	–
	10	2	4	10	10	28	22	–	–	–
*s*BuLi	5.5	–	–	–	–	–	–	30	27	37
	10	–	–	–	–	–	–	12	12	70
*t*BuLi	5.5	–	–	–	10	18	15	14	22	11
	10	–	–	–	–	–	–	20	13	62

[a] All reactions were run in THF at –78 °C; yields are the average of at least two reactions. [b] Product is chiral and was isolated as racemate. [c] Compounds **6** and **7** could not be separated by column chromatography.

With similar product distributions seen for dimethylformamide[9] and methyl chloroformate, we were also interested in examining other, non-carbon electrophiles. As a first example, we chose trimethyl borate, the resulting borate cavitands being oxidized with alkaline H_2O_2 in situ to yield a range of phenols. With this electrophile, the extent of substitution with *n*BuLi increased to four groups whilst five could be introduced with *s*BuLi. Thus, the use of 2 equiv. of *n*BuLi gave in addition to starting material the readily separable mono-*endo* phenol **11** and the mono-*exo*-phenol **12**, a mixture of di-substituted products, and the A/B-*exo* diphenol **14** (Table 2 and Figure 2). The mixture of di-substituted products proved difficult to separate, but repetitive chromatography did yield trace amounts of the A/C-*exo* diphenol **13**. It is noteworthy that this method offers an alternative route to the mono-*endo* phenol **11**, which was previously obtained in a low yielding, multi-step procedure.[8c] With 5 equiv. of *n*BuLi, di-, tri- and tetra-substituted products were isolated, whereas 10 equiv. increased the amounts of tri- and tetra-substituted products at the expense of di-phenols. In both cases, although it was possible to separate the tri-phenol from the tetra-phenol products, flash chromatography did not allow the separation of the individual tri- or tetra-phenols. As expected, switching the base to *s*BuLi gave higher substitution patterns. Unexpected however, was the observation of penta-phenol products. Thus, the use of 5 equiv. of *s*BuLi afforded **14**, an inseparable mixture of tri-substituted products, tetra-*exo* phenol **16**,[11] and an inseparable mixture of penta-substituted products. The observation of penta-substituted products confirms that the nature of the electrophile does influence the product distribution in these D*o*M reactions. When the number of equivalents of *s*BuLi was increased to ten, tri-*exo* phenol **15**, tetra-*exo* phenol **16** and the penta-substituted tetra-*exo*, mono-*endo* phenol **17** were formed. Both phenols **15** and **17** contained respectively < 2% and ca. 5% impurities; a reminder that it is often difficult to separate poly-functionalized molecules.

Table 2. Range and yield of products arising from treatment of **1** with different butyllithium compounds and quenching with $B(OMe)_3$ followed by oxidation with alkaline H_2O_2.[a]

Base	Equiv.	Range and yield (%) of products							
		1	**11**	**12**	*[b]	**14**	**15**	**16**	**17**
*n*BuLi	2	8	18	35	19	2	–	–	–
	5	–	2	2	40	8		*[c] (15%)	
	10	–	1	1	17	2		*[c] (31%)	
*s*BuLi	5	–	–	–	–	8	*[d] (13%)	43	*[e] (9%)
	10	–	–	–	–	–	10[f]	33	21[g]

[a] All reactions were run in THF at –78 °C; Yields are the average of at least two reactions. [b] A mixture of di-substituted products, from which **13** could be isolated in trace amounts by repetitive chromatography. [c] Two inseparable mixtures of tri- and tetra-substituted products. [d] A mixture of tri-substituted products. [e] A mixture of penta-substituted products. [f] Contained < 2% impurities. [g] Contained ca. 5% impurities.

We also examined incorporating thioether groups to **1** as potential precursors to their corresponding sulfonic acids. Thus, dimethyl disulfide (MeSSMe) was used as an electrophile to quench the lithiate mixtures of **1**. With 5 equiv. of *n*BuLi, it afforded the A/C-*endo* dithioether **18**, chiral A-*exo*, B-*endo* dithioether **19** (containing ca. 8% isomeric impurities), the A/C-*exo* dithioether **20**, the A/B-*exo*, C-*endo* trithioether **21** and the A/B/C-*exo* trithioether **22** (Table 3 and Figure 2). Increasing the amount of base to 10 equiv. altered the yields somewhat, but gave the same range of products. The use of 5 equiv. of *s*BuLi gave **21**, an inseparable mixture containing **22** and unknown tetra-substituted

Table 3. Range and yield of products arising from treatment of **1** with different butyllithium compounds and quenching with Me_2S_2.[a]

Base	Equiv.	Range and yields (%) of products							
		18	**19**[b]	**20**	**21**	**22**	**23**[d]	**24**	**25**
*n*BuLi	5	17	35	12	8	2	–	–	–
	10	10	24	14	9	12	–	–	–
*s*BuLi	5	–	–	–	21	*[c] (27%)		2	22
	10	–	–	–	–	–	22	13	31

[a] All reactions were run in THF at –78 °C; yields are the average of at least two reactions. [b] Contained ca. 8% isomeric impurities. [c] A mixture of **22** and unknown tetra-substituted product(s) (44:56). [d] Contained ca. 7% impurities.

compound(s) (44:56), the penta-substituted tetra-*exo*, mono-*endo* thioether **24** and tetra-*exo* thioether **25**. With 10 equiv. of *s*BuLi, a new penta-substituted product, A/B/C-tri-*exo*, C/D-di-*endo* **23** (containing ca. 7% impurities) was also isolated along with **24** and **25**.

