Total Synthesis of (−)-Cylindrocyclophanes A and F Exploiting the Reversible Nature of the Olefin Cross Metathesis Reaction

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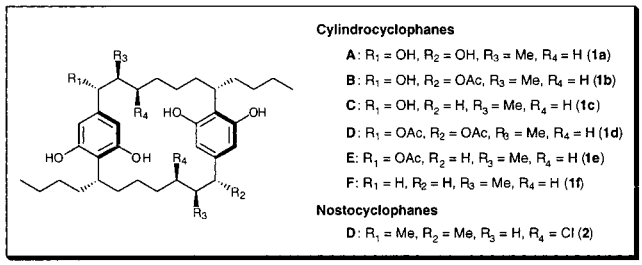
Received March 7, 2001

Abstract: Efficient total syntheses of the C_2-symmetric (−)-cylindrocyclophanes A and F (**1a** and **1f**) have been achieved. The initial strategy featured the use of a common advanced intermediate to assemble in stepwise fashion the required macrocycle of **1f**, exploiting in turn a Myers reductive coupling followed by ring-closing metathesis. In a second-generation strategy, a remarkable cross olefin metathesis dimerization cascade was discovered and exploited to assemble the requisite [7,7]-paracyclophane macrocycles of both **1a** and **1f** from dienyl monomers. The successful syntheses also featured the effective use of the Danheiser annulation to construct substrates for both the Myers reductive coupling and the metathesis dimerizations strategies. Finally, the Kowalski two-step chain homologation of esters to siloxyalkynes proved superior over the original one-step protocol.

A wide variety of bridged aromatic compounds, known as cyclophanes,[1,2] have become available as a result of extensive research over the past 50 years. The unique physical and chemical properties of cyclophanes, a direct result of their unusual architecture, vary considerably on the basis of size and constitution.[3] Notably, larger cyclophanes possess intramolecular cavities suitable for the formation of inclusion complexes, leading to applications in host−guest chemistry[3a,c,4] and mimicry of natural enzymes.[3a,c,5]

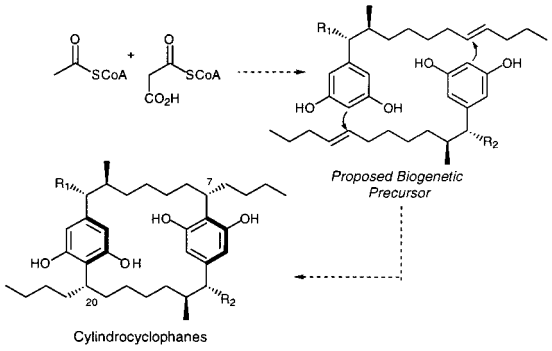
Despite the structural diversity of synthetic cyclophanes, naturally occurring paracyclophanes were not reported until 1990, when Moore and co-workers disclosed the isolation of cylindrocyclophane A (**1a**) and nostocyclophane D (**2**).[6a] Five additional members of the cylindrocyclophane family (**1b**−**f**) were then reported in 1992.[6b] Interestingly, these 22-member [7,7]-paracyclophanes were found to be the major cytotoxic components in three different strains of the terrestrial blue-green algae *Cylindrospermum lichenforme*,[6a] displaying in vitro cytotoxicity against the KB and LoVo tumor cell lines (IC_{50} 2−10 μg/mL).[6a,b]



Initially, detailed NMR analysis, in conjunction with high-resolution mass spectrometry, permitted structural assignments, including the relative stereochemistry of cylindrocyclophane A (**1a**).[6a] An X-ray structure of nostocyclophane D (**2**), exploiting the anomalous dispersion of chlorine, revealed the absolute stereochemistry of (−)-**2** and, by implication, the same absolute stereochemistry for (−)-**1a**.[6a] The latter was confirmed by the Mosher ester NMR protocol.[6b,7,8]

Biosynthetically, the [7,7]-paracyclophane skeleton of the cylindrocyclophanes was envisioned to arise via dimerization of two identical resorcinol fragments, presumably involving electrophilic aromatic substitution at C(2), with an olefin appropriately positioned in the side chain (Scheme 1).[6] Feeding experiments with ^{2}H-, ^{13}C-, and ^{18}O-labeled sodium acetate in

Scheme 1



(1) Smith, B. H. *Bridged Aromatic Compounds*; Academic Press: New York, 1964.

(2) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691.

(3) (a) *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983. (b) Vögtle, F. *Cyclophane Chemistry*; Wiley: New York, 1993. (c) *Cyclophanes*; Diedrerich, F., Ed.; The Royal Society of Chemistry: Cambridge, 1991. (d) Weber, E. *Top. Curr. Chem.* **1994**, *172*, 1.

(4) (a) Cerrini, S.; Giglio, E.; Mazza, F.; Pavel, N. V. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2605. (b) Hyatt, J. A.; Duesler, E. N.; Curtin, D. Y.; Paul, I. C. *J. Org. Chem.* **1980**, *45*, 5074. (c) Weber, E.; Vögtle, F. *Top. Curr. Chem.* **1981**, *98*, 1. (d) Gabard, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1137. (e) Vögtle, F.; Müller, W. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 147.

(5) (a) Benson, D. R.; Valentekovich, R.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *2*, 191. (b) Habicher, T.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1999**, *82*, 1066. (c) Mattei, P.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 1555. (d) Marti, T.; Peterson, B. R.; Fürer, A.; Mordasini-Denti, T.; Zarske, J.; Jaun, B.; Diederich, F. *Helv. Chim. Acta* **1998**, *81*, 109.

(6) (a) Moore, B. S.; Chen, J.-L.; Patterson, G. M.; Moore, R. M.; Brinen, L. S.; Kato, Y., Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 4061. (b) Moore, B. S.; Chen, J.-L.; Patterson, G. M.; Moore, R. E. *Tetrahedron* **1992**, *48*, 3001. (c) Bobzin, S. C.; Moore, R. E. *Tetrahedron* **1993**, *49*, 7615.

(7) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

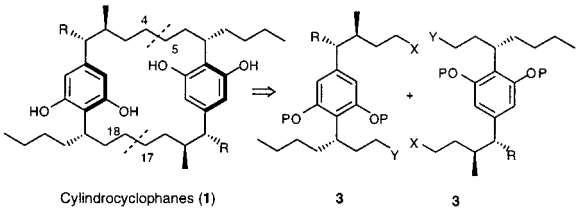
(8) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

10.1021/ja0106164 CCC: $20.00
Published on Web 06/05/2001

C. lichenforme cultures suggested that the dimerization precursors arise via successive polyketide synthase-mediated Claisen condensations, followed by appropriate modifications. One acetyl-CoA starter unit and eight malonyl-CoA fragments would be required.

