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Directed *Ortho* Metallation of Deep Cavity Cavitands: Functionalizing Molecular Concavity

Zachary R. Laughrey and Bruce C. Gibb*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

bgibb@uno.edu

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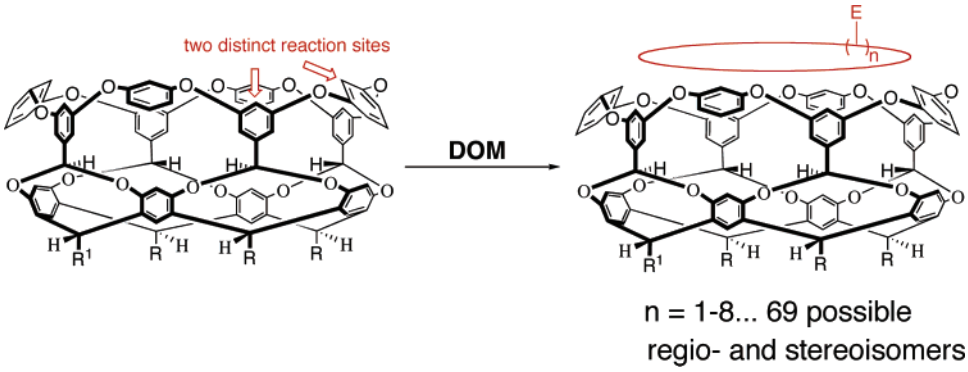

Directed *ortho* metallation (DOM) processes have been used to functionalize the cavity and rim of title cavitand **1**. The preorganization of the host resulted in a considerable reduction in the range of products produced. Thus, whereas sixty-nine products are possible from per-functionalization, only twelve were observed when the host was treated with three different alkyllithiums.

Introduction

The essence of host−guest chemistry is molecular concavity. By careful design, hosts are synthesized so that they display a concave surface, the function of which is to recognize a guest or guests. Enzymes have gone one step further than this. Their concave surfaces (active sites) are capable of not just recognition but also transformation. To a first approximation these two functions can be viewed to originate from separate qualities; the concavity of the binding site bestows guest selection and engenders desolvated space where noncovalent forces that are weak in bulk water can predominate, while built into this concavity is the catalytic machinery or functional groups primarily responsible for transforming the guest.

There are relatively few families of molecules possessing large areas of preorganized concavity. Cyclodextrins,[1−7] calixarenes,[8,9] resorcinarenes,[8,10,11] and cucurbiturils[12,13] are perhaps the most studied and have played an important role in the development of host−guest chemistry. In particular, the ready

(1) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011.
(2) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153.
(3) Reichwein, A. M.; Verboom, W.; Reinhoudt, D. N. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 343−349.
(4) Schneider, H.-J.; Hacket, F.; Rüdiger, V. *Chem. Rev.* **1998**, *98*, 1755−1785.
(5) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325−1358.
(6) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875−1917.
(7) Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev.* **2003**, *103*, 4147−4586.
(8) Zouhair, A.; Böhmer, V.; Harrowfield, J.; Vicens, J.; Saadioui, M., Eds. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, 2001.
(9) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: London, 2000.
(10) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*, 1st ed.; Royal Society of Chemistry: Cambridge, 1994.
(11) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663−2704.
(12) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630.

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availability of cyclodextrins has resulted in these naturally occurring hosts being the focus of attention for synthesizing molecules that both bind and transform.[1−3,7,14−18] To complement these advances, synthetic innovations in calixarene[19−26] and resorcinarene chemistry[27−32] have recently yielded alterative examples of functionalized concavity. These hosts possess only one significant portal and so offer a unique opportunity to investigate the relationship between host structure and substrate transformation.[27−29]

Further progress in these matters will be greatly facilitated by the development of general strategies for efficiently synthesizing functionalized concavity. In this regard, it is desirable to devise strategies that: (1) allow functionality to be incorporated at chemically distinct positions in a cavity. (2) Avoid the regioselectivity difficulties encountered with cyclodextrins when more than one functional group is added to the bare host. Here we report on the directed *ortho* metallation of deep-cavity cavitand **1** (R = CH_2CH_2Ph, Figure 1)[33−36] In theory, a possible seventy products (including starting material) can arise from such reactions.[37,38] However, a combination of host preorganization and reaction control greatly constrains product distribution. This molecule therefore offers ready access to a wide variety of internally functionalized hosts.