Reactions adding between one and eight functional groups to the rim of **1** can lead to theoretically sixty-nine products. Why are relatively few formed? The answer appears to be that functionalization patterns containing A,B-*endo* or A-*exo*, A-*endo* motifs (Figure 3) must necessarily involve high energy di- (or poly) anions. With the carbon electrophiles DMF or chloroformate, only one product has ever been observed with such patterning.[9] With non-carbon electrophiles this rule is violated more frequently (**17**, **23** and **24**), but when compared to the total range of products this "no proximal dianions" rule seems a useful guiding principle.

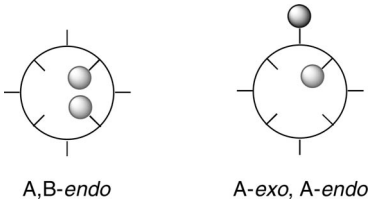


Figure 3. Rarely observed functionalization patterns.

Conclusions

Although the primary driving force for the product distribution during the D*o*M strategy to functionalize the cavitand **1** is the high preorganization of the cavitand, the nature of the electrophile does indeed influence the outcome. This would tend to suggest a mechanism more complex than a kinetic quenching of a pool of equilibrated carbanions. We are currently exploring this point, as well as studying a number of possibilities engendered by the now wide range of functionalized cavitands.

Experimental Section

General Lithiation Procedure: A solution of **1** (0.3 g; 0.178 mmol) in dry THF (20 mL) was cooled to –78 °C with a dry ice/acetone bath. The alkyllithium (*n*-/*sec*-/*tert*-butyllithium) was added dropwise and the solution was stirred for 20 min. A solution of the electrophile (methyl chloroformate/trimethyl borate/dimethyl disulfide) in THF (1 mL) was added dropwise and stirred at –78 °C for 2 h. The solution was then brought to room temp. and acidified with 10% HCl (in the case of trimethyl borate, before acidification, the reaction mixture was treated with excess alkaline hydrogen peroxide and stirred at room temp. for 6 h). THF was evaporated, water added and extracted with $CHCl_3$ (3×). The organic layers were combined, dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the resulting solid was purified by column chromatography.

Methyl Esters

2.2 Equiv. of *n*BuLi: For this reaction, 0.16 mL (0.4 mmol) of *n*BuLi and 83 μL (1.08 mmol) of methyl chloroformate were used. For column chromatography, a mobile phase of 50% DCM/hexane changing to 70% DCM/hexane was used. Both starting material (**1**, 28%) and products (**2** and **3**) are colorless solids.

Mono-*endo* Ester 2: Yield 29%, m.p. above 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.58 (m, 16 H), 3.44 (s, 3 H), 4.59 (s, 2 H), 4.65 (s, 2 H), 4.85 (m, 4 H), 6.00 (s, 2 H), 6.09 (s, 1 H), 6.13 (s, 1 H), 6.52 (br. s, 2 H), 6.54 (m, 4 H), 6.58 (br. s, 2 H), 6.61 (br. s, 2 H), 6.64 (t, J = 2.0 Hz, 1 H), 6.96 (m, 4 H), 7.13 (m, 8 H), 7.19–7.26 (m, 24 H), 7.58 (m, 3 H), 7.64 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 32.98, 33.04, 34.55, 36.81, 36.83, 52.47, 105.89, 106.69, 106.77, 107.60, 108.15, 109.52, 110.04, 115.54, 115.60, 115.71, 116.07, 120.73, 120.81, 120.84, 121.10, 122.19, 122.49, 122.70, 126.42, 128.57, 128.88, 131.45, 132.74, 136.81, 136.91, 137.01, 137.06, 139.40, 139.57, 141.58, 141.61, 153.49, 156.63, 156.65, 156.72, 156.74, 156.76, 156.86, 157.04, 160.64, 161.04, 161.2, 161.37, 164.35 ppm. MS (MALDI-TOF): calcd. for $[C_{114}H_{82}O_{18} + Ag]^+$ 1847.73; found 1846.49. $C_{114}H_{82}O_{18}\cdot 1/2CH_2Cl_2$ (1782.33): calcd. C 77.24, H 4.68; found C 77.28, H 4.52.

