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Stereo- and Regioselective Synthesis of Molecular Baskets

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ABSTRACT: We describe a stereoselective method for obtaining multigram quantities of molecular basket $\mathbf{1}_{syn}$ in overall 11% yield, using inexpensive cyclopentadiene and diethyl fumarate as starting materials. First, an asymmetric synthesis of enantioenriched bromo(trimethylstannyl)alkene (−)−**8** was accomplished by stereoselective bromination of dibromonorbornene (+)−**4** guided by anchimeric assistance, and subsequent *syn*-*exo*-elimination of tetrabromonorbornane (−)−**5a** as the key steps. Subsequent Cu(I)-catalyzed cyclotrimerization of (−)−**8** was optimized to give $\mathbf{1}_{syn/anti}$ in 85% yield and 1:1 ratio of diastereomers. Importantly, the results of our mechanistic experiments were in line with the cyclotrimerization occurring in a chain-type fashion with racemization of a Cu(I) homochiral dimeric intermediate reducing the stereoselectivity of the transformation. Enabled by a more facile access to molecular baskets of type $\mathbf{1}_{syn}$, a range of recognition studies can now be completed for producing novel supramolecular catalysts, organophosphorus scavengers and nanostructured materials.

Introduction

Molecular baskets with α-amino acids at their periphery possess hydrophobic pockets (Figure 1) that are complementary to tetrahedral organophosphorus (OP) compounds.[1] These C_3 symmetric hosts are responsive to light,[2] and after decarboxylation, they assemble into organic nanoparticles which we have probed for spatiotemporal sequestration and/or degradation of OP nerve agent simulants[3] and pesticides.[4] Furthermore, baskets are complementary to small hydrocarbons from natural gas,[5] haloalkanes,[6] ammonium cations,[7] fullerenes[8] and other functional molecules.[9] As a result, one could envision their future development into (a) supramolecular and "green" catalysts capable of converting hydrocarbon gases into feedstock chemicals under mild conditions,[10] (b) micro-to-mesoporous materials for storage of gases and/or sequestration of pollutants,[11] and (c) surface-based devices for detection of toxic analytes.[12] The concave framework of baskets has also been used in the preparation of carbon-based materials,[13] the examination of unusual chemical bonds,[14] and the study of gated molecular encapsulation.[15]

In order to facilitate and broaden the scope of fundamental and application-oriented studies, a more effective way for accessing larger quantities of baskets is needed.[16] Indeed, we recently reported[17] an improved methodology for preparing the common precursor of baskets $\mathbf{1}_{syn}$ (Figure 1), with 6.9 g (70 mmol) of maleic anhydride giving 0.5 g of this hexa-ester in overall 3% yield. In the key synthetic step, CuI-catalyzed cyclotrimerization of racemic bromo(trimethylstannyl)alkene **8** into $\mathbf{1}_{syn}$ in 24% yield, albeit providing 61% of undesired $\mathbf{1}_{anti}$ (Figure 1). This begged a question: is such Cu(I)-catalyzed transformation[18] regioselective so that enantiopure $\mathbf{8}_{RS}$ (Figure 1) can be exclusively turned into $\mathbf{1}_{syn}$?[19] As the mechanism of copper-catalyzed Stille couplings and cyclotrimerizations remains debatable,[20] we, for the sake of argument, began our reasoning with the formalism[21] in which transmetallation of CuI and trimethylstannyl $\mathbf{8}_{RS}$ gives nucleophilic RCu[22] that, via oxidative addition, reacts with C_{sp2}–Br of another $\mathbf{8}_{RS}$ (Figure 1). After reductive elimination, the sequence ought to be repeated to furnish the annulation. Importantly, the postulated chain-type mechanism would require more than one molar equivalent of Cu(I) due to, perhaps, reversible and thermodynamically unfavorable transmetallation step.[20a] As the homochiral couplings of enantiopure $\mathbf{8}_{RS}$ are expected to give $\mathbf{1}_{syn}$, both homochiral and heterochiral couplings of racemic $\mathbf{8}_{RS}/\mathbf{8}_{SR}$ (Figure 1) could take place simultaneously to give $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$. If the rates of competing reactions are comparable (though, not necessarily the case),[18] the expected ratio of $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ becomes statistical (1:3). In this respect, De Lucchi and coworkers showed that copper(I) thiophene-2-carboxylate (CuTC) could be used to promote regio- and stereoselective cyclotrimerizations for a limited number of enantiopure norbornenes.[19] Furthermore, Lin and Wang used density functional theory to examine CuTC-promoted Stille coupling of vinylstannane and vinyl iodide, thereby reporting that the transformation occurs by a mechanism similar to the one shown in Figure 1.[21] Finally, Sakurai and coworkers dis

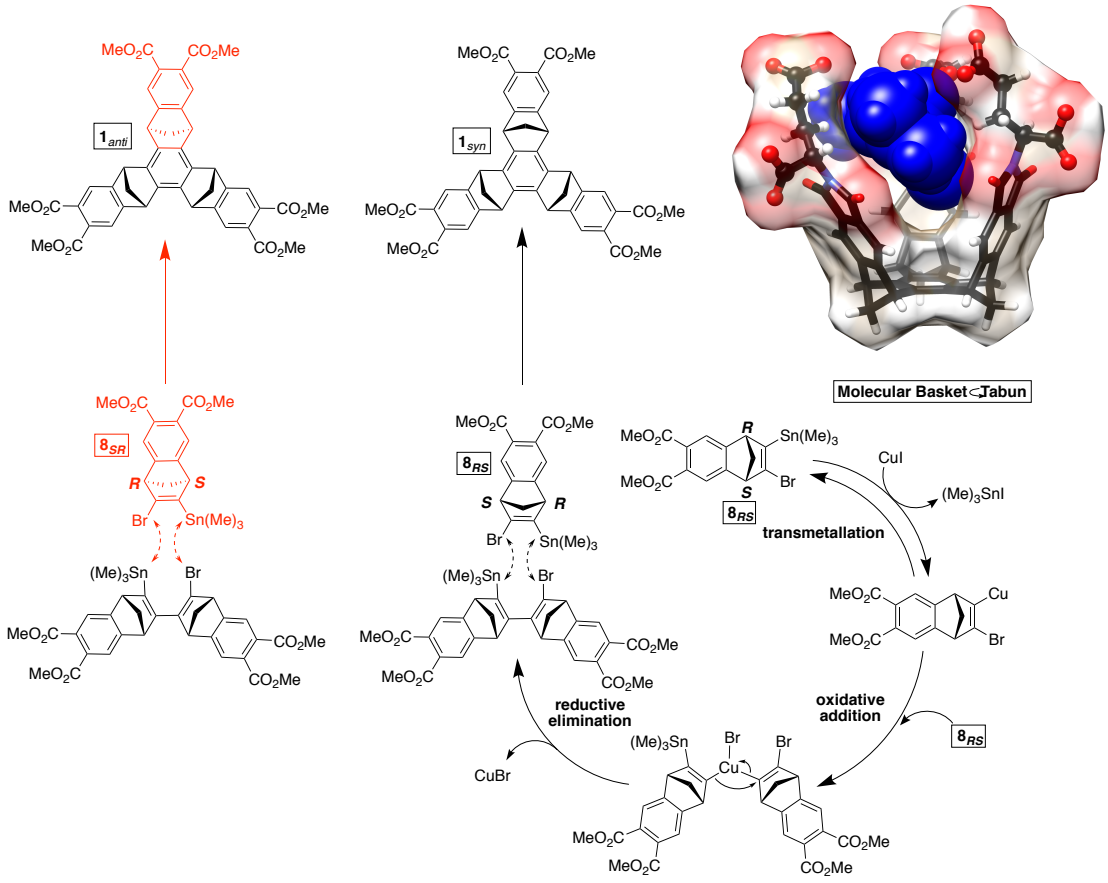
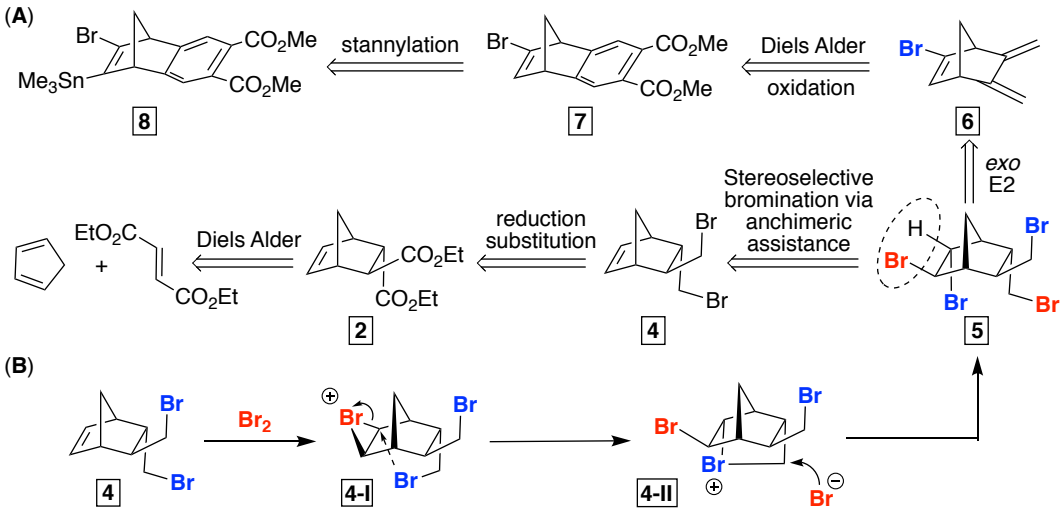