Results and Discussion

The synthesis of host **1** from the corresponding phenethyl-footed resorcinarene has been previously reported.[35] First, benzal bridging[39−41] of the resorcinarene with 3,5-dibromobenzal bromide yields the benzal-bridged cavitand in 70% yield. Second, an 8-fold Ullman ether reaction with resorcinol gives host **1** in 88% yield.[33,35] The efficiency of these two processes allows multigram quantities of the host to be readily synthesized.

Host **1** possesses eight (readily accessible) aromatic hydrogen atoms located *ortho* to two oxygen atoms. These hydrogens are located on or near the rim of the cavity, with four on the inner surface, and four on the rim directed with the cavity wall. We

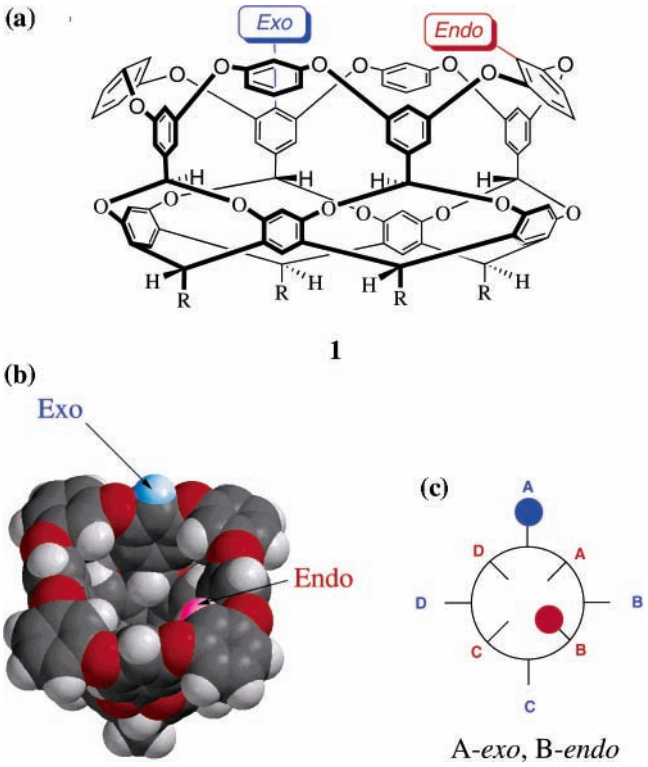


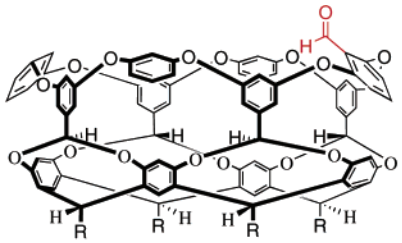
FIGURE 1. Structure (a) and space-filling model (b) of host **1**, showing the distinct *endo* and *exo* positions. (c) Representation of a disubstituted cavitand to illustrate the nomenclature used (see text).

TABLE 1. Range and Yield of Products Arising from Treatment of Host 1 with Different Alkyllithiums and Quenching with DMF[a]

		range and yield (%) of products									
base	equiv	**1**	**2**	**3**	**4**	**5**/**6**[b]	**7**[c]	**8**	**9**	**10**	**11**[c]
n-BuLi[d]	2.2	68	11	12							
	5.5		7	8	13	31	24				
	10.0		4	6	10	43	22				
s-BuLi[e]	5.5							20	20	30	3
	10.0							14	8	60	
t-BuLi[e]	5.5		9	10		19	10	12	11		
	10.0							18	23	19	13

[a] The host had limited solubility in diethyl ether. All reactions were run in THF at −78 °C. Yields are the average of at least two reactions. [b] Compounds **5** and **6** could not be separated chromatographically. [c] Product is chiral and was isolated as the (±) racemate; only one enantiomer is shown in Figure 2. [d] Only starting material was recovered when 1.1 equiv of base was employed. [e] Only starting material was recovered when 1.1 or 2.2 equiv of base was employed.