Mono-*exo* Ester 3: Yield 28%, m.p. above 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.58 (m, 16 H), 3.99 (s, 3 H), 4.54 (m, 3 H), 4.56 (s, 1 H), 4.85 (m, 4 H), 5.98 (s, 2 H), 6.01 (s, 2 H), 6.50 (br. s, 2 H), 6.53 (m, 4 H), 6.60 (s, 2 H), 6.65 (t, J = 2.0 Hz, 2 H), 6.68 (t, J = 2.0 Hz, 2 H), 6.99 (t, J = 2.0 Hz, 2 H), 7.01 (t, J = 2.0 Hz, 1 H), 7.12 (m, 8 H), 7.19–7.26 (m, 24 H), 7.59 (t, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 32.99, 34.55, 36.82, 53.14, 105.66, 105.78, 105.85, 106.24, 107.80, 107.90, 109.44, 109.89, 115.00, 115.49, 115.61, 115.95, 120.75, 120.87, 121.17, 122.30, 122.37, 126.43, 128.55, 128.88, 131.43, 131.46, 136.92, 137.01, 137.13, 139.32, 140.36, 141.50, 156.48, 156.53, 156.70, 156.73, 156.78, 156.83, 158.15, 161.36, 161.42, 165.41 ppm. MS (MALDI-TOF): calcd. for $[C_{114}H_{82}O_{18} + Ag]^+$ 1847.73; found 1846.77. $C_{114}H_{82}O_{18}\cdot H_2O$ (1757.88): cacld. C 77.89, H 4.82; found C 77.77, H 4.84.

5.5 Equiv. of *n*-BuLi: For this reaction, 0.4 mL (0.99 mmol) of *n*BuLi and 0.21 mL (2.7 mmol) of methyl chloroformate were used. For column chromatography, a mobile phase of 100% DCM changing to 5% EtOAc/DCM was used. All products are colorless solids. In addition to the starting material **1** (12%), the mono-*endo* ester **2** (12%) and the mono-*exo* ester **3** (22%), the products **4** and **5** and inseparable **6/7** were isolated (see Table 1 for yields).

A/C-*endo* Diester 4: Yield 8%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.58 (m, 16 H), 3.37 (s, 6 H), 4.65 (s, 4 H), 4.86 (t, J = 8.0 Hz, 4 H), 6.00 (s, 2 H), 6.10 (s, 2 H), 6.51 (t, J = 2.4 Hz, 2 H), 6.54 (br. s, 4 H), 6.59 (br. s, 4 H), 6.49 (br. s, 4 H), 7.13 (m, 8 H), 7.18–7.32 (m, 24 H), 7.58 (t, J = 8.0 Hz, 2 H), 7.66 (t, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 33.01, 34.56, 36.83, 52.33, 106.20, 106.29, 107.72, 109.64, 115.44, 115.63, 115.83, 120.89, 121.67, 122.17, 122.32, 122.92, 126.42, 128.58, 128.89, 131.51, 132.50, 136.93, 137.04, 139.39, 141.60, 153.59, 156.61, 156.71, 156.82, 160.91, 161.09, 164.00 ppm. MS (MALDI-TOF): calcd. for $[C_{116}H_{84}O_{20} + Ag]^+$ 1905.76; found 1906.06. $C_{116}H_{84}O_{20}\cdot 1/2CH_2Cl_2$ (1840.37): calcd. C 76.11, H 4.64; found C 76.30, H 4.84.

Racemate A-*exo*, B(C) *endo* Diester 5 (and its enantiomer): Yield 14%, m.p. above 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.58 (m, 16 H), 3.47 (s, 3 H), 3.98 (s, 3 H), 4.58 (m, 2 H), 4.64 (s, 2 H), 4.85 (m, 4 H), 5.97 (s, 1 H), 6.00 (s, 1 H), 6.06 (s, 1 H), 6.13 (s, 1 H), 6.52 (m, 2 H), 6.55 (t, J = 2.0 Hz, 1 H), 6.58 (m, 5 H), 6.61 (m, 2 H), 6.69 (t, J = 2.0 Hz, 1 H), 6.97 (m, 3 H), 7.13 (m, 8 H), 7.19–7.30 (m, 24 H), 7.58 (m, 3 H), 7.64 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 33.03, 34.56, 36.83,

52.63, 53.11, 105.76, 105.86, 106.37, 106.53, 106.81, 107.63, 108.18, 108.24, 109.50, 109.56, 110.06, 114.82, 115.55, 115.63, 115.74, 116.07, 120.71, 120.83, 121.04, 121.14, 122.19, 122.28, 122.49, 122.81, 126.44, 128.59, 128.90, 131.47, 132.70, 136.87, 136.97, 137.01, 137.08, 139.34, 139.36, 139.53, 140.59, 141.60, 153.44, 156.47, 156.59, 156.63, 156.70, 156.82, 157.04, 157.08, 158.04, 158.19, 160.62, 160.70, 161.01, 161.06, 161.25, 161.35, 164.36, 165.50 ppm. MS (MALDI-TOF): calcd. for $[C_{116}H_{84}O_{20} + Ag]^+$ 1905.76; found 1906.01. $C_{116}H_{84}O_{20}$ (1797.90): calcd. C 77.49, H 4.71; found C 77.19, H 4.76.

10 Equiv. of *n*-BuLi: For this reaction, 0.72 mL (1.8 mmol) of *n*BuLi and 0.42 mL (5.4 mmol) of methyl chloroformate were used. Purification conditions were as per reaction with 5.5 equiv. of *n*BuLi. The same products formed with 5.5 equiv. of *n*BuLi were isolated (see Table 1 for yields).