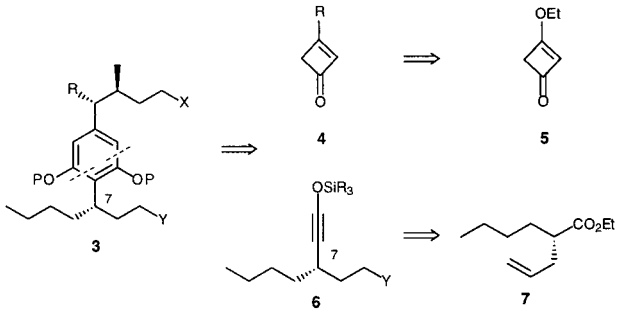
Synthetic Analysis. Exploitation of the proposed biosynthetic pathway, while appealing, appeared difficult due to both regio- and stereochemical issues associated with bond formation at C(7) and C(20). We therefore explored an alternate tactic involving disconnections at C(4−5) and C(17−18) (Scheme 2).[9]

Scheme 2



The approach would entail dimerization of two identical fragments (**3**), involving initial bimolecular coupling between the appropriate X and Y functional groups, followed by intramolecular cyclization. By employing the proper dilution conditions, dimerization should comprise the dominant reaction pathway. Such an approach would take full advantage of the C_2 symmetry offered by the cylindrocyclophane skeleton. In addition, the requisite stereogenic centers at C(1), C(2), and C(7) could be securely installed in the acyclic precursor **3** prior to construction of the macrocycle. Importantly, this strategy would permit significant flexibility in fragment coupling and thereby minimize end game manipulations. We further envisioned that the common resorcinol **3** could arise via Danheiser annulation[10] of cyclobutenone **4** with siloxyalkyne **6** (Scheme 3). This

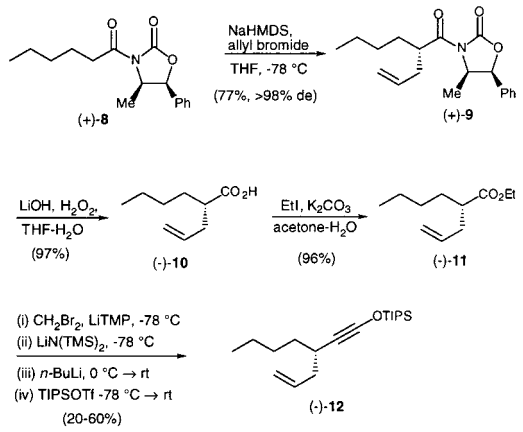
Scheme 3



strategic transform would permit the efficient, stereocontrolled installation of the highly congested C(7) stereogenic center. Cyclobutenone **4** in turn would readily derive from ethoxy enone **5**, while siloxyalkyne **6** would be constructed via a Kowalski chain homologation[11] starting with ester **7** (vide infra). Herein we describe the evolution of synthetic studies that resulted in a highly efficient unified strategy for the construction of the cylindrocyclophane family of natural products, illustrated by the total synthesis of (−)-cylindrocyclophanes A and F (**1a** and **1f**).[12] During the course of this synthetic venture, we discovered a remarkable cross olefin metathesis dimerization cascade (vide infra). An alternative elegant approach to (−)-cylindrocyclophane A (**1a**) was also recently reported by Hoye and co-workers.[13]

Synthesis of Siloxyalkyne 12: Modification of the Kowalski Protocol. At the outset, we required a reliable preparation of (−)-**12** (Scheme 4), the requisite siloxyalkyne for the

Scheme 4



Danheiser annulation. The method developed by Kowalski and co-workers,[11] requiring ester (−)-**11**, appeared particularly attractive. Toward this end, Evans asymmetric alkylation[14] of known imide (+)-**8**[15] with allyl bromide proceeded in 77% yield (de > 98%).[16] Removal of the chiral auxiliary with basic lithium peroxide, followed by alkylation with ethyl iodide and K_2CO_3, furnished ester (−)-**11** (93%, two steps). Initial studies exploiting the original one-pot Kowalski homologation[11] of ester (−)-**11** revealed the process to be highly dependent on scale, the quality of the reagents, and temperature control. The yields of (−)-**12** varied substantially, ranging from 20 to 60%. The lability of the siloxyalkyne also proved challenging during chromatographic purification.

A two-step modification of the Kowalski protocol,[11] amenable to scale-up, was therefore explored. The first step entailed conversion of ester (−)-**11** to dibromoketone (+)-**13**, employing CH_2Br_2 and LiTMP; yields ranged from 72 to 80% (Scheme 5). Subsequent treatment of the lithium enolate of (+)-**13** with *n*-BuLi at −78 °C resulted in facile rearrangement; silylation of the resulting ynolate with TIPSOTf then furnished the siloxyalkyne (−)-**12** in 92−100% yield, after bulb-to-bulb distillation.

Danheiser Annulation: Assembly of Resorcinol (+)-20. With a reliable protocol established for the preparation of

(9) Paone, D. V., Ph.D. Dissertation, University of Pennsylvania, 1998.

(10) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1670. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (d) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844.

(11) (a) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (b) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. (c) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (d) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194.

(12) For preliminary accounts of this work, see: (a) Smith, A. B., III; Kozmin, S. A.; Paone, D. V. *J. Am. Soc. Chem.* **1999**, *121*, 7423. (b) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984. (c) For the preparation of related unnatrural [7,7]-paracyclophanes, see: (i) Schubert, W. B.; Sweeney, W. A.; Latourette, H. K. *J. Am. Chem. Soc.* **1954**, *76*, 6462. (ii) Staab, H. A.; Matzke, G.; Frieger, C. *Chem. Ber.* **1987**, *120*, 89. (iii) Mascal, M.; Kerdelhue, J.-L.; Batsanov, A. S.; Begley, M. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1141.

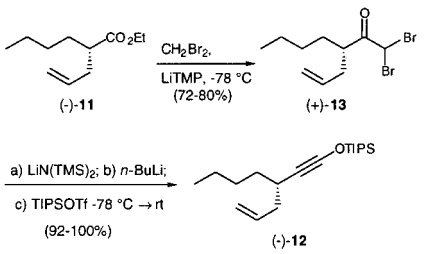
(13) Hoye, T. R.; Humpal, P. E.; Moon, B. *J. Am. Soc. Chem.* **2000**, *122*, 4982.

(14) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(15) Imide (+)-**10** was prepared in 97% yield from the (1*S*,2*R*)-(+)-norephedrine-derived oxazolidinone and hexanoyl chloride (*n*-BuLi, THF, −78 °C).

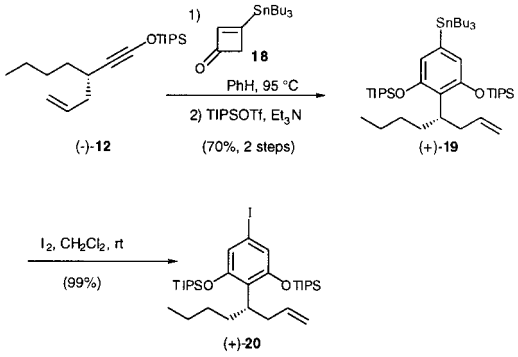
(16) The structural assignment to each new pure compound is in accord with its IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectra.