(13) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24.
(14) Tee, O. S. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: San Diego, 1996; Vol. 29, pp 1−83.
(15) Breslow, R. *Isr. J. Chem.* **1992**, *32*, 23−30.
(16) Groves, J. T. *Nature* **1997**, *389*, 329−330.
(17) Breslow, R. *J. Mol. Catal.* **1994**, *91*, 161−174.
(18) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317−324.
(19) Rondelez, Y.; Rager, M. N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334−1340.
(20) Rondelez, Y.; Bertho, G.; Reinaud, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 1044−1046.
(21) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2001**, *123*, 8442−8443.
(22) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183−6189.
(23) Blanchard, S.; Le Clainche, L.; Rager, M.-N.; Tuchagues, J.-P.; Dupart, A. F.; Le Mest, Y.; Reinaud, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2732−2735.
(24) Zeng, X.; Hucher, N.; Reinaud, O.; Jabin, I. *J. Org. Chem* **2004**, *69*, 6886−6889.
(25) Darbost, U.; Giorgi, M.; Reinaud, O.; Jabin, I. *J. Org. Chem* **2004**, *69*, 4879−4884.
(26) Jabin, I.; Reinaud, O. *J. Org. Chem* **2003**, *68*, 3416−3419.
(27) Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7424−7425.
(28) Purse, B. W.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 14682−14683.
(29) Gibson, C.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 1887−1890.
(30) Renslo, A. R.; Rebek, J. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281−3283.
(31) Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 4659−4669.
(32) Wash, P. L.; Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2001**, *40*, 1221−1222.
(33) Li, X.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650−651.
(34) Laughrey, Z. R.; Gibb, C. L. D.; Senechal, T.; Gibb, B. C. *Chem. Eur. J.* **2003**, *9*, 130−139.
(35) Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2001**, *123*, 5849−5850.
(36) Gibb, C. L. D.; Xi, H.; Politzer, P. A.; Concha, M.; Gibb, B. C. *Tetrahedron* **2002**, *58*, 673−681.
(37) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.
(38) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376−393.
(39) Xi, H.; Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *Chem. Commun.* **1998**, 1743−1744.
(40) Xi, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286−9288.
(41) Green, J. O.; Baird, J.-H.; Gibb, B. C. *Org. Lett.* **2000**, *2*, 3845−3848.



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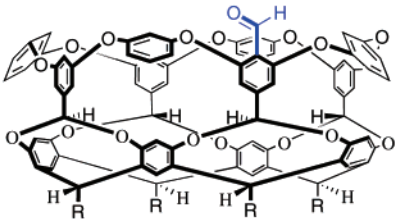

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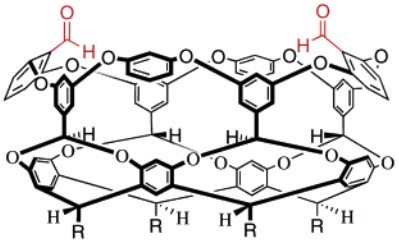

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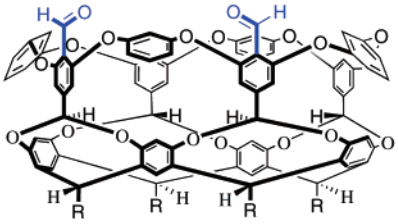

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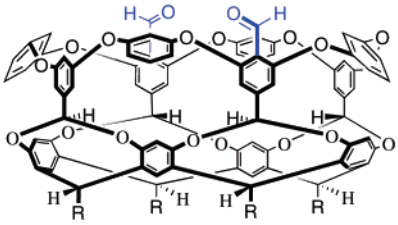

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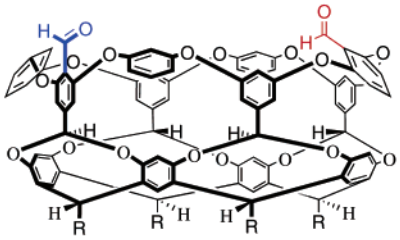