Figure 1. (Top right) Energy-minimized (MMFF, Spartan) structure of a molecular basket with three (*S*)-Glu residues holding the OP nerve agent tabun (van der Waals surface, Chimera) in its hydrophobic pocket. (Left and Bottom) A chain-type mechanism for CuI-promoted homochiral coupling of enantiopure $\mathbf{8}_{RS}$ into $\mathbf{1}_{syn}$. With a racemic mixture of $\mathbf{8}_{RS}$ and $\mathbf{8}_{SR}$ (red) and comparable rates of competing homochiral and heterochiral couplings, the ratio of $\mathbf{1}_{syn}$ to $\mathbf{1}_{anti}$ is statistical (1:3); in line with this, obtaining any other ratio of $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ stereoisomers is hereby referred to as stereoselective.



Scheme 1. (A) Retrosynthetic scheme for obtaining enantiopure **8**. (B) A postulated mechanism for electrophilic bromination of **4**.

covered that palladium nanoclusters could be used for the preparation of a few substituted *syn*-benzocyclotrimers via stereoselective Heck couplings of enantiopure iodonorbornenes.[23] Encouraged by these and our[16-17] findings and the

notion that regio- and stereoselective cyclotrimerization of enantiopure norbornenes could, in some cases, be realized, we set out to investigate the first asymmetric synthesis of enantiopure **8** and its conversion into desired $\mathbf{1}_{syn}$ using CuI as a catalyst.[18] We posited that if we developed a preparative method for obtaining larger quantities of enantiopure **8**, we should facilitate efforts toward optimizing its cyclotrimerization into the desired $\mathbf{1}_{syn}$.

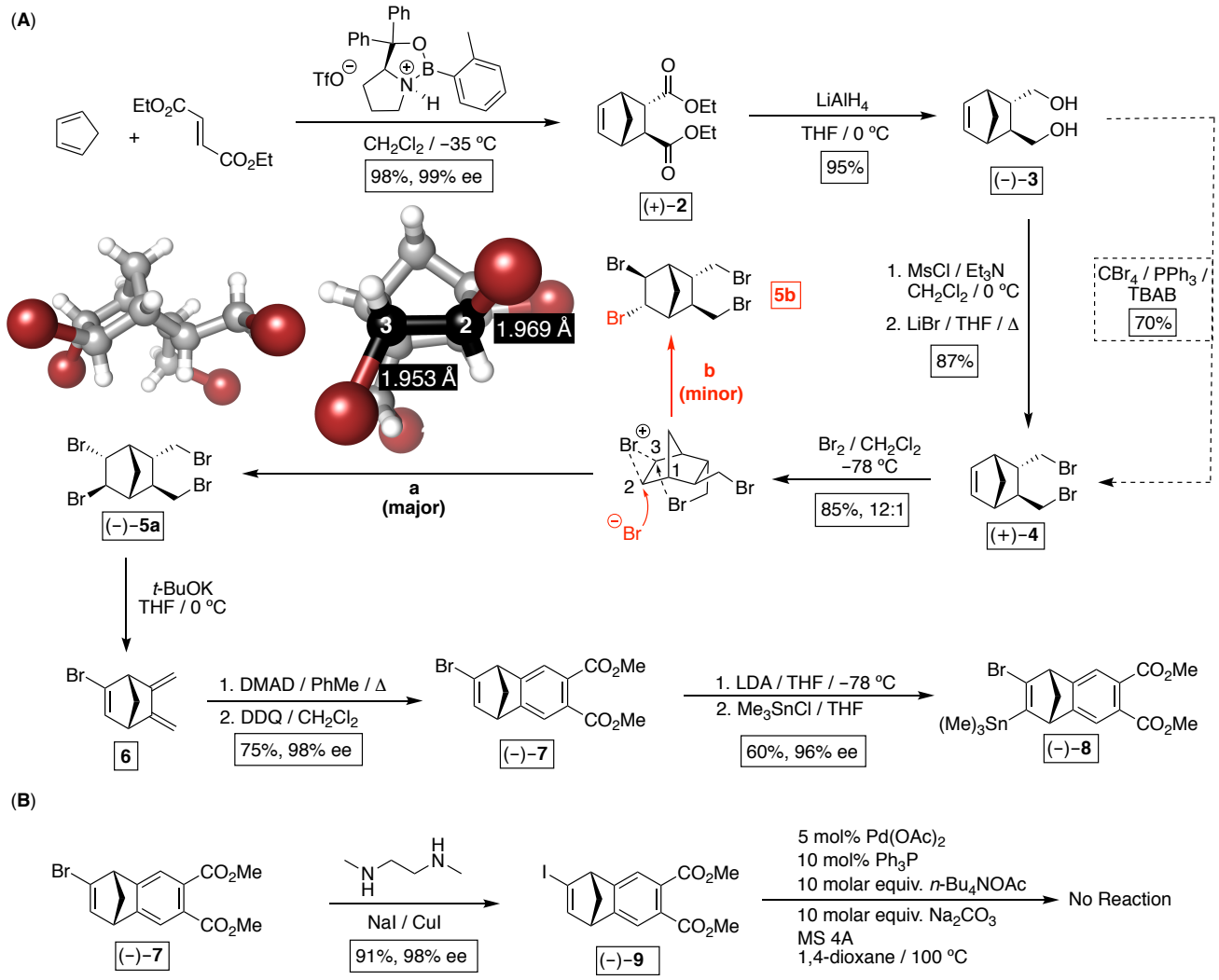


Figure 2. (A) Stereoselective synthesis of bromo(trimethylstannyl)alkene (−)−**8**. Solid-state structure of tetrabromo compound (−)−**5a**. (B) Cyclotrimerization of (−)−**9** with palladium nanoclusters.

Results and Discussion

As described in our retrosynthetic analysis in Scheme 1A, compound **8** could be obtained from **6** by Diels-Alder reaction followed by oxidation and stannylation of enantiopure **7** under established conditions.[17] To prepare enantiopure bromotriene **6**, we anticipated[24] that E2 elimination of **5** should preferentially occur on the *exo* side of this tetrabromo norbornane. On the basis of an earlier study,[24] we then hypothesized that regio- and stereoselective bromination of norbornene **4** should, via anchimeric assistance, give enantiopure **5** (Scheme 1B). In line with the proposed mechanistic scenario,[24] the *exo* addition of bromine to **4** leads to three-membered bromonium **4-I** that after a regioselective opening, by the juxtaposed bromomethylene from the *endo* side of the norbornane, rearranges into the more stable five-membered bromonium **4-II**. Ensuing S_N2 attack by bromide on the primary carbon in **4-II** furnishes enantiopure **5**. And finally, enantioselective Diels-Alder reaction of cyclopentadiene and diethyl fumarate (DEF) should[25] give *bis*-ester **2**, which after reduction and substitution was expected to form the dibromo **4** (Scheme 1A).