Scheme 5



siloxyalkyne (−)-**12**, we turned to the Danheiser annulation.[10] In the event, siloxyalkyne (−)-**12** underwent facile addition to known stannyl cyclobutenone **18**.[17] Silylation, followed by iododestannylation, afforded aryl iodide (+)-**20** in 69% yield for the three steps (Scheme 6). Notably, this reaction sequence

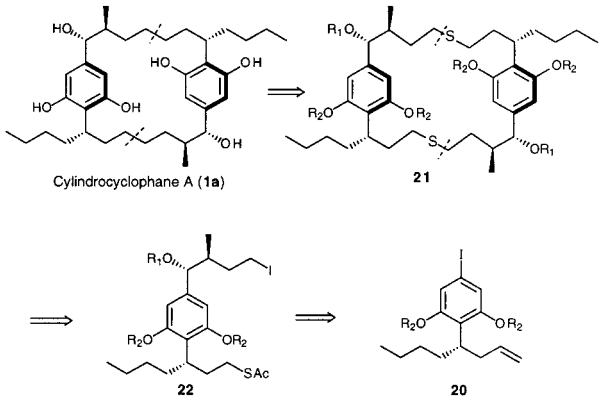
Scheme 6



represents the first use of a stannyl-substituted cyclobutenone in the Danheiser annulation to install an iodide on a resorcinol, amenable for further elaboration via either metal−halogen exchange or a Pd-mediated process.

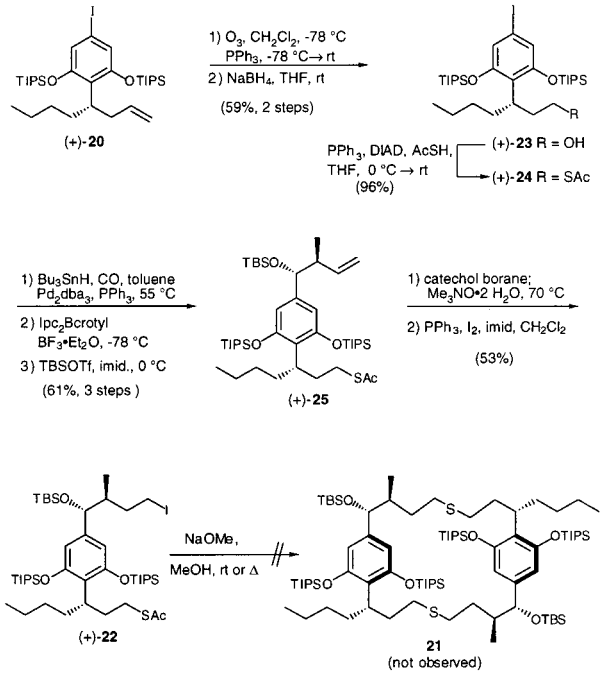
Macrocyclization Strategies: The Thiolate Dimerization Tactic. Our initial approach to the cylindrocyclophane macrocycle entailed dimerization via thiolate alkylations of two identical acyclic precursors (**22**) (Scheme 7). Extrusion of sulfur

Scheme 7



(or sulfur dioxide)[18] with concomitant olefin formation, followed by hydrogenation, was then envisioned to provide the requisite macrocycle. Dimerization precursor **22** in turn would arise from aryl iodide **20** via Stille carbonylation[19] followed by Brown asymmetric crotylboration[20] (vide infra). Execution of this plan began with ozonolysis of alkene (+)-**20** (Scheme 8); reduction

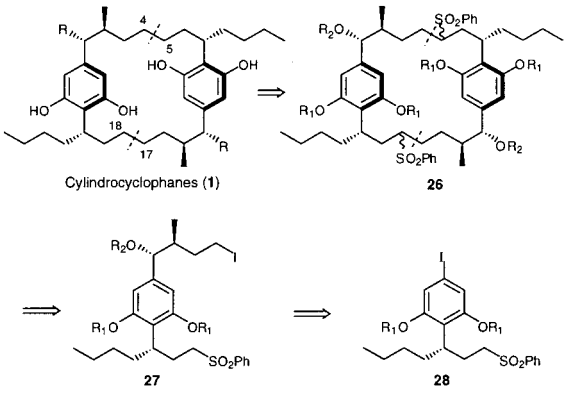
Scheme 8



of the derived aldehyde furnished alcohol (+)-**23**, which was converted to thioester (+)-**24** via a modified Mitsunobu protocol[21] (57% yield for three steps). Stille palladium-catalyzed carbonylation[19] followed by Brown crotylboration[20] of the resulting aldehyde and hydroxyl protection then yielded olefin (+)-**25** with excellent diastereoselectivity (de > 95%). Dimerization substrate (+)-**22** was then available via hydroboration and conversion of the primary hydroxyl to the corresponding iodide. Unfortunately, despite extensive efforts toward dimerization of (+)-**22,** neither dimer **21** nor monocoupled products were observed.

The Sulfone Alkylation Tactic. We next turned to the prospect of a phenyl sulfone−iodide dimerization strategy.[22,23] (Scheme 9). Disconnections of (−)-**1** at C(4−5) and C(17−18)

Scheme 9



would furnish sulfone **27**, which was envisioned to arise from aryl iodide **28**. Toward this end, ozonolysis of (−)-**11**, followed by reduction and conversion of the resulting alcohol to sulfide

(17) Liebeskind, L. S.; Stone, G. B.; Zhang, S. *J. Org. Chem.* **1994**, *59*, 7917.

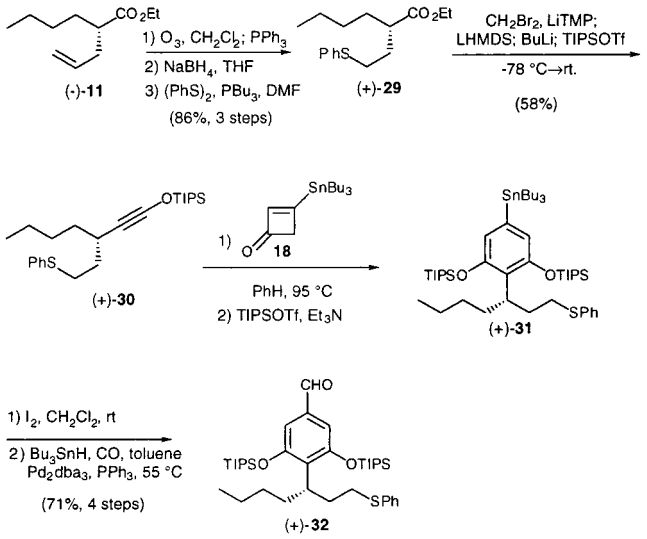
(18) This strategy is commonly employed in the construction of unnatural cyclophanes: see refs 3a,b.