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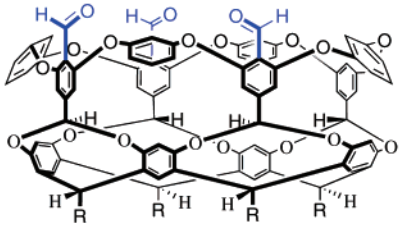

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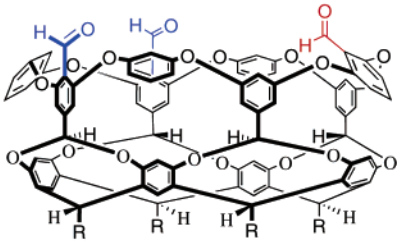

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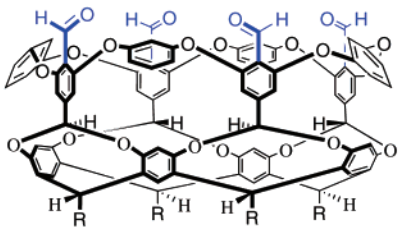

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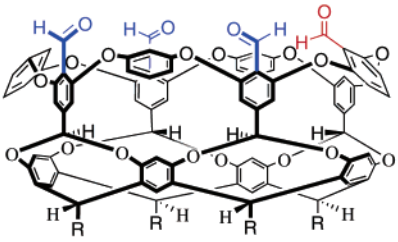

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FIGURE 2. Products arising from this study. Structures **7** and **11** are chiral. Although only one enantiomer is shown, products were isolated as racemates.

term these positions *endo* and *exo*, respectively (Figure 1). These hydrogens are weakly acidic. Hence, they can be removed using directed *ortho* lithiation procedures,[37,38] and the resulting carbanion(s) quenched with electrophiles. In theory, per-lithiation and quenching can give products ranging from starting material through to octasubstituted cavitand. With two positions for functional group attachment, monosubstitution gives rise to two regioisomers, while higher substitutions lead to larger numbers of both regio- and stereoisomers. Thus, disubstitution engenders eight isomers, trisubstituted fourteen, tetrasubstituted twenty, pentasubstituted fourteen, hexasubstituted eight, and heptasubstituted two. Combined with starting material and the one octasubstitution product, a possible seventy compounds (see the Supporting Information) can arise from this reaction. For convenience, the following nomenclature is used to describe the different possible products (see Figure 1c). Looking down into the pocket, the four *exo* positions are labeled A−D in a clockwise manner. Substituents are given the lowest possible alphabetical designation. The four *endo* groups are labeled similarly, beginning at the site immediately clockwise of the *exo*-A position. The alphabetical designation is again kept as low as possible. Hence, the disubstituted host in Figure 1c, with one *exo* group and one *endo* group in the B-position, is termed A-*exo*, B-*endo*, whereas its enantiomer is the A-*exo*, C-*endo* derivative.

Host **1** was treated with varying equivalents of *n*-butyl, *sec*-butyl, and *tert*-butyllithium and quenched with dimethylformamide (DMF) to form the corresponding aldehyde derivatives (Table 1 and Figure 2). Twenty minutes was required for equilibration; a shorter time period of 5 min gave mostly starting material, while longer periods, e.g., 3 h, gave the same product distribution outlined in Table 1. Symmetry considerations and a combination of 1D and 2D NMR identified the products. For 1D NMR, four distinct protons proved useful in characterization: the benzal protons at the base of the cavity, the H atoms *para* to the *endo*-position, the H-2 on the lower resorcinarene moiety, and the aldehyde protons. In regard to the aldehyde groups, by and large there was a difference of 0.7 ppm between *exo* and *endo* functionalization, the latter being shielded by the aromatic walls of the cavity.