Following our retrosynthetic scheme, we used chiral and commercially available oxazaborolidine catalyst (Figure 2A) to differentiate two enantiotopic faces of DEF which in the reaction with cyclopentadiene gave (+)–**2** in excellent 98% yield with 99% *ee*.[25] The reaction can be run on a large scale (12 g of DEF), to give 16 g of practically enantiopure (+)–**2** with its absolute configuration established by Seebach and coworkers.[26] Lithium aluminum hydride reduction of dextrorotatory (+)–**2** in tetrahydrofuran led to the formation of the expected *bis*-alcohol (–)–**3** in 95% yield. An alternate and cheaper method for obtaining enantiopure **3** that utilizes a Diels-Alder reaction between (–)-dimenthylfumarate and cyclopentadiene,[27] in the presence of Et_2AlCl[27a] or $SnCl_4$ as Lewis acids,[26] has been reported. A diastereomeric cycloadduct dominates the reaction's outcome (>95% *de*), which after reduction gives desired *bis*-alcohol in overall 65% yield (due to

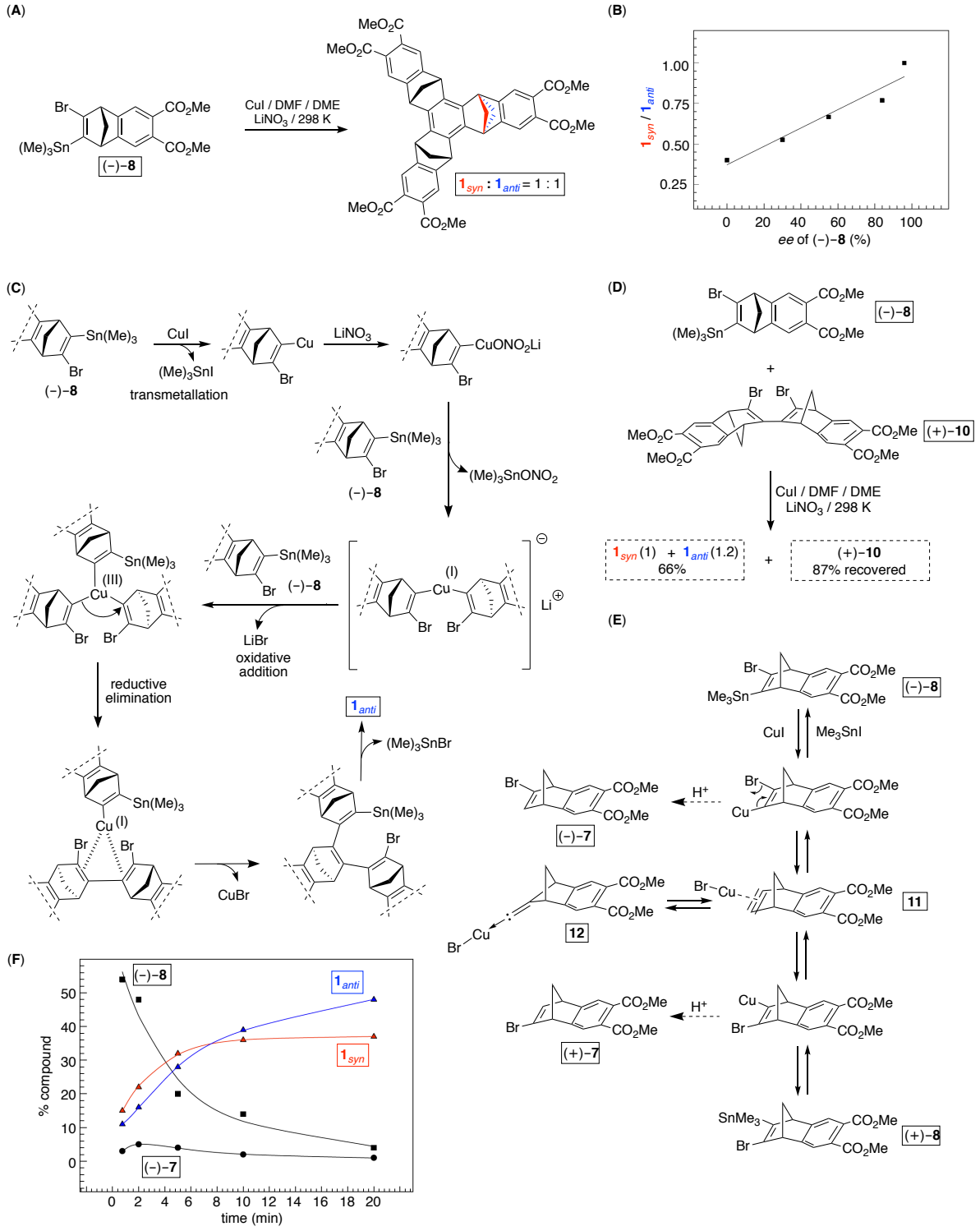


Figure 3. (A) Cu(I) catalyzed cyclotrimerization of enantioenriched (–)–**8** (96% *ee*) gave both $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$ in equal ratio. (B) A plot showing the product ratio of $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ (^{1}H NMR spectroscopy) as a function of enantiopurity (*ee*) of (–)–**8** used in the cyclotrimerization (CuI, DMF). (C) A cyclotrimerization mechanism occurring via homochiral Sn–to–Sn coupling of (–)–**8**. (D) Cu(I) catalyzed cyclotrimerization of enantioenriched (–)–**8** in the presence of homochiral dimer (+)–**10**. (E) Postulated mechanism for the racemization of (–)–**8**. (F) We used ^{1}H NMR spectroscopy and HPLC chromatography (Figure S28) to monitor the progress of CuI catalyzed conversion of (–)–**8** (84% *ee*) with time at 298 K.

the lower yield, we refrained from using this synthetic alternative). After mesylation (92%) of (–)–**3** and S_N2 substitution of the mesylate with lithium bromide (95%), we obtained (+)–**4**. Indeed, the conversion of (–)–**3** into dextrorotatory (+)–**4** could be completed in a single step using the Appel reaction, but we encountered difficulties with the reaction's reproducibility and product isolation. The low temperature bromination of (+)–**4** in dichloromethane gave two diastereomeric products in 12:1 ratio and overall 85% isolated yield (Figure 2A). The major product (–)–**5a** (^{1}H–^{1}H NOESY and COSY, Figures S16-17) formed via the neighboring group participation of the *endo* bromomethylene (pathway a, Figure 2; see also Scheme 1). On the other hand, the minor product **5b** (^{1}H–^{1}H COSY, Figure S19) formed by the opening of the bromonium cation via *endo* attack of the external bromide on carbon **2** (pathway b in Figure 2A) – note that the bromomethylene group on the *exo* side is unable to participate in the anchimeric assistance. The same type of competition (pathways a and b in Figure 2A) was observed in electrophilic selenylation and sulfenylation of norbornenes[24] for which more persistent onium cations mediated the transformation. The base-promoted elimination of (–)–**5a** gave volatile and reactive bromotriene **6**, which in the cycloaddition with dimethyl acetylenedicarboxylate (DMAD) and subsequent DDQ oxidation, formed (–)–**7** in 75% yield (98% *ee*). With stereoselective conversion of enantioenriched (+)–**4** into (–)–**7** (Figure 2A), we surmised that synthesized **5a** ought to be enantioenriched as well. Moreover, the X-ray crystal structure of (–)–**5a** (Figure 2A) corroborated its absolute configuration thereby providing evidence for the proposed mechanism of rearrangement. To elucidate the absolute configuration of (–)–**7**, however, we noted that *syn*-periplanar E2 elimination of (–)–**5a** could be occurring on either the *exo* or *endo* side of the norbornane framework. In this regard, the solid-state structure of (–)–**5a** shows that C_2–Br^{exo} (1.969 Å, Figure 2A) is longer than C_3–Br^{endo} (1.953 Å, Figure 2A) and, perhaps, easier to break in the elimination. Secondly, the *exo* elimination was already observed to prevail with a norbornane compound akin to **5**.[24]

To probe if the anticipated (–)–**7** in Figure 2A formed, we computed its specific rotation $[\alpha]_D$.[28] Using molecular mechanics, we determined the diverse conformations that contributed to the Boltzmann distribution, and then re-optimized each of these structures with density functional theory (B3LYP with 6-31+G(d) for C, H, and O and 6-311+G(2d) for Br). The six energy-minimized conformers (derived from the Boltzmann populations) of (–)–**7** had $[\alpha]_D = -46.3$, which is in good agreement with the experimental value of –48.8. In a similar manner, we found that computed $[\alpha]_D$ values of chloro- (**16**, Table S2) and iodonorbornenes (**9**, Table S2) analogues of (–)–**7** agreed with the experimental values as well.