(19) (a) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452. (b) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175.

(20) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

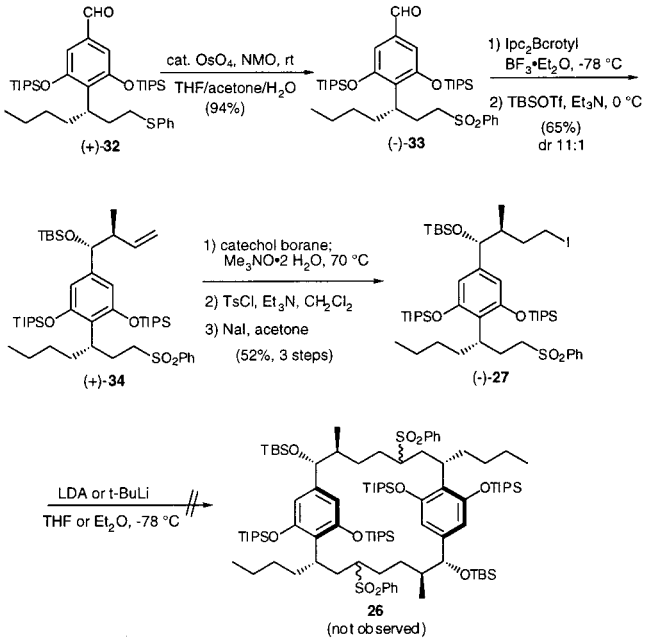
(21) (a) Loibnen, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 10



(+)-**29**, proceeded in 80% yield for three steps (Scheme 10). Homologation[11] again proceeded to give siloxyalkyne (+)-**30**.[24] The latter was subjected to annulation[10] with stannyl cyclobutenone **18**,[17] followed directly by silylation to furnish aryl stannane (+)-**31**. Iododestannylation and palladium-catalyzed carbonylation[19] completed the four-step sequence to aldehyde (+)-**32**; the overall yield was 71%. Oxidation of sulfide (+)-**32** provided sulfone (+)-**33** (Scheme 11). Brown crotylbora-

Scheme 11



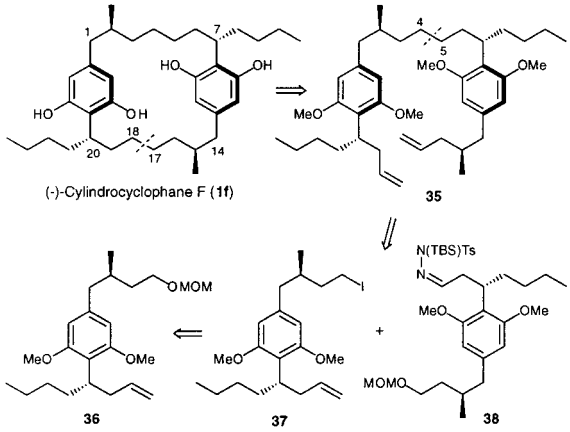
tion[20] (dr 11:1) and protection of the resulting hydroxyl furnished (+)-**34** in 71% yield for the two steps. Hydroboration, tosylation, and S_N2 displacement with NaI completed construction of iodosulfone (−)-**27**, the prospective dimerization substrate. Unfortunately, despite our best efforts, macrocyclization could not be achieved.

(22) (a) Takayanagi, H.; Uyehara, T.; Kato, T. *J. Chem. Soc., Chem. Commun.* **1978**, 359. (b) For an in-depth review of sulfone chemistry, see: Simpkins, N. S. In *Sulphones in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Tetrahedron Organic Chemistry Series 10; Pergamon: New York, 1993.

(23) Boekman, R. K.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.

Design of a Low-Risk, Stepwise Strategy. Although the Danheiser annulation[10] permitted rapid and efficient access to a variety of fully functionalized resorcinol fragments, our inability to effect dimerization prompted a revision of the initial strategy. The goal was to devise a low-risk approach to the less substituted cylindrocyclophane F (**1f**), which in turn would permit exploration of the key macrocyclization process (Scheme 12). Accordingly, the plan was to assemble the cyclophane via

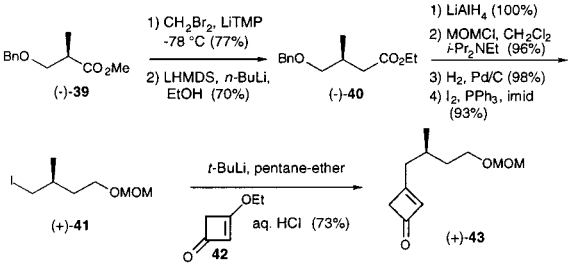
Scheme 12



a two-step process involving union of iodide **37** with hydrazone **38**, exploiting the reductive alkylation protocol developed by Myers and Movassaghi.[25] Ring-closing metathesis (RCM) would then furnish the macrocyclic skeleton.[26] The synthesis of resorcinol **36**, a common precursor for **37** and **38**, would again employ the Danheiser annulation.[10]

Resorcinol 36: The Common Precursor. We began with the preparation of ester (−)-**40** (Scheme 13). Again, the two-

Scheme 13



step homolgation,[11] in this case with known ester (−)-**39**,[27] proved superior to the original one-pot method. Reduction of (−)-**40** and protection of the primary hydroxyl as a MOM ether were followed by hydrogenolysis and conversion of the revealed hydroxyl to iodide (+)-**41**. Generation of the corresponding organolithium (*t*-BuLi, 2 equiv) and addition to ethoxy cyclobutenone **42**[28] furnished cyclobutenone (+)-**43** in 73% yield. With both cyclobutenone (+)-**43** and siloxyalkyne (−)-**12** in hand, annulation, followed by treatment with TBAF,[10] proceeded

(24) The integrity of the stereogenic center in (−)-**5** was established via derivatization and subsequent NMR analysis. Paone, D. V., Ph.D. Dissertation, University of Pennsylvania, 1998.

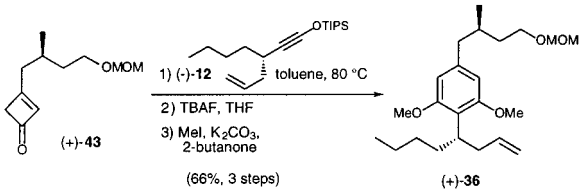
(25) Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891.

(26) For recent reviews on the use of the RCM reaction in organic synthesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(27) Widmer, U. *Synthesis* **1987**, *6*, 568.

(28) Wasserman, H. H.; Piper, J. U.; Dehmlow, E. V. *J. Org. Chem.* **1973**, *38*, 1451.