Only starting material was recovered using methyllithium as base. In contrast, with the slightly stronger *n*-butyllithium a range of mono- and dialdehydes were isolated (Table 1). Yields of the mono-*endo* and mono-*exo* aldehydes **2** and **3** were optimal with 2.2 equiv of base. However, at higher equivalents it was the A/C-*endo* dialdehyde **4**, the two (inseparable) A/B- and A/C-*exo*-dialdehydes **5** and **6**, and the chiral A-*exo*, B-*endo* dialdehyde **7** (and its mirror image) that were isolated. Neither improvement in yields nor higher products were observed when 20 equiv of base was used. Apparently *n*-BuLi can only remove two protons from host **1**.

A different patterning of functionalization was observed with *sec*-butyllithium. Only starting material was obtained when this base was used in small excess. However, higher equivalents allowed the isolation of A/B/C-*exo* (tri-*exo*) aldehyde **8**, A/B-*exo* C-*endo* trialdehyde **9**, tetra-*exo* aldehyde **10**, and chiral A/B/C-*exo* C-*endo* **11** (and its enantiomer). The exceptional 60% yield (an average yield of 88% per site) for tetra-*exo* **10** suggests that a sizable kinetic barrier exists to removing more than four protons from the host. Indeed, using 20 equiv of *sec*-butyllithium led to a 70% yield of **10** (an average yield of 91% per site), but no sign of higher products.

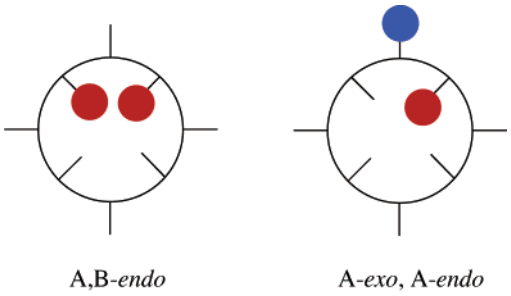

FIGURE 3. Functional group patterning that is seldom or never observed.

The product distribution using *tert*-butyllithium was intermediate between the *n*-butyl and *sec*-butyl lithiates. In general, higher substitution products were favored; however, with 5.5 equiv mono derivates **2** and **3** and disubstituted derivatives **5**−**7** were also formed. In large excess, the tertiary lithiate proved to be the best base for forming chiral derivative **11** and its enantiomer.

Overall, lithiation with 5.5 or 10 equiv of base efficiently generates formylated host; the sum of the different aldehyde products in these reactions ranged from 71% to 85%. Within the different ranges of products, it is apparent that *exo* substitution is preferred over *endo*. For example, overall there are six products with multiple *exo* functionality (**5**, **6**, and **8**−**11**) and only one with multiple *endo* functionality (**4**).

Why are there relatively few products arising from the metallation of **1**? An analysis of what is *not* produced from these metallation processes is illustrative. For example, there are no products with two aldehyde groups in an A/B-*endo* relationship (Figure 3). This pattern of functionality can only arise through a (presumably) high-energy dicarbanion intermediate whose two negative charges are in close proximity. Similarly, the only compounds observed with A-*exo* A-*endo* patterning within its functionality are **11** and its enantiomer. Here too the close proximity of carbanion centers inhibits products of this type.

Indeed with the exception of this pair of enantiomers, if all the structures with A/B-*endo* and A-*endo* A-*exo* functional group patterning are removed from the list of seventy possible products, only compounds **1**−**10** remain. Thus, the preorganized nature of the host *limits* formation of products with less than four functional groups and *prevents* the formation of those with more than five substituents because these necessarily involve carbanions with either A/B-*endo* or A-*endo* A-*exo* patterning.

In summary, the metallation of host **1** is subject to two distinct types of direction. In the traditional sense of the word, the reaction is being controlled by sterics and suitably placed ether oxygen atoms that focus the reaction to only eight sites. Still though, a theoretically sixty-nine products are possible. In addition, however, metallation is also directed by the innate preorganization of the host, a phenomenon that constrains the range of products to manageable numbers. The expansion of this protocol to alternative electrophiles, and the development of stepwise procedures for introducing different functional groups, will lead to a wide range of functionalized hosts. We are currently exploring some of these possibilities.