5.5 Equiv. of *s*BuLi: For this reaction, 0.71 mL (0.99 mmol) of *s*BuLi and 0.21 mL (2.7 mmol) of methyl chloroformate were used. For column chromatography, a mobile phase of 100% DCM followed by 5% EtOAc/DCM and then 10% EtOAc/DCM was used. All products are colorless solids.

A/B-*exo*, C-*endo* Triester 8: Yield 30%, m.p. above 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.57 (m, 16 H), 3.48 (s, 3 H), 3.98 (s, 6 H), 4.58 (s, 2 H), 4.63 (s, 2 H), 4.85 (t, J = 8.0 Hz, 4 H), 5.97 (s, 2 H), 6.02 (s, 1 H), 6.13 (s, 1 H), 6.58 (m, 10 H), 6.73 (m, 1 H), 6.97 (m, 2 H), 7.12 (m, 8 H), 7.18–7.28 (m, 24 H), 7.58 (m, 3 H), 7.64 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 33.00, 34.56, 36.85, 52.77, 53.10, 106.24, 106.30, 106.54, 106.80, 108.23, 109.57, 114.82, 115.55, 115.65, 116.05, 120.71, 121.05, 121.12, 122.26, 122.37, 122.47, 122.90, 126.45, 128.56, 128.89, 131.46, 132.63, 136.94, 137.00, 139.30, 140.51, 141.53, 153.40, 156.45, 156.53, 156.60, 156.68, 157.05, 158.05, 158.11, 160.66, 161.01, 164.33, 165.41 ppm. MS (MALDI-TOF): calcd. for $[C_{118}H_{86}O_{22} + Ag]^+$ 1963.80; found 1962.93. $C_{118}H_{86}O_{22}{\cdot}CH_2Cl_2$ (1940.86): calcd. C 73.64, H 4.57; found C 73.46, H 4.76.

A/B/C-*exo* Triester 9: Yield 27%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.62 (m, 16 H), 4.07 (s, 9 H), 4.60 (m, 4 H), 4.92 (m, 4 H), 6.02 (s, 2 H), 6.05 (s, 2 H), 6.57 (br. s, 2 H), 6.64 (br. s, 4 H), 6.68 (br. s, 2 H), 6.78 (m, 2 H), 6.81 (m, 2 H), 7.08 (br. s, 1 H), 7.20 (m, 8 H), 7.27–7.35 (m, 24 H), 7.67 (t, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 32.97, 34.52, 36.82, 53.13, 105.70, 106.03, 106.08, 106.26, 107.85, 109.47, 109.94, 114.96, 115.01, 115.44, 115.57, 116.01, 116.04, 120.82, 121.15, 121.23, 122.38, 122.45, 126.47, 128.55, 128.90, 131.45, 131.49, 136.91, 137.04, 137.12, 137.14, 139.27, 140.30, 141.48, 156.40, 156.47, 156.50, 156.56, 156.57, 156.76, 156.79, 158.14, 158.16, 158.22, 161.42, 165.38 ppm. MS (MALDI-TOF): calcd. for $[C_{118}H_{86}O_{22} + Ag]^+$ 1963.80; found 1962.90. $C_{118}H_{86}O_{22}{\cdot}1/2CH_2Cl_2$ (1898.40): calcd. C 74.97, H 4.62; found C 75.14, H 4.74.

Tetra-*exo* Ester 10: Yield 37%, m.p. above 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.57 (m, 16 H), 4.01 (s, 12 H), 4.53 (s, 4 H), 4.85 (t, J = 8.0 Hz, 4 H), 5.95 (s, 4 H), 6.58 (s, 8 H), 6.76 (t, J = 2.0 Hz, 4 H), 7.13 (m, 8 H), 7.21–7.30 (m, 24 H), 7.61 (t, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 33.00, 34.54, 36.84, 53.14, 106.07, 109.51, 114.99, 115.49, 116.10, 121.18, 122.43, 126.48, 128.55, 128.91, 131.48, 137.08, 140.25, 141.44, 156.42, 156.56, 158.15, 165.35 ppm. MS (MALDI-TOF): calcd. for $[C_{120}H_{88}O_{24} + Ag]^+$ 2021.84; found 2020.79. $C_{120}H_{88}O_{24}$ (1913.97): calcd. C 75.30, H 4.63; found C 75.46, H 4.83.

10 Equiv. of *s*BuLi: For this reaction, 1.29 mL (1.8 mmol) of *s*BuLi and 0.42 mL (2.7 mmol) of methyl chloroformate were used. Purification conditions were as per reaction with 5.5 equiv. of *s*BuLi. The same products formed with 5.5 equiv. of *s*BuLi were isolated (see Table 1 for yields).

5.5 Equiv. of *t*BuLi: For this reaction, 0.58 mL (0.99 mmol) of *t*BuLi and 0.21 mL (2.7 mmol) of methyl chloroformate were used. Purification conditions were as per reaction with 5.5 equiv. of *s*BuLi (see above). Products **4**–**10** were isolated (see Table 1 for yields).