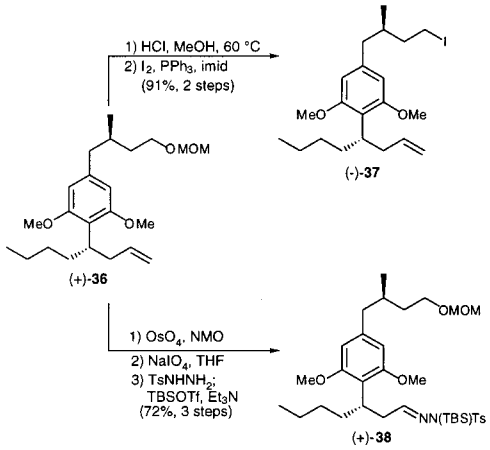
Scheme 14



smoothly to yield the tetrasubstituted resorcinol in 71% for the two steps (Scheme 14). Methylation then furnished (+)-**36**, the common precursor.

Stepwise Construction of the Paracyclophane Skeleton. To set the stage for macrocyclization, (+)-**36** was converted to iodide (−)-**37** and hydrazone (+)-**38**, the requisite coupling partners (Scheme 15). For (−)-**37**, the sequence entailed removal

Scheme 15



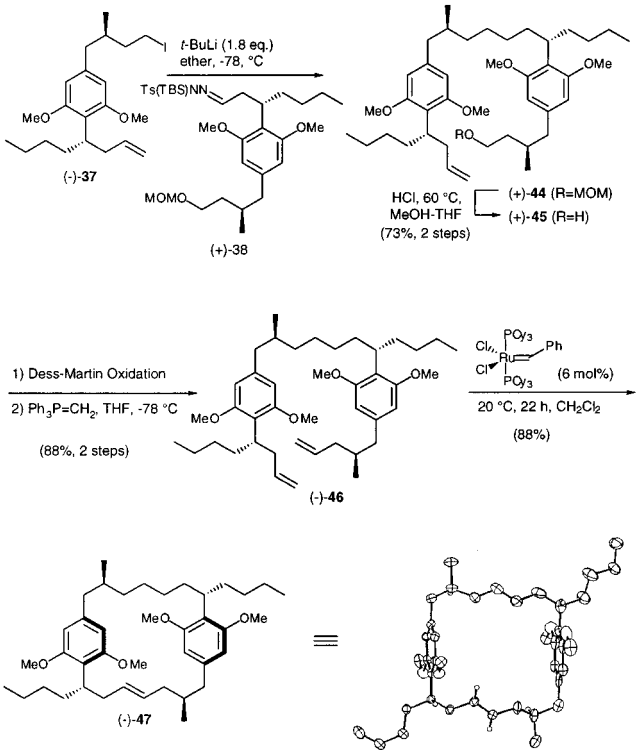
of the MOM moiety and transformation of the resulting primary hydroxyl to the iodide (91%, two steps). Alternatively, dihydroxylation of the olefin, followed by oxidative cleavage, furnished the requisite aldehyde, which was converted to the hydrazone followed by silylation[25] (72%, three steps). Coupling of (−)-**37** and (+)-**38** employing the Myers protocol[25] entailed generation of the organolithium reagent from iodide (−)-**27** and addition of the hydrazone (Scheme 16); the coupled product (+)-**44** was isolated in 73% yield. Quantitative removal of the MOM group under acidic conditions followed by Dess−Martin oxidation[29] and Wittig[30] methylenation (88%, three steps) then provided diene (−)-**46**, the required ring-closing metathesis precursor. Pleasingly, treatment of a dilute solution of (−)-**46** (0.004 M, CH_2Cl_2, 20 °C) with the Grubbs ruthenium catalyst[31a] (6 mol %) furnished the desired paracyclophane (−)-**47** in 88% yield as a white crystalline solid. NMR analysis revealed exclusive formation of the *E*-olefin. Subsequently, the structure of macrocycle (−)-**47** was secured via single-crystal X-ray analysis. The solid-state conformation of (−)-**47** features a highly ordered [7,7]-paracyclophane ring system, with the parallel, aromatic rings separated by ca. 7.65 Å and the hydrocarbon linkers in their fully extended conformation.

(29) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(30) (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

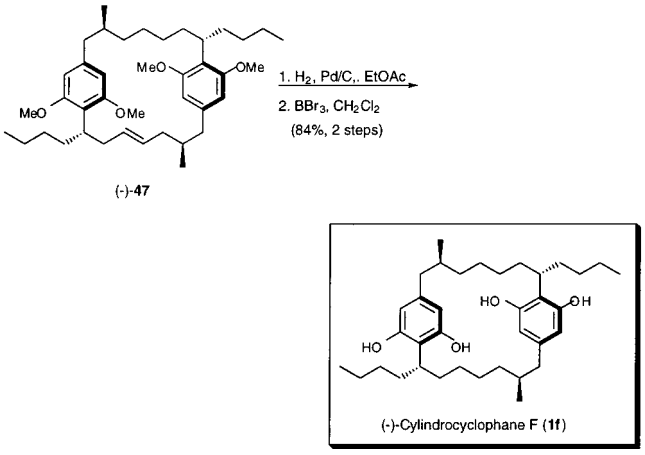
(31) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H.; *Org. Lett.* **1999**, *1*, 953. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Reagan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

Scheme 16



Total Synthesis of Cylindrocyclophane F (1f). Hydrogenation of macrocycle (−)-**47** followed by BBr_3 liberation[32] of the phenolic hydroxyl groups afforded (−)-cylindrocyclophane F (**1f**), identical in all respects with a sample of the natural material (Scheme 17).[33] Our first-generation synthesis of (−)-**1f** proceeded in 20 steps with an 8.3% overall yield.

Scheme 17

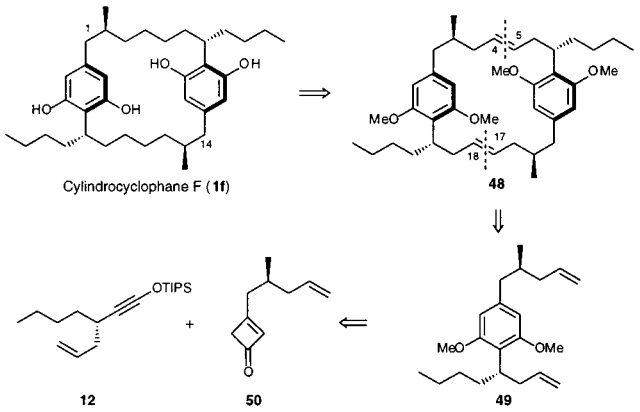


Discovery of a Remarkable Cross Olefin Metathesis Dimerization. Encouraged by both the high efficiency and stereoselectivity of the ring-closing metathesis, we revisited our original strategy for assembly of the cyclophane skeleton: dimerization of an advanced C20 intermediate, now by cross olefin metathesis. To our knowledge, this tactic had not been exploited previously in natural product total synthesis.[34] The strategy called for simultaneous disconnection of macrocycle **48** at C(4−5) and C(17−18); incorporation of the requisite

(32) Combes, S.; Finet, J.-P. *Synth. Commun.* **1997**, *27*, 3769.