Finally, the stannylation of (–)–**7** occurred with the retention (Figure S28) to give (–)–**8** in 60% yield (96% *ee*). When **5a**/**5b** = 12:1 mixture (84% *de*) was used in the synthesis (*vide infra*), we obtained enantioenriched (–)–**8** (84% *ee*).

To probe the preparation of $\mathbf{1}_{syn}$ (Figure 1) using palladium nanoclusters,[29] we proceeded with the synthesis of enantioenriched iodonorbornene **9** (Figure 2B). In Cu(I)-catalyzed exchange of bromide with iodide,[30] compound (–)–**7** was converted into (–)–**9** with the retention (Table S2) of configuration (91%, 98% *ee*). However when (–)–**9** was subjected to cyclotrimerization,[23] we only recovered the starting material; note that racemic **9** was, under the same reaction conditions, also found to be unreactive.

Next, we examined the CuI-catalyzed cyclotrimerization of enantioenriched (–)–**8** (96% *ee*, Figure 3A) in DMF[18] following our earlier established protocol.[17] As a reminder, in the CuI-catalyzed reaction, racemic **8** would form $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ in 84% yield with a 1:2.5 ratio of diastereomers. However, enantioenriched (–)–**8** (96% *ee,* Figure 3A) was found to give $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ in similar 85% yield but with a 1:1 ratio of diastereomers. Moreover, reducing the enantiopurity of (–)–**8** was found to have a steady and adverse effect on the quantity of the desired *syn* diastereomer formed in the process, as depicted with the linear relationship in Figure 3B. In line with the chain-type mechanism (Figure 1), the enantiopure **8** should, via homochiral Sn–to–Br couplings, lead to the exclusive formation of the *syn* diastereomer, which clearly was not the case. On the other hand, following the mechanism for Cu(I)-catalyzed cyclotrimerizations proposed by De Lucchi and coworkers (Figure 3C),[20b] the homochiral coupling of (–)–**8** ought to exclusively yield $\mathbf{1}_{anti}$, which also did not take place. In line with this mechanistic scenario, the Italian team reported that enantioenriched substrates would often give homodimers along with a greater quantity of the *anti*-cyclotrimer.[18, 31] In light of the arguments above, the linear dependence in Figure 3B could be interpreted by rendering mechanisms in Figures 1 and 3C as either inapt or incomplete. Accordingly, we noted that in the cyclotrimerization of (–)–**8** there was no detectable formation (^{1}H NMR spectroscopy) of the C_2-symmetric and homochiral dimer **10** (Figure 3D).[18, 20b] To additionally examine the role of **10**, and the mechanism in Figure 3C, we synthesized this molecule by completing Sn–to–Sn coupling of (–)–**8** using $Cu(OTf)_2$.[32] When one molar equivalent of (+)–**10** was added to three molar equivalents of (–)–**8** (Figure 3D) and the mixture subjected to CuI in DMF, the catalytic conversion took place giving $\mathbf{1}_{syn/anti}$ = 1:1.2 in 66% yield with (+)–**10** almost fully (87%) recovered. A rather insignificant effect of the homodimer (+)–**10** on the reaction's outcome can, perhaps, be interpreted by this molecule not participating in the cyclotrimerization to favor chain-type (Figure 1) over the Sn–to–Sn (Figure 3C) mechanistic alternative.[20b] If enantiopure (–)–**8** were to racemize (Figure 3E), however, both $\mathbf{1}_{syn/anti}$ would be forming as the time progresses regardless of the mechanism. In this regard, a departure of CuBr from Cu(I)-norbornene could give bicyclo[2.2.1]heptyne **11**[33] (Figure 3E) in equilibrium with achiral Cu(I) carbene complex **12**,[34] which then turns back into enantiomer (+)–**8**; note that related palladium-containing intermediates occur in *cine* substitutions.[35] In support of the racemization, Gassman and coworkers[33] discerned the formation of highly-strained bicyclo[2.2.1]heptyne (norbornyne) akin to **11**. More recently, Gilbert and coworkers demonstrated[34, 36] that norbornyne acts more as a dicarbene that is in equilibrium with alkylidenecarbene **12** (Figure 3E). Both Komatsu's and Hart's research groups confirmed the transient formation of bicyclo[2.2.2]octynes[37] by trapping them with 1,3-diphenylisobenzofuran.[38] To probe if the proposed racemization of (–)–**8** (84% *ee*, Figure 3E) occurred in the cyclotrimerization, we set five simultaneous reactions to take place under identical conditions. Each reaction was terminated at different time, and the reaction mixtures subjected to HPLC and ^{1}H NMR analyses to reveal a gradual disappearance of (–)–**8** with the concomitant formation of $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$ (Figure 3F). In addition, the appearance of (–)–**7** manifested

the transient formation of copper(I)-transmetallated (–)–**8** (that was protonated during the work-up) at a steady state concentration. Importantly, both enantioenriched (–)–**8** and (–)–**7** persisted (84% *ee*) for the entire course of the reaction therefore refuting the anticipated racemization of the reactant and its transmetallated product! Can another intermediate from two mechanisms under consideration (Figure 1 and 3C) undergo racemization? For the mechanism starting with Sn-to-Sn homocoupling[20b] of (–)–**8** (Figure 3C), it is difficult to envision any of intermediates undergoing a facile loss of stereochemical information. On the contrary, the chain-type cyclotrimerization[20a, 20c, 21] (Figure 4A) could occur via **13** undergoing an intramolecular oxidative addition to give *meso* Cu(III) metallacyclopentadiene **14**.[40] Following, reductive eliminations from **14** produce racemic **13**/**15** from which $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$ are, respectively, generated. A faster formation of $\mathbf{1}_{syn}$ over $\mathbf{1}_{anti}$ early in the transformation (Figure 3F) could have resulted from relatively slow conversion of **13** into **15** permitting the initial build up of the desired *syn* product. Indeed, providing experimental evidence for **13** and learning about its racemization (Figure 4A) is an objective worth pursuing for perfecting the synthetic procedure.

In an attempt to optimize the cyclotrimerization of (–)–**8** for obtaining more of $\mathbf{1}_{syn}$, we ran the reaction at various temperatures (Figure 4B/C). First, we noted that the yields of $\mathbf{1}_{syn/anti}$ showed a similar parabolic dependence with temperature for both enantioenriched (96% *ee*) and racemic **8** (Figure 4B). It follows that homochiral and heterochiral couplings of (+) and (–) enantiomers of **8** occur at comparable rates with a small degree of enantiomeric discrimination: each enantiomer chooses its coupling partner with no particular preference resulting in similar quantity of diastereomeric $\mathbf{1}_{syn/anti}$ products.[18] Furthermore, for racemic **8**, the diastereomeric *syn*/*anti* product ratio did not change with temperature and was close to the expected statistical value of 0.33 (Figure 4C). However, in the cyclotrimerization of enantioenriched **8**, the yield of $\mathbf{1}_{syn}$ was higher and showed a parabolic dependence with temperature (Figure 4C). First, we reason that at a room temperature, homochiral and heterochiral **13**/**15**-to-(–)–**8** couplings could (in accord with Figure 4A) dominate the reaction's outcome to give roughly 1:1 ratio of products. Next, we noted lower yields of diastereomeric $\mathbf{1}_{syn/anti}$ at temperatures below and above 298 K (Figure 3D). With more extensive and "non-productive" depletion of (–)–**8**, additional reaction channels may open to