10 Equiv. of *t*BuLi: For this reaction, 1.12 mL (1.8 mmol) of *t*BuLi and 0.42 mL (5.4 mmol) of methyl chloroformate were used. Purification conditions were as per reaction with 5.5 equiv. of *s*BuLi (see above). Products **8**–**10** were isolated (see Table 1 for yields).

Phenols

2 Equiv. of *n*BuLi: For this reaction, of *n*BuLi (0.15 mL, 0.357 mmol), trimethyl borate (0.2 mL, 1.78 mmol) and excess alkaline hydrogen peroxide [10% NaOH (2.5 mL) and 50% H_2O_2 (5 mL)] were used. For column chromatography, a mobile phase of 70% DCM/hexane changing to 100% DCM and then 2.5% EtOAc/DCM was used. Both starting material (**1**, 8%) and products **11**–**14** are colorless solids.

Mono-*endo* Phenol 11: Yield 18%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 16 H), 4.52 (s, 2 H), 4.57 (s, 2 H), 4.81–4.86 (m, 4 H), 4.89 (s, 1 H), 5.99 (s, 1 H), 6.00 (s, 2 H), 6.01 (s, 1 H), 6.48 (m, 2 H), 6.52 (m, 2 H), 6.58–6.59 (m, 4 H), 6.60 (t, J = 2.4 Hz, 1 H), 6.66 (t, J = 2.2 Hz, 2 H), 6.98 (t, J = 2.2 Hz, 2 H), 7.07–7.12 (m, 14 H), 7.18–7.25 (m, 20 H), 7.55–7.60 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 33.01, 34.56, 36.84, 104.40, 105.69, 105.74, 106.41, 107.30, 107.79, 109.81, 109.92, 115.46, 115.61, 115.79, 115.96, 120.74, 120.88, 122.09, 122.31, 126.44, 128.58, 128.89, 131.43, 136.96, 137.02, 139.36, 139.52, 141.54, 142.06, 142.62, 156.59, 156.73, 156.76, 156.82, 156.92, 160.58, 161.42, 161.51 ppm. MS (MALDI-TOF): calcd. for $[C_{112}H_{80}O_{17} + Ag]^+$ 1805.69; found 1805.36. $C_{112}H_{80}O_{17}$ (1697.82): calcd. C 79.23, H 4.75; found C 79.18, H 4.90.

Mono-*exo* Phenol 12: Yield 35%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 16 H), 4.53 (s, 1 H), 4.54 (s, 3 H), 4.83 (m, 4 H), 5.82 (br. s, 1 H), 6.00 (s, 4 H), 6.51–6.53 (m, 6 H), 6.55 (br. s, 2 H), 6.63 (t, J = 2.2 Hz, 2 H), 6.66 (t, J = 2.2 Hz, 2 H), 6.99 (t, J = 2.0 Hz, 3 H), 7.10–7.12 (m, 8 H), 7.18–7.27 (m, 24 H), 7.55–7.61 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 33.06, 34.57, 36.85, 105.75, 105.87, 105.92, 106.47, 107.87, 107.93, 109.92, 110.05, 115.60, 115.91, 115.95, 120.90, 121.12, 122.34, 122.39, 126.45, 128.15, 128.60, 128.92, 131.48, 131.54, 135.77, 136.95, 137.03, 137.04, 139.40, 139.47, 141.60, 148.23, 156.59, 156.74, 156.76, 156.82, 156.86, 161.35, 161.41, 161.45 ppm. MS (MALDI-TOF): calcd. for $[C_{112}H_{80}O_{17} + Ag]^+$ 1805.69; found 1805.44. $C_{112}H_{80}O_{17}{\cdot}H_2O$ (1715.84): calcd. C 78.40, H 4.82; found C 78.05, H 4.83.

A/C-*exo* Diphenol (13): Obtained in trace amounts from a mixture of di-substituted phenols by repetitive column chromatography; m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 16 H), 4.53 and 4.54 (2×s, 4 H), 4.83 (2×t, J = 7.9 Hz, 4 H), 5.85 (br. s, 2 H), 6.00 (s, 4 H), 6.52 (d, J = 2.4 Hz, 4 H), 6.55 (s, 4 H), 6.67 (t, J = 2.2 Hz, 4 H), 6.99 (t, J = 2.2 Hz, 2 H), 7.10–7.12 (m, 8 H), 7.18–7.28 (m, 24 H), 7.59 (t, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 32.98, 33.03, 34.55, 34.52, 36.80, 36.84, 105.83, 106.44, 108.00, 109.88, 109.99, 115.56, 115.88, 120.88, 121.09, 122.33, 126.43, 128.14, 128.56, 128.89, 131.52, 135.70, 136.93, 137.00, 139.50, 141.54, 148.20, 156.57, 156.70, 156.72, 156.80, 161.31 ppm. MS (MALDI-TOF): calcd. for

$[C_{112}H_{80}O_{18} + Ag]^+$ 1821.69; found 1820.91. $C_{112}H_{80}O_{18}·H_2O$ (1731.84): calcd. C 77.67, H 4.77; found C 77.60, H, 5.01.