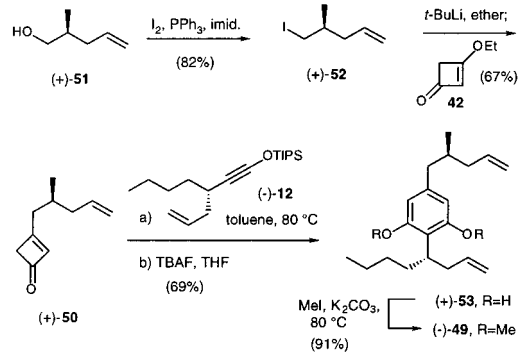
(33) We thank Professor Moore (University of Hawaii) for a generous sample of authentic (−)-cylindrocyclophane F (**1f**).

Scheme 18



terminal olefins revealed diene **49** (Scheme 18). Assembly of **49** would again rely on the Danheiser annulation,[10] in this case involving cyclobutenone **50** and siloxyalkyne **12**. Importantly, this strategy held the promise of significant improvement in overall efficiency. To begin, known alcohol (+)-**51**[35] (Scheme 19) was converted to iodide (+)-**52** via a Mitsunobu[21]-like

Scheme 19



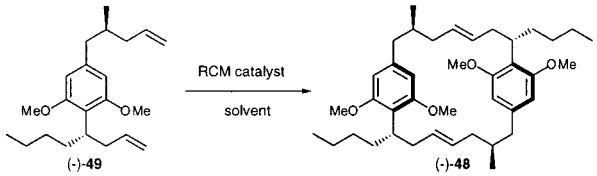
process[36] (82% yield). Metal−halogen exchange with *t*-BuLi in ether at −78 °C, followed by addition to the ethoxy cyclobutenone, furnished cyclobutenone (+)-**50** in 62%. Annulation[10] with siloxyalkyne (−)-**12**, desilylation with TBAF, and methylation then led to the fully functionalized dimerization substrate (−)-**49** in 63% yield for the three steps. To our delight, treatment of diene (−)-**49** with Grubbs catalyst **A**[31a] (15 mol %; Table 1) for 25 h at ambient temperature provided paracyclophane (−)-**48** in 55% yield. Moreover, only the *E*,*E*-isomer was observed. With 20 mol % of catalyst and a longer reaction time (72 h), (−)-**48** was produced in 61% yield. The perhydroimidazolidine catalyst (**B**), recently introduced by Grubbs and co-workers,[31b] also promoted the dimerization with similar efficiency when performed at 40 °C for 4 h in benzene. The

(34) For representative syntheses of dimeric natural products, see: (a) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818. (b) Schregenberger, C.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 5881. (c) White, J. D.; Vedananda, T. R.; Kang, M.; Choudrhy, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105. (d) Paterson, I.; Yeung, K.-S.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (e) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847. (f) Paterson, I.; Lombart, H. G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19. (g) Boger, D. L.; Ledeboere, M. W.; Kume, M. *J. Am. Chem. Soc.* **1999**, *121*, 1098. (h) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762.

(35) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

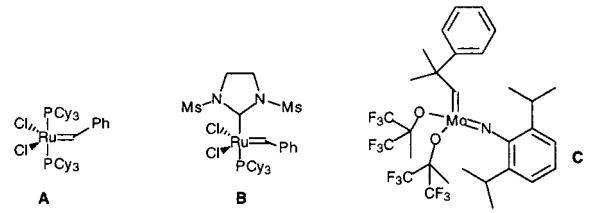
(36) Garegg, P. J.; Samuelsson B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

Table 1. Cross Metathesis Dimerization Studies



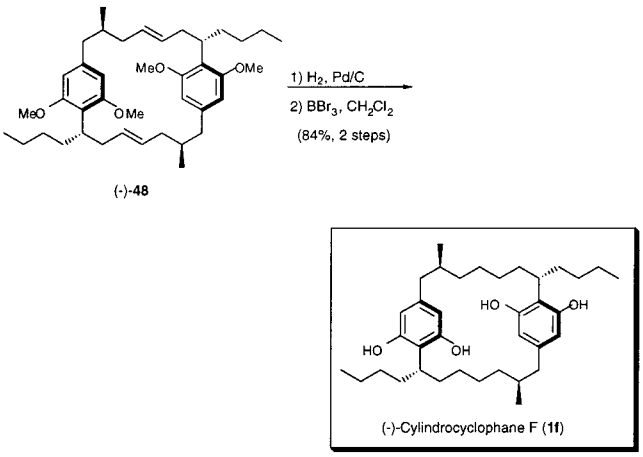
entry	catalyst (mol %)	solvent	reaction time, temperature	product yield[a] (%)
1	**A** (15)	CH_2CI_2	25 h, 20 °C	55
2	**A** (20)	CH_2CI_2	75 h, 20 °C	61
3	**B** (15)	CH_2CI_2	4 h, 40 °C	48
4	**B** (15)	C_6H_6	27 h, 40 °C	58
5	**C** (30)	C_6H_6	2 h, 20 °C	72

[a] Refers to isolated yield after chromatographic purification.



Schrock catalyst (**C**),[31c] however, proved most effective, furnishing (−)-**48** in 72% in 2 h at 20 °C. It is noteworthy that the alternative "head-to-head" dimerization products were not detected in these experiments. We will return later to a discussion of this remarkable dimerization reaction. Continuing with the synthesis, heterogeneous hydrogenation of diene (−)-**48** (Scheme 20), followed by cleavage of the methyl ether

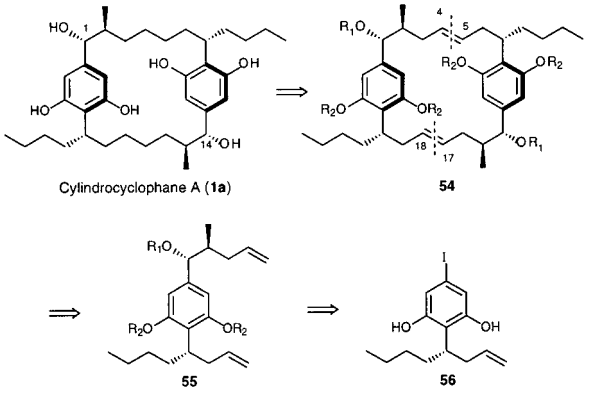
Scheme 20



linkages with BBr_3, then completed the synthesis of (−)-cylindrocyclophane F (**1f**), which was identical in all respects with an authentic sample[33] as well as with the sample from our first-generation synthesis. As anticipated, the second-generation synthesis of (−)-cylindrocyclophane F (**1f**) proved more efficient, requiring only 11 steps with a 22% overall yield, compared to our first synthesis (20 steps, 8.3% overall yield).