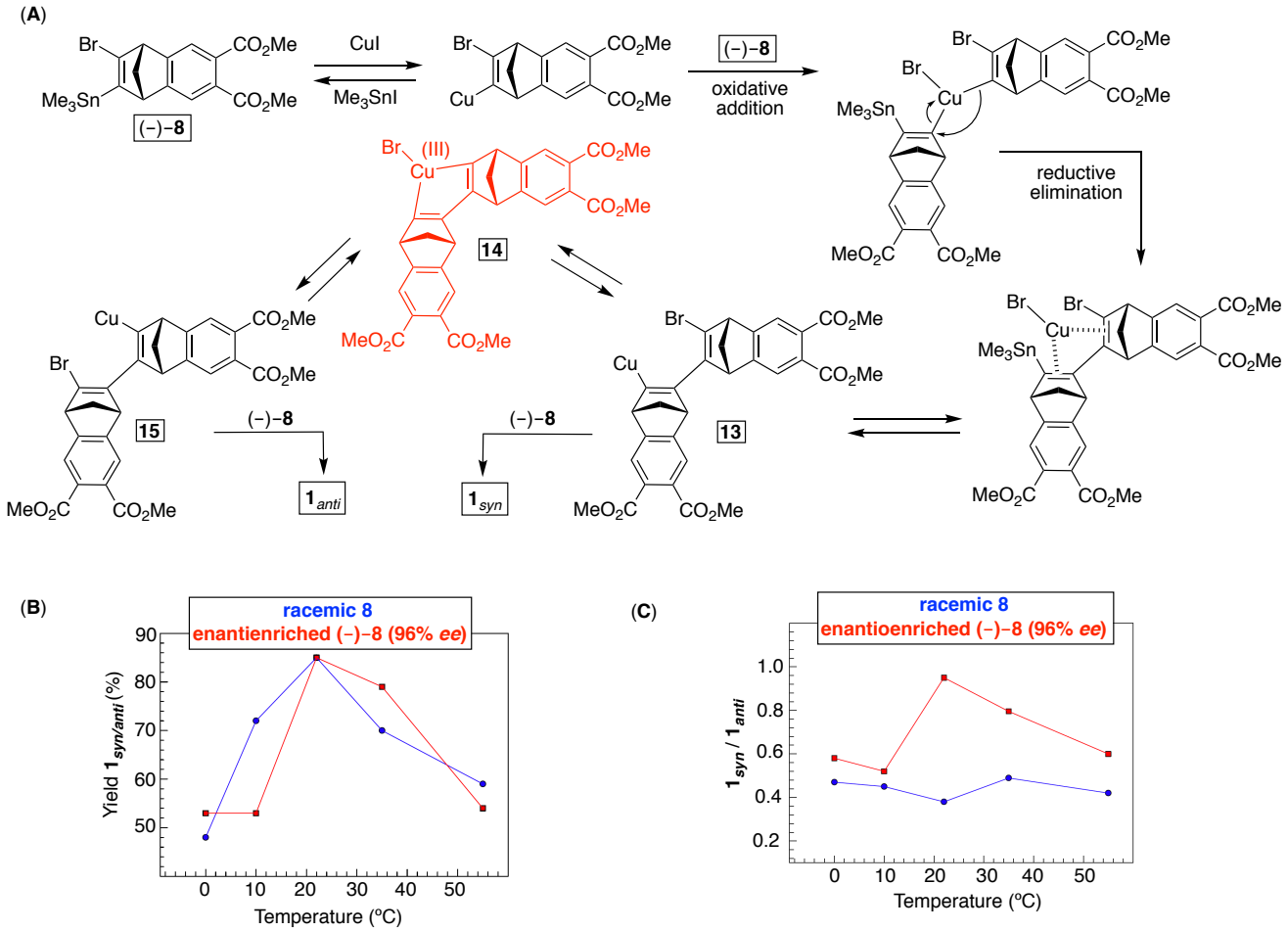


Figure 4. (A) A chain-type mechanism for CuI-promoted cyclotrimerization of enantiopure (–)–**8** with homochiral dimer **13** undergoing intramolecular oxidative addition to give achiral (*meso*) Cu(III) intermediate which after a reductive elimination forms enantiomeric **14**. (B) A plot showing yields of $\mathbf{1}_{syn/anti}$ as a function of temperature for cyclotrimerizations of enantioenriched (red) and racemic (blue) **8**. (C) Ratio of $\mathbf{1}_{syn}/\mathbf{1}_{anti}$ as a function of temperature from cyclotrimerizations described in (D).

steer the reaction's diastereoselectivity toward $\mathbf{1}_{anti}$ (Figure 3E).

Conclusion

In conclusion, we developed regio- and stereoselective methodology for obtaining molecular baskets of type $\mathbf{1}_{syn}$. In the key synthetic step, Cu(I)-catalyzed cyclotrimerization of enantioenriched bromo(trimethylstannyl)norbornene (−)−**8** gave cup-shaped $\mathbf{1}_{syn}$ in 43% yield. Following our optimized procedure, one can now use 12 g (70 mmol) of inexpensive diethyl fumarate and, in roughly two weeks, obtain 1.8 g of basket $\mathbf{1}_{syn}$ (9%). Due to difficulties in chromatographic separation of (−)−**5a** and **5b** (Figure 2), however, we realized that completing the synthesis with (−)−**5a**/**5b** mixture (12:1, Figure 2) would give 2.0 g of $\mathbf{1}_{syn}$ (11 %); the preparative route for using (−)−**5a**/**5b** mixture is described in the experimental section. With more facile access to gram quantities of functionalized molecular baskets, the stage is now set for broadening the scope of experimental studies toward creating novel catalysts, OP scavengers and nanostructured soft materials.

Experimental Section

General Information. All chemicals were purchased from commercial sources and used as received unless stated otherwise. All solvents were dried prior to use according to standard literature procedures. Chromatographic purifications were performed with silica gel 60 (SiO_2, Sorbent Technologies 40-75 μm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed on silica-gel plate w/UV254 (200 μm). Chromatograms were visualized by UV-light or stained with I_2. All NMR samples were kept in class B glass NMR tubes (Wilmad Lab Glass). NMR experiments were performed with Bruker 400, 600, 700 and 850 MHz spectrometers. Chemical shifts are expressed in parts per million (δ, ppm) while coupling constants (J) are given in Hertz (Hz). Residual solvent protons were used as internal standards: for ^{1}H NMR spectra $CDCl_3$ = 7.26 ppm while for ^{13}C NMR spectra $CDCl_3$ = 77.2 ppm; $CDCl_3$ was purchased from Cambridge Isotope Laboratories. High-resolution mass spectra (HRMS) were obtained using positive electron impact (EI), chemical ionization (CI) recorded on a VG 70-VSE(B) instrument or positive electrospray ionization techniques (ESI) recorded on a Bruker-ESI TOF instrument. Optical rotation was measured on a Perkin-Elmer 241 Polarimeter (c is in g/100 mL and the path length was 1 decimeter). Enantiomeric excesses of chiral compounds were determined by either chiral stationary phase gas chromatographic (CSP GC) or high performance liquid chromatography (HPLC) analysis. CSP GC was performed on an Agilent 7820A using hydrogen as the carrier gas, equipped with a Cyclosil-B (30 m x 0.25 mm, 0.25 μm film thickness), capillary GC columns purchased from Agilent. Each GC was equipped with FID detectors and integrators or a computer. HPLC was performed on an Agilent 1260 Infinity II Quaternary LC, using Chiralpak AD-H column (250 x 4.6 mm, 5 μm particle size) eluting with hexane:^{i}PrOH and monitored by DAD (Diode Array Detector). Retentions times are quoted in minutes.

Diethyl(1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (+)−2: Following the published procedure,[25] compound **2** was obtained as a yellow oil (98%, >99% *ee*) with ^{1}H NMR and ^{13}C NMR data in line with the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.27 (dd, 1H, J = 3.3, 5.8 Hz), 6.06 (dd, 1H, J = 2.8, 5.3 Hz), 4.16 (q, 2H, J = 7.5 Hz), 4.06-4.12 (m, 2H), 3.37 (app. t, 1H, J = 4.0 Hz), 3.25 (m, 1H), 3.11 (m, 1H), 2.67 (dd, 1H, J = 1.5, 4.5 Hz), 1.61 (d, 1H, J = 8.5 Hz), 1.43-1.45 (m, 1H), 1.27 (t, 3H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 174.5, 173.3, 137.6, 135.0, 60.8, 60.5, 47.8 (2C), 47.2 (2C), 45.7, 14.2 (2C). Enantioselectivity was determined by GC analysis using a Cyclosil-B column (110 °C, 25 psi); retention times: 93.2 mins (minor stereoisomer −) and 95.4 mins (major stereoisomer +). $[\alpha]_D^{23}$ +103 (c = 1.00, $CHCl_3$).