Experimental Section

General Methods. All reagents and deuterated solvents were purchased from commercial suppliers. THF was distilled from sodium benzophenone ketyl. DMF was stored over molecular sieves and degassed prior to use. All reactions were run under a nitrogen atmosphere. Flash chromatography (silica gel 60 Å, 200−400 mesh) was used for product purification. At frequent intervals, solutions of *n*-BuLi, *s*-BuLi, and *t*-BuLi were titrated using diphenyl acetic acid. Melting points are uncorrected.

Standard Reaction Procedure. To a dried flask was added 0.3 g (0.18 mmol) of **1** and 20 mL of distilled THF. This solution was brought to −78 °C with a dry ice/acetone bath. The alkyl lithiate (variable) was then slowly injected, and the solution was allowed to stir for 20 min. DMF (variable) was then injected slowly, and the solution was allowed to stir at −78 °C for 2 h. The solution was then allowed to warm to approximately −20 °C and acidified with 10% HCl. The mixture was then partitioned between $CHCl_3$ and water. The organic layer was collected and the water layer extracted twice with $CHCl_3$. The organic layers were combined, dried with anhydrous Na_2SO_4, and filtered, and the solution was concentrated under reduced pressure. The resulting white solid was dried under high vacuum at 210 °C for 16 h.

2.2 equiv of *n*-BuLi. For this reaction,0.16 mL (0.4 mmol) of *n*-BuLi and 74.5 μL (1.08 mmol) of DMF in 1 mL of THF were used. The crude product was dry loaded on to a silica column. An initial mobile phase of 70% CH_2Cl_2/hexane changing to 90% CH_2Cl_2/hexane was used. Both starting material (**1**, 67% yield) and products were colorless solids:

Mono-*endo* aldehyde **2**: yield = 11%; mp >250 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.56 (m, 16H), 4.42 (s, 2H), 4.48 (s, 2H), 4.79 (m, 4H), 5.94 (s, 1H), 5.97 (m, 3H), 6.41 (s, 2H), 6.47 (s, 2H), 6.54 (s, 2H), 6.62 (s, 2H), 6.67 (t, 1H, *J*(H,H) = 2.0 Hz), 6.74 (t, 2H, *J* (H,H)=2.0 Hz), 7.00 (t, 2H, *J*(H,H) = 2.0 Hz), 7.05 (t, 2H, *J*(H,H) = 2.0 Hz), 7.13 (m, 8H), 7.17−7.30 (m, 22H), 7.38 (d, 2H, *J*(H,H) = 8.5 Hz), 7.60 (m, 3H), 7.85 (t, 1H, *J*(H,H) = 8.0 Hz), 9.98 (s, 1H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1817.73, found 1816.97. Anal. Calcd for $C_{113}H_{80}O_{17}\cdot{}^1/_2CH_2Cl_2$: C, 77.80; H, 4.66. Found: C, 77.77; H, 4.82.

Mono-*exo* aldehyde **3**: yield = 12%; mp >250 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.59 (m, 16H), 4.45 (m, 4H), 4.80 (m, 4H), 5.95 (s, 2H), 5.99 (s, 2H), 6.52 (m, 6H), 6.63 (s, 2H), 6.66 (t, 2H, *J*(H,H) = 2.0 Hz), 6.69 (t, 2H, *J*(H,H) = 2.0 Hz), 6.99 (m, 2H), 7.13 (m, 8H), 7.18−7.30 (m, 25H), 7.62 (m, 4H), 10.67 (s, 1H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1817.73, found 1817.45. Anal. Calcd for $C_{113}H_{80}O_{17}\cdot H_2O$: C, 78.55; H, 4.78. Found: C, 78.85; H, 4.69.

5.5 equiv of *n*-BuLi. For this reaction, 0.4 mL (0.99 mmol) of *n*-BuLi and 210 μL (2.7 mmol) of DMF in 1 mL of THF were used. The crude product was dry loaded on to a silica column. An initial mobile phase of 90% CH_2Cl_2/hexane, followed by CH_2Cl_2 was used. All products were colorless solids. In addition to mono-*endo* aldehyde **2** (yield = 7%) and mono-*exo* aldehyde **3** (yield = 8%), the following products were isolated.