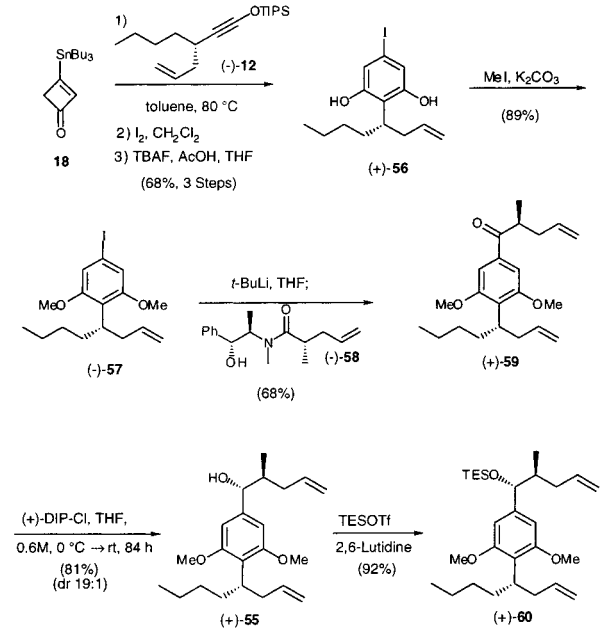
Return to (−)-Cylindrocyclophane A (1a). With a successful second-generation synthesis of (−)-**1f**, we returned to the more elaborate (−)-cylindrocyclophane A (**1a**), with the expectation that the metathesis dimerization strategy could be extended to this target, thereby providing a unified approach to this family of natural products. Accordingly, disconnection of macrocycle **54** at C(4−5) and C(17−18) revealed alcohol **55**, which could be constructed from aryl iodide **56** (Scheme 21).

Scheme 21



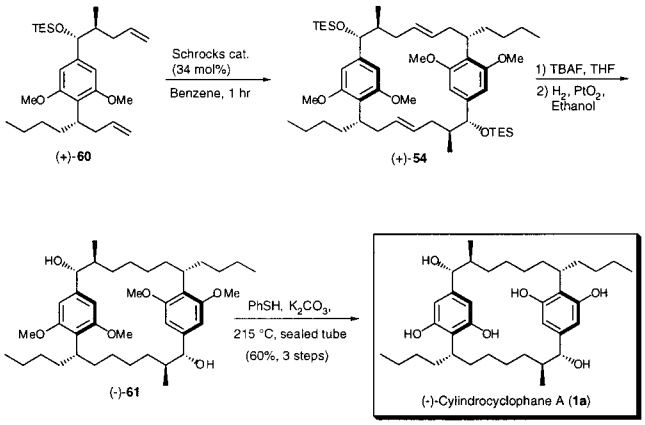
Toward this end, annulation[10] of stannyl cyclobutenone **18**[17] with siloxyalkyne (−)-**12** gave the corresponding aryl stannane, which upon iododestannylation and desilylation furnished resorcinol (+)-**56** (Scheme 22); methylation led to iodide (−)-

Scheme 22



57. Installation of the side chain began with the formation of the organolithium reagent derived from iodide (−)-**57** (*t*-BuLi, 2 equiv); addition to the lithium alkoxide obtained from the Myers amide (−)-**58**[37] furnished ketone (+)-**59**.[38] This tactic represents a significant improvement in efficiency compared to our previous approach for installation of the side chain, which relied on carbonylation and crotylboration (Schemes 8 and 11). We next explored the reduction of ketone (+)-**59**. To probe the inherent substrate selectivity, we initially examined $NaBH_4$ and K-selectride; both reagents effected reduction without significant stereoselectivity. To surmount the lack of inherent diastereofacial bias, we turned to reduction with (+)-*B*-chlorodiisopinocampheylborane [(+)-DIPCl], a reagent-controlled process.[39] Reduction at high concentration after an extended reaction time (84 h) provided the desired alcohol (+)-**55** in 81% yield with excellent diastereoselectivity (dr 19:1). Mosher ester analysis,[7] employing the Kakisawa test,[8] confirmed the absolute configuration at C(1). Silylation then led to the fully elaborated dimerization substrate (+)-**60**. Since the Schrock catalyst (**C**)[31c] (see Table 1) produced the best results in the dimerization of (−)-**49**, we employed this catalyst. As anticipated, the desired [7,7]-paracyclophane (+)-**54** (Scheme 23) was obtained as the

Scheme 23



major product (77% yield). Again only the *E*,*E*-olefin isomer[40] was observed. Desilylation with TBAF, followed by hydrogenation (Adams' catalyst), provided (−)-**61**. All that remained to complete the construction of (−)-cylindrocyclophane A (**1a**) was removal of the four phenolic methyl groups. Attempted deprotection of (−)-**61** with BBr_3 proved incompatible with the benzylic hydroxyl groups, resulting in material decomposition. Nucleophilic displacement appeared a more promising alternative. Indeed, treatment with PhSH[41] in the presence of K_2CO_3 in a sealed tube at 215 °C afforded (−)-cylindrocyclophane A (**1a**), identical in all respects with the spectral data and chiroptic properties reported for the natural material.[6b] In summary, the synthesis of (−)-cylindrocyclophane A (**1a**) required 16 steps and proceeded in 8.1% overall yield.

Dimerization via Cross Olefin Metathesis.[42] The unexpected efficiency and selectivity in the dimerization reactions suggested that the [7,7]-paracyclophane skeleton is the thermodynamically more favored isomer. That is, a cascade of reversible olefin metatheses drives the reaction toward formation of the energetically most favorable isomer.[43] This idea was supported by recent work from the Grubbs,[44] Hoveyda,[45] and Sanders[46] laboratories implicating the reversible nature of the olefin metathesis process. To explore this possibility from the theoretical perspective, we carried out a series of Monte Carlo conformational searches[47] utilizing the MM2 force field[48] to determine the relative energies of the seven possible cyclic dimers of (−)-**49**, including those having either seven methyl-

(37) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(38) We anticipated that (+)-**59** would be a suitable dimerization substrate; the resulting diketone could then be reduced stereoselectively after formation of the macrocycle. However, all attempts at dimerization of (+)-**59** using the various conditions employed to dimerize (−)-**41** (Table 1) resulted in polymeric products.

(39) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

(40) The olefin geometry of desilylated (+)-54 was elucidated by NOESY experiments.

(41) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749.

(42) For an initial report, see: Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990.