((1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-diyl)dimethanol (−)−3: To a suspension of lithium aluminum hydride (3.10 g, 81.7 mmol) in THF (80 mL) at 0 °C, a solution of compound **(+)−2** (5.00 g, 21.0 mmol) in THF (50 mL) was added dropwise. The resulting solution was warmed to 25 °C and stirred for 30 minutes. The solution was cooled to 0 °C and then quenched with aqueous NaOH (3 mL, 3.5 M). Ethyl acetate (20 mL) and water (20 mL) were added followed by filtration through a pad of celite. The organic filtrate was dried with Na_2SO_4 and concentrated in vacuo to give 3.20 g of **(−)−3** as a clear oil (95%). ^{1}H NMR and ^{13}C NMR data corresponding to this compound were in line with the literature.[41] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.23 (dd, J = 3.20, 5.47 Hz, 1H), 5.98 (dd, J = 2.76, 5.54 Hz, 1H), 3.77 (dd, J = 5.52, 9.75 Hz, 1H), 3.66 (dd, J = 5.23, 9.72 Hz, 1H), 3.42 (t, J = 9.95 Hz, 1H), 3.03 (t, J = 9.85 Hz, 1H), 2.82 (s, 1H), 2.59 (s, 1H), 1.91–1.96 (m, 1H), 1.45 (bs, 2H), 1.28–1.33 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 138.0, 133.4, 66.5, 66.0, 47.9, 47.1, 46.9, 44.6, 44.5. $[\alpha]_D^{23}$ = −23.9 (c = 1.00, $CHCl_3$).

(1*R*,4*S*,5*S*,6*S*)-5,6-bis(bromomethyl)bicyclo[2.2.1]hept-2-ene (+)−4: To a solution of freshly distilled Et_3N (36 mL, 260 mmol) and *bis*-alcohol **(−)−3** (10.0 g, 65 mmol) in dry CH_2Cl_2 (260 mL), MsCl (20 mL, 260 mmol) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature to be stirred overnight. The reaction mixture was then cooled to 0 °C and quenched with H_2O (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), washed with $NaHCO_3$, dried with Na_2SO_4, and concentrated *in vacuo* to give 18.5 g of the crude mesylate as a brown oil (R_f = 0.38; on SiO_2 chromatographic plates with hexanes:ethyl acetate = 1:1; I_2 stain). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.30 (dd, J = 5.7, 3.2 Hz, 1H), 6.11 (dd, J = 5.7, 2.9 Hz, 1H), 4.24 (ddd, J = 18.0, 9.9, 7.6 Hz, 2H), 3.97 (dd, J = 7.9, 1.2 Hz, 2H), 3.04 (s, 3H), 3.01 (s, 3H), 3.00-2.97 (m, 1H), 2.81-2.78 (m, 1H), 2.17-2.12 (m, 1H), 1.60-1.56 (m, 1H), 1.51–1.44 (m, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 138.3, 134.1, 72.5 (2C), 46.5, 44.4, 44.2, 43.7, 43.1, 37.7, 37.6. HRMS (ESI-MS): m/z calcd for $C_{11}H_{18}S_2O_6Na$: 333.0437 [M+Na]+; found: 333.0425. The mesylate (10.70 g, 34.5 mmol) was disolved in THF (320 mL) and LiBr (38.50 g, 443 mmol) was added in one portion. The susspession was heated at reflux for 8 h. The reaction was cooled and concentrated in vacuo. The oil was dissolved in CH_2Cl_2 and washed with water. Organic layer was dried with Na_2SO_4 and concentrated in vacuo to give 15.8 g of **(+)−4** as a yellow oil (87%); R_f = 0.82 on SiO_2 chromatographic plates with hexanes:ethyl acetate = 6:1. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.31 (dd, J = 5.7, 3.2 Hz, 1H), 6.13 (dd, J = 5.7, 2.9 Hz, 1H), 3.56 (dd, J = 9.8, 7.5 Hz, 1H), 3.39 (dt, J = 9.7, 7.6 Hz, 2H), 3.07-3.03 (m, 2H), 2.87-2.85 (m, 1H), 2.15-2.10 (m, 1H), 1.57-1.54 (m, 1H), 1.52-1.49 (m, 1H), 1.47-1.42 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 138.5, 133.9, 50.3, 49.9, 47.5, 46.4, 46.3, 37.5, 37.0. HRMS (TOF CI, methane): m/z calcd for $C_9H_{13}Br_2$: 278.9384 $[M+H]^+$; found: 278.9382. $[\alpha]_D^{23}$ +8.8 (c = 1.21, $CHCl_3$).

(1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-2,3-dibromo-5,6-bis(bromomethyl)bicyclo[2.2.1]heptane (−)−5a: Compound **(+)−4** (3.50 g, 12.5 mmol) was dissolved in 155 mL of dry CH_2Cl_2 and cooled to -78 °C. A solution of Br_2 (0.67 ml, 12.6 mmol) in 110 mL of dry CH_2Cl_2 was added dropwise to the reaction mixture over 20 min. The resulting solution was then stirred for 10 min. The reaction was quenched with aqueous saturated $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3 x 50 mL). Organics were dried with Na_2SO_4 and concentrated in vacuo to give 4.70 g of **5a**:**5b** = 12:1 (determined from ^{1}H NMR spectrum of the reaction mixture, Figure S25) as a brown oil (85%). The major diastereomer (−)−**5a** was purified by recrystallization from hexanes:CH_2Cl_2 = 3:1 to give 3.30 g of this compound as a white solid (60%). m.p. 90-91ºC; **(−)−5a:** ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.40 (td, J = 4.1, 1.2 Hz, 1H, H_f), 4.02 (dd, J = 4.2, 2.8 Hz, 1H, H_a), 3.98-3.89 (m, 2H, H_m and H_l), 3.63 (dd, J = 10.2, 5.4 Hz, 1H, H_k), 3.26 (dd, app t, J = 9.9 Hz, 1H, H_j), 2.88-2.85 (m, 1H, H_e), 2.70 (s, 1H, H_b), 2.22-2.16 (m, 1H, H_d), 1.98-1.94 (m, 1H, H_g), 1.91-1.86 (m, 1H, H_c), 1.64-1.60 (m, 1H, H_i). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 58.5 (C-2), 56.8 (C-3), 52.3 (C-1), 51.4 (C-5),

51.2 (C-6), 49.4 (C-4), 35.4 (C-7), 34.9 (C-*endo*), 33.9 (C-*exo*); for additional information, see Figure S1. HRMS (EI): *m/z* calcd for $C_9H_{12}Br_3$: 356.8489 $[M\text{-}Br]^+$; found: 356.8484. $[\alpha]_D^{23}$ = –37.4 (c = 1.06, $CHCl_3$).

(1*S*,4*S*)-2-bromo-5,6-dimethylenebicyclo[2.2.1]hept-2-ene 6: A solution of a compound **(–)–5a** (5.00 g, 11.4 mmol) in anhydrous THF (250 mL) was cooled to 0 °C. Potassium tert-butoxide (9.00 g, 80.2 mmol) was added in portions to the solution. The reaction was warmed up to room temperature and stirred for 7 h. The reaction was then cooled to 0 ºC and neutralized with dilute HCl (~1.0 M, 50mL). Solution was extracted with hexanes (3 x 100mL), dried with Na_2SO_4, and concentrated in vacuo to obtain 2.20 g of **6** (92%) as a yellow oil; R_f = 0.69 on SiO_2 chromatographic plates with hexanes. ^{1}H NMR and ^{13}C NMR data from **6** were in line with the literature.[42] ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.20 (d, *J* = 3.0 Hz, 1H), 5.31 (s, 1H), 5.25 (s, 1H), 5.14 (s, 1H), 5.01 (s, 1H), 3.37 (s, 1H), 3.30 (s, 1H), 2.05 (d, *J* = 8.3 Hz, 1H), 1.64 (d, *J* = 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 146.9, 146.5, 135.4, 127.7 103.4, 102.4, 58.7, 52.2, 50.9.