A/B-*exo* Diphenol 14: Yield 2%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 16 H), 4.53 (s, 2 H), 4.55 (s, 2 H), 4.83 (2×t, J = 7.7 Hz, 4 H), 5.86 (br. s, 2 H), 5.99 (s, 4 H), 6.50 (distorted d, 2 H), 6.52 (distorted d, 2 H), 6.54 (s, 2 H), 6.56 (s, 2 H), 6.64 (t, J = 2.2 Hz, 1 H), 6.67 (t, J = 2.2 Hz, 2 H), 6.70 (t, J = 2.2 Hz, 1 H), 6.99 (t, J = 2.2 Hz, 2 H), 7.10–7.12 (m, 8 H), 7.17–7.29 (m, 24 H), 7.56–7.63 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 33.00, 33.04, 34.54, 36.81, 105.76, 105.93, 106.37, 106.53, 107.93, 109.87, 110.02, 115.56, 115.83, 115.88, 115.92, 120.85, 121.12, 122.34, 126.44, 128.18, 128.57, 128.89, 131.46, 131.53, 131.60, 135.78, 136.92, 136.95, 136.99, 137.02, 139.43, 141.55, 148.10, 148.17, 156.54, 156.56, 156.73, 156.82, 156.85, 161.35, 161.41 ppm. MS (MALDI-TOF): calcd. for $[C_{112}H_{80}O_{18} + Ag]^+$ 1821.69; found 1821.65. $C_{112}H_{80}O_{18}·3H_2O$ (1767.87): calcd. C 76.09, H 4.90; found C 76.03, H 4.97.

5 Equiv. of *n*BuLi: For this reaction, *n*BuLi (0.37 mL, 0.892 mmol), trimethyl borate (0.2 mL, 1.78 mmol) and excess alkaline hydrogen peroxide [10% NaOH (2.5 mL) and 50% H_2O_2 (5 mL)] were used. For column chromatography, a mobile phase of 70% DCM/hexane changing to 100% DCM, then 5% EtOAc/DCM and finally 5% MeOH/$CHCl_3$ was used. The products **11**, **12**, **14** and two inseparable mixtures of tri- and tetra-substituted products were isolated (see Table 2 for yields).

10 Equiv. of *n*BuLi: For this reaction, *n*BuLi (0.74 mL, 1.78 mmol), trimethyl borate (0.4 mL, 3.57 mmol) and excess alkaline hydrogen peroxide [10% NaOH (2.5 mL) and 50% H_2O_2 (5 mL)] were used. Purification conditions were as per reaction with 5 equiv. of *n*BuLi (see above). The same products formed with 5 equiv. of *n*BuLi were isolated (see Table 2 for yields).

5 Equiv. of *s*BuLi: For this reaction, *s*BuLi (0.69 mL, 0.892 mmol), trimethyl borate (0.2 mL, 1.78 mmol) and excess alkaline hydrogen peroxide [10% NaOH (2.5 mL) and 50% H_2O_2 (5 mL)] were used. For column chromatography, a mobile phase of 1% MeOH/$CHCl_3$ changing to 5% MeOH/$CHCl_3$ was used. All products are colorless solids. Phenol **14**, an inseparable mixture of tri-substituted products, **16** and another inseparable mixture of penta-substituted products were isolated (see Table 2 for yields).

Tetra-*exo* Phenol 16: Yield 43%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 16 H), 4.53 (s, 4 H), 4.83 (t, J = 7.8 Hz, 4 H), 5.89 (br. s, 4 H), 5.99 (s, 4 H), 6.55 (s, 8 H), 6.71 (t, J = 2.2 Hz, 4 H), 7.10–7.12 (m, 8 H), 7.17–7.22 (m, 16 H), 7.26–7.29 (m, 8 H), 7.61 (t, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 33.04, 34.56, 36.85, 106.51, 109.99, 115.53, 115.79, 121.08, 122.35, 126.42, 128.21, 128.55, 128.86, 131.58, 135.86, 136.93, 141.54, 148.09, 156.57, 156.71 ppm. MS (MALDI-TOF): calcd. for $[C_{112}H_{80}O_{20} + Ag]^+$ calcd, 1853.69; found, 1853.87. $C_{112}H_{80}O_{20}·2H_2O$ (1781.85): calcd. C 75.49, H 4.75; found C 75.31, H 4.79.

10 Equiv. of *s*BuLi: For this reaction, *s*BuLi (1.37 mL, 1.78 mmol), trimethyl borate (0.4 mL, 3.57 mmol) and excess alkaline hydrogen peroxide [10% NaOH (2.5 mL) and 50% H_2O_2 (5 mL)] were used. Purification conditions were as per reaction with 5 equiv. of *s*BuLi (see above). Products **15**–**17** were isolated (see Table 2 for yields).

Thioethers

5 Equiv. of *n*BuLi: For this reaction, *n*BuLi (0.37 mL, 0.892 mmol) and dimethyl disulfide (0.16 mL, 1.78 mmol) were used. For column chromatography, a mobile phase of 70% DCM/hexane changing to 100% DCM was used. Products **18**–**22** were isolated and all are colorless solids.