A/C-*endo* dialdehyde **4**: yield = 13%; mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (m, 16H), 4.54 (s, 4H), 4.84 (t, 4H, *J*(H,H) = 8 Hz), 5.95 (s, 2H), 5.99 (s, 2H), 6.39 (s, 4H), 6.60 (s, 4H), 6.82 (bs, 2H), 7.07 (bs, 4H), 7.12 (m, 8H), 7.24 (m, 20H), 7.35 (d, 4H *J*(H,H) = 8.4 Hz), 7.58 (t, 2H, *J*(H,H) = 8.4 Hz), 7.82 (t, 2H, *J*(H,H) = 8.4 Hz), 9.99 (s, 2H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1845.74, found 1845.47. Anal. Calcd for $C_{114}H_{80}O_{18}\cdot{}^1/_2CH_2Cl_2$: C, 77.19; H, 4.77. Found: C, 76.84; H, 4.73.

Two (inseparable) A/B- and A/C-*exo*-dialdehydes **5** and **6**: combined yield = 31%; mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (m, 16H), 4.53 (m, 4H), 4.84 (m, 4H), 5.96 (s, 4H), 6.49 (m, 4H), 6.65 (s, 4H), 6.68 (t, 4H, *J*(H,H) = 2.0 Hz), 7.00 (bs, 2H), 7.13 (m, 8H), 7.20−7.30 (m, 24H), 7.29 (t, 4H, *J*(H,H) = 8.0 Hz), 10.74 (s, 2H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1845.47, found 1845.43. Anal. Calcd for $C_{114}H_{80}O_{18}\cdot H_2O$: C, 77.98; H, 4.71. Found: C, 77.97; H, 4.84.

Racemate A-*exo*, B(C)-*endo* dialdehyde (**7** and its enantiomer): yield = 24%; mp > 250 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.56 (m, 16H), 4.42 (m, 2H), 4.47 (m, 2H), 4.80 (m, 4H), 5.94 (m, 3H), 5.98 (s, 1H), 6.40 (m, 2H), 6.47 (s, 1H), 6.54 (s, 1H), 6.58 (s, 1H), 6.63 (s, 2H), 6.65 (s, 1H), 6.69 (t, 1H, *J*(H,H) = 2.0 Hz), 6.74 (t, 1H, *J*(H,H) = 2.0 Hz), 6.78 (t, 1H, *J*(H,H) = 2.0 Hz), 7.01 (bs, 1H), 7.05 (m, 2H), 7.13 (m, 8H), 7.15−7.34 (m, 22H), 7.38 (d, 2H, *J*(H,H) = 8.5 Hz), 7.63 (m, 3H), 7.85 (t, 1H, *J*(H,H) = 8.0 Hz), 9.98 (s, 1H), 10.68 (s, 1H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1845.47, found 1844.78. Anal. Calcd for $C_{114}H_{80}O_{18}\cdot{}^1/_2CH_2Cl_2$: C, 77.25; H, 4.59. Found: C, 77.55; 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 DMF in 1 mL of THF were used. The crude product was dry loaded to a silica column. An initial mobile phase of 90% CH_2Cl_2/hexane followed by CH_2Cl_2 was used. Products **2**−**7** 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 DMF in 1 mL of THF were used. The crude product was dry loaded on to a silica column. An initial mobile phase of CH_2Cl_2 was followed by 5% ethyl acetate/CH_2Cl_2 and then 10% ethyl acetate/CH_2Cl_2. All products were colorless solids.

A/B/C-*exo* trialdehyde **8**: yield = 20%; mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (m, 16H), 4.54 (m, 4H), 4.84 (m, 4H), 5.91 (s, 2H), 5.97 (s, 2H), 6.50 (bs, 2H), 6.63 (s, 6H), 6.68 (bs, 2H), 6.72 (bs, 2H), 7.01 (bs, 1H), 7.12 (m, 8H), 7.20−7.35 (m, 24H), 7.65 (m, 4H), 10.70 (m, 3H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1873.75, found 1873.58. Anal. Calcd for $C_{115}H_{80}O_{19}\cdot H_2O$: C, 77.43; H, 4.63. Found: C, 77.43; H, 4.56.