Dimethyl (1*S*,4*S*)-2-bromo-1,4-dihydro-1,4-methanonaphthalene-6,7-dicarboxylate (–)–7: Compound **(–)–7** was synthesized from **6** following the literature procedure;[5] ^{1}H NMR and ^{13}C NMR spectral data are consistent with the reported values. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 ppm (1H, s), 7.51 (1H, s), 6.73 (d, *J* = 3.2 Hz, 1H), 4.00 (1H, s), 3.88 (6H, s), 3.85 (1H, s), 2.63 (d, *J* = 8.0 Hz, 1H), 2.35 (d, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.4, 168.1 , 153.9, 153.3, 139.8, 135.8, 130.1, 128.9, 122.1, 121.5, 68.8, 58.2, 52.7, 52.6, 51.7. $[\alpha]_D^{23}$ = –48.8 (c = 0.98, $CHCl_3$). Enantiopurity of (–)–**7** was determined to be 98% *ee* by HPLC analysis (Figures S3 and S4) using an AD-H column (hexanes:isopropanol = 96:4, 1 mL/min); retention times: 15.6 min (+)–**7** and 19.4 min (–)–**7**.

Dimethyl (1*S*,4*R*)-2-bromo-3-(trimethylstannyl)-1,4-dihydro-1,4-methanonaphthalene-6,7-dicarboxylate (–)–8: Compound **(–)–8** was synthesized from **(–)–7** following an already published procedure;[43] ^{1}H NMR and ^{13}C NMR spectral data are consistent with the reported values. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (s, 1H), 7.47 (s, 1H), 4.09 (s, 1H), 3.91 (s, 7H), 2.57 (d, *J* = 7.6 Hz, 1H), 2.27 (d, *J* = 7.6 Hz, 1H) and 0.24 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.5, 168.4, 154.0, 153.6, 152.2, 147.0, 129.0, 122.0, 121.1, 68.4, 60.2, 57.0, 52.6, 52.5, -9.3. $[\alpha]_D^{23}$ = –33.1 (*c* = 1.18, $CHCl_3$). Enantiopurity of (–)–**8** was determined to be 96% *ee* by HPLC analysis (Figures S5 and S6) using an AD-H column (hexanes:iosopropanol = 96:4, 1 mL/min); retention times: 6.5 min for (+)–**8** and 8.6 min for (–)–**8**.

Dimethyl (1*S*,4*S*)-2-iodo-1,4-dihydro-1,4-methanonaphthalene-6,7-dicarboxylate (–)–9: Dry copper (I) iodide (0.20 g, 1.1 mmol) and NaI (2.00 g, 13.3 mmol) were added to a round bottom flask. A solution of (–)–(**7**) (0.50 g, 1.5 mmol) in 3 mL of 1,4-dioxane along with *N*,*N*′-dimethylethylenediamine (0.1 mL, 0.9 mmol) were added to the same flask. The suspension was heated to reflux for 10 h under an atmosphere of nitrogen. The reaction mixture was then cooled to ambient temperature, diluted with CH_2Cl_2 (20 mL) and washed with 30% NH_4OH (aq). Organic layer was dried with Na_2SO_4 and concentrated in vacuo. The resulting brown-black oil was filtered through a silica plug (CH_2Cl_2:EtOAc = 3:1) to, after the solvent removal, give 0.52 g of **9** as a yellow oil (91%); R_f = 0.39 on SiO_2 chromatographic plates with hexanes:EtOAc = 4:1. ^{1}H NMR (850 MHz, $CDCl_3$): δ (ppm) 7.66 (s, 1H), 7.51 (s, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 3.97 (m, 1H), 3.95 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.59 (d, *J* = 7.7 Hz, 1H), 2.25 (d, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (214 MHz, $CDCl_3$): δ (ppm) 168.7, 168.3, 153.7, 153.5, 148.8, 130.2, 129.0, 122.3, 121.8, 105.3, 69.2, 61.4, 53.0, 52.8, 52.7. HRMS (EI): *m/z* calcd for $C_{15}H_{13}IO_4Na$: 406.9751 $[M+Na]^+$; found: 406.9746. $[\alpha]_D^{23}$ = –50.6 (*c* = 1.54, $CHCl_3$). Enantiopurity of (–)–**9** was determined to be 98% *ee* by HPLC analysis (Figures S7 and S8) using an AD-H column (hexanes:isopropanol = 96:4, 1 mL/min); retention times: 15.9 min for (+)–**9** and 20.2 min for (–)–**9**.

Bis-3,3'-(dimethyl(1*S*,4*S*)-2-bromo-1,4-dihydro-1,4-methanonaphthalene-6,7-dicarboxylate) (+)–10: Copper(II)triflate (65 mg, 0.18 mmol) and $LiNO_3$ (12 mg, 17 mmol) were added to a dry round bottom flask. Next, the flask was placed under an atmosphere of nitrogen (after being removed from the glove box) followed by the addition of dried DMF (1.5 mL) and dimethoxyethane (0.1 mL). After 60 min of stirring at 25 °C, a solution of (–)–(**8**) (30 mg, 0.06 mmol, 96% *ee*) was added in dry DMF (0.5 mL) to the mixture and was stirred at the desired temperature for 12 h. The reaction mixture was cooled to 0 °C and filtered. The filtrate was diluted with ethyl acetate (1.5 mL), washed with aqueous ammonia (10%, 4 x 0.5 mL) and washed with H_2O (4x1 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the solid residue (SiO_2, dichloromethane:acetone = from 18:1 to 9:1) gave compound **10** (11.5 mg, 57%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.61 (s, 1H), 4.62 (d, *J* = 1.6 Hz, 1H), 3.91 (d, *J* = 1.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.61 (dt, *J* = 7.8, 1.5 Hz, 1H), 2.28 (dt, *J* = 7.8, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 168.4, 168.3, 152.9, 152.4, 144.4, 131.2, 130.2, 129.7, 123.1, 122.1, 66.3, 59.8, 52.8, 52.7, 52.7. HRMS (ESI-MS): m/z calcd for $C_{30}H_{24}Br_2O_8Na$: 692.9730 $[M+Na]^+$; found: 692.9726. $[\alpha]_D^{23}$ +11.2 (*c* = 1.50, $CHCl_3$).

Hexamethyl(5*R*,6*S*,11*R*,12*S*,17*R*,18*S*)-5,6,11,12,17,18-hexahydro-5,18:6,11:12,17-trimethanotrinaphthylene-2,3,8,9,14,15-hexacarboxylate $\mathbf{1}_{syn}$: Within a glove box, $LiNO_3$ (7.82 g, 128.3 mmol) was mixed with CuI (18.89 g, 99.2 mmol) inside an oven-dried flask. Next, the flask was placed under an atmosphere of nitrogen (after being removed from the glove box) followed by the addition of dried DMF (340.0 mL) and dimethoxyethane (22.0 mL). After 60 min of stirring at 25 °C, a solution of compound (–)–**8** (6.70 g, 13.4 mmol) was added in dry DMF (110.0 mL) to the mixture and was stirred at the desired temperature for 12 h; the reaction time could be shorten if, desired, with the same outcome (Figure 3F). The filtrate was diluted with ethyl acetate (350.0 mL), washed with aqueous ammonia (10%, 4 x 100 mL) and washed with H_2O (4 x 60 mL). The organic layer was dried with Na_2SO_4 and then concentrated in vacuo to give a solid residue subjected to column chromatography (SiO_2, CH_2Cl_2:acetone = from 18:1 to 9:1) yielded 1.48 g of $\mathbf{1}_{syn}$ (43%) and 1.44 g of $\mathbf{1}_{anti}$ (42%) as white solids. ^{1}H NMR and ^{13}C NMR data corresponding to compounds $\mathbf{1}_{syn}$ were in line with the literature.[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.54 (s, 6H), 3.80 (s, 18H), 4.43 (s, 6H), and 7.45 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) = 167.7, 152.6, 137.6, 129.3, 121.2, 65.0, 51.8, 48.5.