A/C-*endo* Dithioether 18: Yield 17%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.26 (s, 6 H), 2.46–2.63 (m, 16 H), 4.56 (s, 4 H), 4.83 (t, J = 7.8 Hz, 4 H), 5.95 (s, 2 H), 6.01 (s, 2 H), 6.39 (s, 4 H), 6.55 (s, 4 H), 6.78 (s, 2 H), 7.04 (s, 4 H), 7.10–7.12 (m, 8 H), 7.15–7.25 (m, 20 H), 7.28 (s, 2 H), 7.30 (s, 2 H), 7.52 (t, J = 8.0 Hz, 2 H), 7.57 (t, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.29, 33.00, 34.57, 36.82, 104.58, 105.70, 107.15, 109.81, 115.49, 115.62, 116.23, 120.95, 122.17, 122.31, 122.36, 125.44, 126.41, 128.55, 128.87, 130.11, 131.35, 136.93, 136.97, 139.21, 141.57, 156.59, 156.72, 156.85, 156.97, 161.06, 161.49 ppm. MS (MALDI-TOF): calcd. for $[C_{114}H_{84}O_{16}S_2 + Ag]^+$ 1881.88; found 1881.95. $C_{114}H_{84}O_{16}S_2·H_2O$ (1792.02): calcd. C 76.41, H 4.84, S 3.58; found C 76.60, H 4.90, S 3.45.

A/C-*exo* Dithioether 20: Yield 12%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 22 H), 4.52 (s, 2 H), 4.55 (s, 2 H), 4.80–4.85 (m, 4 H), 5.97 (s, 4 H), 6.50 (d, J = 2.4 Hz, 4 H), 6.58 (s, 4 H), 6.62 (t, J = 2.2 Hz, 4 H), 6.97 (t, J = 2.2 Hz, 2 H), 7.09–7.12 (m, 8 H), 7.18–7.27 (m, 24 H), 7.59 (t, J = 8.4 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.18, 32.95, 33.01, 34.52, 36.78, 36.82, 105.57, 106.55, 107.58, 109.60, 109.97, 115.57, 115.82, 120.78, 120.99, 122.35, 126.45, 128.56, 128.90, 131.51, 136.99, 137.01, 137.99, 139.30, 141.51, 156.60, 156.70, 156.80, 157.03, 161.16, 161.46 ppm. MS (MALDI-TOF): calcd. For $[C_{114}H_{84}O_{16}S_2 + Ag]^+$ 1881.88; found 1881.08. $C_{114}H_{84}O_{16}S_2$ (1774.01): C 77.18, H 4.77, S 3.62; found C 76.95, H 4.72, S 3.57.

A/B-*exo*, C-*endo* Trithioether 21: Yield 8%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.27 (s, 3 H), 2.47–2.63 (m, 22 H), 4.55 (s, 2 H), 4.56 (s, 2 H), 4.81–4.86 (m, 4 H), 5.95 (s, 1 H), 5.96 (s, 1 H), 5.99 (s, 2 H), 6.39 (s, 2 H), 6.55 (s, 4 H), 6.60 (s, 3 H), 6.70 (t, J = 2.2 Hz, 2 H), 7.05 (t, J = 2.4 Hz, 2 H), 7.10–7.12 (m, 8 H), 7.17–7.31 (m, 24 H), 7.52 (t, J = 8.2 Hz, 1 H), 7.57–7.63 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.20, 33.00, 34.55, 36.83, 104.60, 105.75, 106.21, 106.40, 107.25, 109.64, 109.84, 115.47, 115.60, 115.65, 115.79, 115.92, 120.76, 120.92, 120.99, 122.26, 122.36, 125.33, 126.44, 128.55, 128.89, 130.16, 131.45, 131.57, 136.92, 137.00, 137.07, 137.92, 139.18, 141.51, 141.54, 156.60, 156.63, 156.69, 156.76, 156.82, 156.92, 156.96, 161.07, 161.12, 161.17, 161.46 ppm. MS (MALDI-TOF): calcd. for $[C_{115}H_{86}O_{16}S_3 + Ag]^+$ 1927.97; found 1928.60. $C_{115}H_{86}O_{16}S_3·H_2O$ (1838.12): calcd. C 75.14, H 4.83, S 5.23; found C 75.17, H 4.93, S 5.57.