A/B-*exo* C-*endo* **9**: yield = 20%; mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (m, 16H), 4.52 (m, 4H), 4.83 (m, 4H), 5.92 (s, 1H), 5.96 (m, 3H), 6.38 (bs, 2H), 6.59 (s, 2H), 6.62 (s, 2H), 6.65 (m, 3H), 6.77 (bs, 2H), 7.06 (bs, 2H), 7.12 (m, 8H), 7.19−7.36 (m, 27H), 7.64 (m, 3H), 7.83 (t, 1H, *J*(H,H) = 8.5 Hz), 10.00 (s, 1H), 10.71 (s, 2H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1873.75, found 1873.58. Anal. Calcd for $C_{115}H_{80}O_{19}\cdot{}^1/_2CHCl_3$: C, 75.99; H, 4.44. Found: C, 75.96; H, 4.55.

Tetra-*exo* **10**: yield = 30%; mp > 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (m, 16H), 4.51 (s, 4H), 4.83 (t, 4H, *J*(H,H) = 8.0 Hz), 5.91 (s, 4H), 6.62 (bs, 8H), 6.72 (bs, 4H), 7.12 (m, 8H), 7.22 (m, 16H), 7.34 (dd, 8H, *J*(H,H) = 8.2 Hz), 7.67 (t, 4H, *J*(H,H) = 8.2 Hz), 10.70 (s, 4H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1901.76, found 1901.44. Anal. Calcd for $C_{116}H_{80}O_{20}\cdot{}^1/_2CH_2Cl_2$: C, 75.49; H, 4.38. Found: C, 75.77; H, 4.54.

Racemic A/B/C-*exo* C(D)-*endo* (**11** and its enantiomer): yield = 3%; mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (m, 16H), 4.44 (m, 4H), 4.78 (m, 4H), 5.90 (s, 3H), 5.93 (s, 1H), 6.40 (s, 1H), 6.51 (s, 1H), 6.57 (s, 1H), 6.59 (s, 1H), 6.64 (m, 3H), 6.72 (m, 2H), 6.76 (t, 1H, *J*(H,H) = 2.0 Hz), 6.82 (t, 1H, *J*(H,H) = 2.0 Hz), 7.08 (bs, 1H), 7.13 (m, 8H), 7.19−7.39 (m, 22H), 7.43 (d, 2H, *J*(H,H) = 8.4 Hz), 7.67 (m, 3H), 7.89 (t, 1H, *J*(H,H) = 8.4 Hz), 9.95 (s, 1H), 10.68 (m, 3H); MS *m*/*z* $(M + Ag^+)^+$ calcd 1901.76, found 1901.52. Anal. Calcd for $C_{116}H_{80}O_{20}\cdot CH_2Cl_2$: C, 74.57; H, 4.40. Found: C, 74.21; H, 4.42.

10 equiv of *s*-BuLi. For this reaction, 1.29 mL (1.8 mmol) of *s*-BuLi and 0.40 mL (5.4 mmol) of DMF in 1 mL of THF were used. The crude product was dry loaded on to a silica column. The mobile phase was 10% ethyl acetate/CH_2Cl_2. Products **8**−**10** 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 DMF in 1 mL of THF were added. Purification conditions were as per reaction with 5.5 equiv.of *sec*-butyllithium (see above). Products **2**, **3**, and **5**−**9** were isolated (see Table 1 for yields).

10 equiv of *t*-BuLi. For this reaction, 1.1 mL (1.8 mmol) of *t*-BuLi and 0.4 mL (5.4 mmol) of DMF in 1 mL of THF were added. Purification conditions were as per reaction with 10 equiv of *sec*-butyllithium (see above). Products **8**−**11** were isolated (see Table 1 for yields).

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Supporting Information Available: The range of products that can arise from exhaustive lithiation and quenching with an electrophile. NMR and mass spectra of products **2**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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