Cyclotrimerization of (–)–8 in the presence of (+)–10: Within a glove box, $LiNO_3$ (35 mg, 0.51 mmol) was added to CuI (85 mg, 0.45 mmol) inside an oven-dried flask. The flask was placed under an atmosphere of nitrogen (after being removed from the glove box) followed by the addition of dry DMF (1.5 mL) and dimethoxyethane (0.1 mL). After 60 min of stirring at 25 °C, a solution of **(–)–8** (30 mg, 0.06 mmol) and **(+)–10** (13 mg, 0.02 mmol) in dry DMF (0.5 mL) was added to the mixture and stirred for 12 h. The reaction mixture was cooled to 0 °C and filtered. The filtrate was diluted with ethyl acetate (1.5 mL), washed with aqueous ammonia (10%, 4 x 0.5 mL) and washed with H_2O (4 x 1 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the solid residue (SiO_2, dichloromethane:acetone = from 18:1 to 9:1) gave $\mathbf{1}_{syn}$ (4.7 mg), $\mathbf{1}_{anti}$ (5.5 mg) and **(+)–10** (11.3 mg) as white solids.

Compound (–)–7 from mixture of (–)–5a and (1*R*,2*S*,3*S*,4*S*,5*R*,6*R*)-2,3-dibromo-5,6-bis(bromomethyl)bicyclo[2.2.1]heptane 5b. A solution of **(–)–5a:5b** = 12:1 (0.25 g, 0.57 mmol) in anhydrous THF (15 mL), and under an atmosphere of nitrogen, was cooled to 0 °C. To this solution, potassium *tert*-butoxide (0.440 g, 3.92 mmol) was added in portions. The reaction mixture was allowed to warm to room temperature and stirred for 7 h. The reaction was then cooled to 0 °C and neutralized with dilute HCl (15 mL, 1M). Solution was extracted with hexanes (3 x 10 mL), dried with Na_2SO_4, and concentrated *in vacuo* at low temperature to give 0.10 g of **6** as yellow oil. To a solution of **6** (0.10 g, 0.52 mmol) in dry toluene (3 mL), dimethyl acetylenedicarboxylate (0.1 mL, 0.82 mmol) was added. The solution was brought to reflux and stirred overnight. The reaction was then concentrated in vacuo to give 0.18 g of the cycloaddition product as a yellow oil. To a

solution of (0.18g, 0.52 mmol) of the cycloaddition adduct in CH_2Cl_2 (8 mL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added (0.270 g, 1.19 mmol). The solution was stirred overnight at room temperature, then filtered to remove excess of DDQ, washed with aq. $NaHCO_3$ and filtered again. Next, the solution was extracted with aq. $NaHCO_3$, the organic layer dried with Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography (SiO_2) with hexanes:ethyl acetate = from 15:1 to 3:1, gave 0.14 g of **(−)−7** as a viscous yellow oil (75% over 3 steps). R_f = 0.39 on SiO_2 chromatographic plates with hexanes:ethyl acetate = 4:1. $^1H/^{13}C$NMR spectroscopic data was in agreement with those reported above. Enantiopurity of (−)−(**7**) was determined to be 84 % *ee* by HPLC analysis (Figure S11) using an AD-H column (hexanes:isopropanol = 96:4, 1 mL/min); retention times: 15.6 min for (+)−(**7**) and 19.4 min for (−)−(**7**).

Compound (−)−8 from (−)−5a/5b mixture: Compound **8** was synthesized following the same literature procedure[5] as enantiopure **8**; ^{1}H NMR and ^{13}C NMR spectral data are consistent with the reported values. $^1H/^{13}C$NMR spectroscopic data was in agreement with those reported above. Enantiopurity of (−)−(**8**) was determined to be 84 % *ee* by HPLC analysis (Figures S12) using an AD-H column (hexanes:isopropanol = 96:4, 1 mL/min); retention times: 6.5 min for (+)−(**8**) and 8.6 min for (−)−(**8**).

Compound 1_{syn} from (−)−5a/5b mixture: Within a glove box, $LiNO_3$ (5.60 g, 91.9 mmol) was mixed with CuI (13.60 g, 71.4 mmol) inside an oven-dried flask. Next, the flask was placed under an atmosphere of nitrogen (after being removed from the glove box) followed by the addition of dried DMF (240 mL) and dimethoxyethane (16 mL). After 60 min of stirring at 25 °C, a solution of compound (−)−**8** (4.80 g, 9.6 mmol; 84% *ee*) was added in dry DMF (80 mL) to the mixture and was stirred at the desired temperature for 12 h. The filtrate was diluted with ethyl acetate (250 mL), washed with aqueous ammonia (10%, 4 x 75 mL) and washed with H_2O (4 x 50 mL). The organic layer was dried with Na_2SO_4 and then concentrated in vacuo to give a solid residue subjected to column chromatography (SiO_2, CH_2Cl_2:acetone = from 18:1 to 9:1) yielded 0.91 g of $\mathbf{1}_{syn}$ (37 %) and 1.18 g $\mathbf{1}_{anti}$ (48 %) as white solids. ^{1}H NMR and ^{13}C NMR data corresponding to compound $\mathbf{1}_{syn}$ were in line with the literature.[43] $^1H/^{13}C$NMR spectroscopic data was in agreement with those reported above.

Dimethyl(1*S*,4*S*)-2-chloro-1,4-dihydro-1,4-methanonaphthalene-6,7-dicarboxylate (−)−**16:** Dry copper (I) iodide (0.20 g, 1.1 mmol) and tetramethyl ammonium chloride (1.50 g, 13.7 mmol) was added to a round bottom flask. A solution of compound **(−)−7** (0.50 g, 1.5 mmol) in 1,4-dioxane (3 mL) along with *N*,N′-dimethylethylenediamine (0.1 mL, 0.9 mmol) were added to the same flask. The suspension was heated to reflux for 10 h under an atmosphere of nitrogen. The reaction mixture was cooled down, diluted with CH_2Cl_2 (20 mL) and washed with 30% NH_4OH (aq). Organic layer was dried with Na_2SO_4 and concentrated in vacuo. The resulting brown-black oil was filtered through a silica plug (CH_2Cl_2:EtOAc = 3:1) to, after the solvent removal, give 0.36 g of (−)−**16** as a yellow oil (82%); R_f = 0.39 on SiO_2 chromatographic plates with hexanes:EtOAc = 4:1. ^{1}H NMR (850 MHz, $CDCl_3$): δ (ppm) 7.66 (s, 1H), 7.52 (s, 1H), 6.47 (d, J = 3.2 Hz, 1H), 3.99-3.98 (m, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 3.79-3.77 (m, 1H), 2.62 (d, J = 7.6 Hz, 1H), 2.34 (d, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (214 MHz, $CDCl_3$): δ (ppm) 168.6, 168.3, 154.4, 153.4, 148.3, 135.2, 130.2, 129.1, 122.3, 121.7, 68.7, 56.7, 52.7, 52.7, 50.7. HRMS (ESI-MS): m/z calcd for $C_{15}H_{13}ClO_4Na$: 315.0395 $[M+Na]^+$; found: 315.0388. $[\alpha]_D^{23}$ = −43.8 (c = 1.17, $CHCl_3$). Enantiopurity of (−)−(**16**) was determined to be 98% *ee* by HPLC analysis (Figures S9 and S10) using an AD-H column (hexanes:isopropanol = 96:4, 1 mL/min); retention times: 14.7 min for (+)−**16** and 18.0 min for (−)−**16**.

ASSOCIATED CONTENT

Supporting Information

Additional synthetic, X-ray crystallography (cif file), spectroscopic and computational details. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

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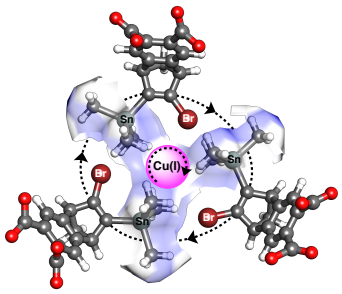

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