A/B/C-*exo* Trithioether 22: Yield 2%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 25 H), 4.52 (s, 1 H), 4.54 (m, 3 H), 4.80–4.85 (m, 4 H), 5.94 (s, 2 H), 5.97 (s, 2 H), 6.50 (d, J = 1.6 Hz, 2 H), 6.57 (m, 6 H), 6.62 (t, J = 2.2 Hz, 2 H), 6.63 (t, J = 2.2 Hz, 2 H), 6.98 (t, J = 2.0 Hz, 1 H), 7.09–7.12 (m, 8 H), 7.17–7.27 (m, 24 H), 7.57–7.63 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.17, 32.97, 34.52, 36.78, 105.60, 106.21, 106.37, 106.42, 107.65, 109.63, 109.97, 115.54, 115.58, 115.66, 115.81, 120.82, 120.94, 121.01, 122.35, 126.46, 128.56, 128.90, 131.51, 131.57, 136.96, 137.00, 137.07, 137.86, 137.92, 139.27, 141.49, 156.63, 156.72, 156.80, 156.87, 156.94, 156.98, 161.18, 161.45 ppm. MS (MALDI-TOF): calcd. for $[C_{115}H_{86}O_{16}S_3 + Ag]^+$ 1927.97; found 1928.01. $C_{115}H_{86}O_{16}S_3·H_2O$ (1838.12): calcd. C 75.14, H 4.83, S 5.23; found C 75.39, H 5.04, S 5.04.

10 Equiv. of *n*BuLi: For this reaction, *n*BuLi (0.74 mL, 1.78 mmol) and dimethyl disulfide (0.32 mL, 3.57 mmol) were used. Purification conditions were as per reaction with 5 equiv. of *n*BuLi (see above). The same products formed with 5 equiv. of *n*BuLi were isolated (see Table 3 for yields).

5 Equiv. of *s*BuLi: For this reaction, *s*BuLi (0.69 mL, 0.892 mmol), and dimethyl disulfide (0.16 mL, 1.78 mmol) were used. For col-

umn chromatography, a mobile phase of 70% DCM/hexane changing to 100% DCM was used. All products are colorless solids. A/B-*exo*, C-*endo* trithioether **21** (21%), an inseparable mixture of **22** and unknown tetra-substituted products (27%), the penta-substituted tetra-*exo*, mono-*endo* thioether **24** and tetra-*exo* thioether **25** were isolated.

Tetra-*exo*, Mono-*endo* Thioether 24: Yield 2%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.39 (s, 3 H), 2.46–2.62 (m, 28 H), 4.55 (s, 4 H), 4.80–4.83 (m, 4 H), 5.89 (s, 1 H), 5.95 (s, 1 H), 5.96 (s, 2 H), 6.45 (m, 2 H), 6.55 (m, 2 H), 6.57–6.59 (m, 5 H), 6.70 (t, J = 2.2 Hz, 2 H), 7.09–7.11 (m, 8 H), 7.16–7.29 (m, 22 H), 7.33 (s, 1 H), 7.35 (s, 1 H), 7.55–7.63 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.01, 18.15, 19.29, 32.96, 34.51, 36.78, 114.91, 115.46, 115.51, 115.61, 115.77, 115.86, 120.85, 120.95, 122.30, 122.39, 105.01, 106.07, 106.17, 106.36, 109.59, 109.66, 124.81, 126.45, 128.55, 128.89, 130.81, 131.52, 136.98, 137.04, 137.84, 137.89, 141.50, 156.56, 156.66, 156.69, 156.85, 157.00, 157.02, 157.98, 161.15, 161.19, 161.53 ppm. MS (MALDI-TOF): calcd. for $[C_{117}H_{90}O_{16}S_5 + Ag]^+$ 2020.16; found 2020.04. $C_{117}H_{90}O_{16}S_5{\cdot}H_2O$ (1930.30): calcd. C 72.80, H 4.80, S 8.31; found C 72.75, H 4.93, S 8.22.

Tetra-*exo* Thioether 25: Yield 22%, m.p. above 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.63 (m, 28 H), 4.53 (s, 4 H), 4.82 (t, J = 7.8 Hz, 4 H), 5.95 (s, 4 H), 6.57 (s, 8 H), 6.63 (t, J = 2.2 Hz, 4 H), 7.09–7.12 (m, 8 H), 7.18–7.28 (m, 24 H), 7.61 (t, J = 8.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.18, 33.01, 34.53, 36.81, 106.29, 109.69, 115.56, 115.60, 115.81, 120.95, 122.39, 126.48, 128.58, 128.92, 131.59, 137.04, 137.87, 141.51, 156.69, 156.93, 161.18 ppm. MS (MALDI-TOF): calcd. for $[C_{116}H_{88}O_{16}S_4 + Ag]^+$ 1974.06; found 1974.89. $C_{116}H_{88}O_{16}S_4{\cdot}H_2O$ (1884.21): C 73.94, H 4.81, S 6.81; found C 73.95, H 4.68, S 6.72.

10 Equiv. of *s*BuLi: For this reaction, *s*BuLi (1.37 mL, 1.78 mmol) and dimethyl sulfide (0.32 mL, 3.57 mmol) were used. Purification conditions were as per reaction with 5 equiv. of *s*BuLi (see above). Products **23**–**25** were isolated (see Table 3 for yields).

Supporting Information (see also the footnote on the first page of this article): The general experimental methods and data for inseparable compounds **6/7** and compounds with inseparable impurities **15**, **17**, **19** and **23**. NMR and mass spectra for products **2**–**25**.

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[11] We note in passing that tetrol **16** is reminiscent of the cavitand subunits used with such great effect by Cram and subsequently Sherman for the formation of carceplexes.[1a,1c]

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