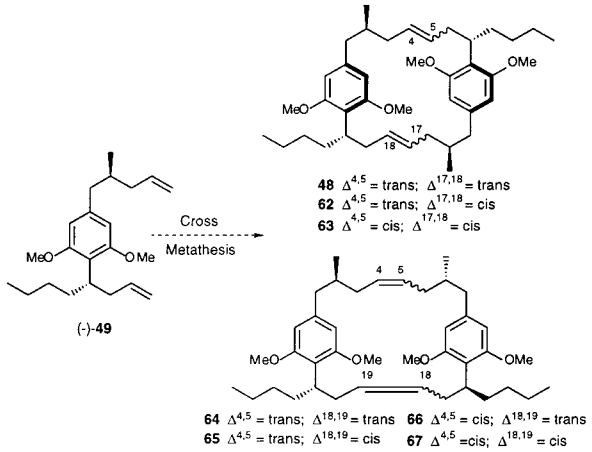
(43) For related work, see: Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449.

(44) (a) Marsella, N. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101. (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.

(45) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302.

(46) Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, K. M. *New J. Chem.* **1998**, *22*, 1019.

Scheme 24



enes between the aromatic rings (**48, 62, 63**) or eight and six (**64**−**67**) (Scheme 24). The calculations indicated that **48**, possessing the [7,7]-*E*,*E*-macrocyclic skeleton, is the lowest energy isomer by ca. 2.6−4.7 kcal/mol relative to the other possible dimers (Figure 1).[49] To obtain experimental evidence

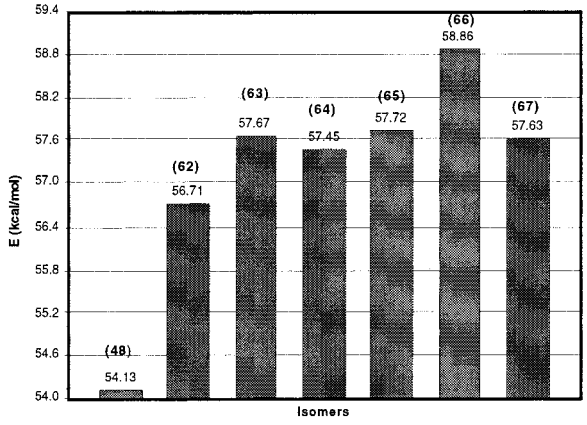
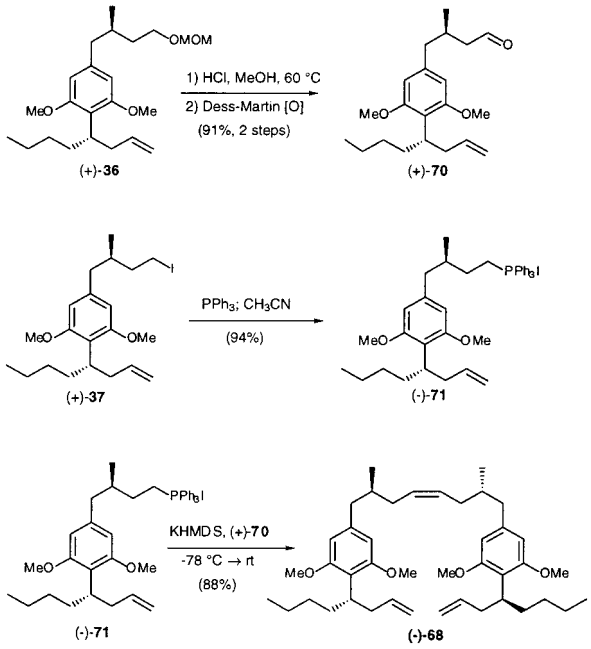


Figure 1. Energy values for the lowest energy conformation of the seven possible geometrical/constitutional isomers (see Scheme 25).

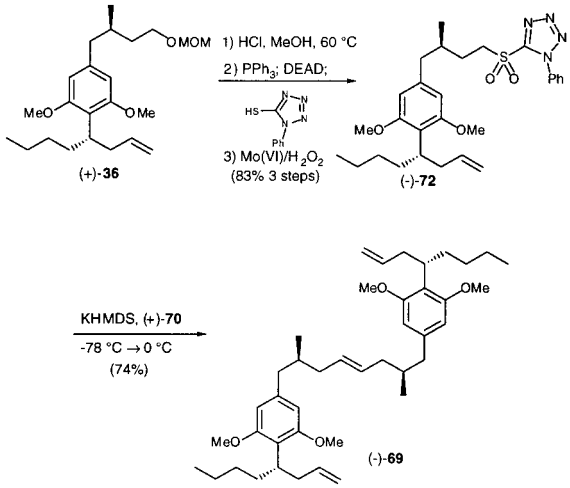
for the predicted reversible olefin metatheses cascade, we prepared trienes **68** and **69** (Schemes 25 and 26), both predisposed to form the [8,6]-macrocycle via RCM. The conversion of **68** and **69** to the [7,7]-macrocycle (−)-**48**, instead of the analogous RCM products, would provide clear evidence for the proposed cascade. Wittig[30] and Kocienski-modified Julia[50] olefinations were envisioned to provide ready access to the requisite *Z*- and *E*-trienes (−)-**68** and (−)-**69**. The synthesis of (−)-**68** began with the previously prepared MOM ether (+)-**36**. Acidic hydrolysis followed by Dess−Martin oxidation[29] afforded the requisite aldehyde (+)-**70**. Similarly, treatment of the previously prepared iodide (−)-**37** (Scheme 15) with PPh_3 in acetonitrile at reflux provided Wittig salt (−)-**71** (94% yield). With the coupling partners in hand, Wittig olefination of (−)-**71** (Scheme 25) with aldehyde (+)-**70** furnished the *Z*-triene (−)-**68** (88% yield, *Z*:*E* > 15:1). Preparation of the *E*-isomer (−)-**69** (Scheme 26) began with conversion of (+)-**36** to sulfone

Scheme 25



(−)-**72** via acidic hydrolysis, Mitsunobu reaction[21] with 1-phenyl-1*H*-tetrazole-*S*-thiol, and hydrogen peroxide oxidation promoted by ammonium heptamolybdate tetrahydrate[51] (83% yield, three steps). Deprotonation of (−)-**72** with KHMDS followed by addition of aldehyde (+)-**70** furnished (−)-**69** in 74% yield (*E*:*Z* > 15:1).

Scheme 26



In the event, despite the predisposition of the substrates to form the [8,6]-cyclophane, trienes (−)-**68** and (−)-**69** afforded only the [7,7]-*E*,*E*-paracyclophane (−)-**48** (Scheme 27) in yields ranging from 66 to 70% for the Grubbs catalyst (**B**) and from 75 to 81% for the more reactive Schrock catalyst (**C**). Presumably, both substrates undergo a cascade of olefin metathesis reactions which eventually leads, via a self-editing process, to the [7,7]-*E*,*E*-paracyclophane skeleton.

Summary. We have devised and executed a highly efficient, unified strategy to the cylindrocyclophane family of natural products. The requisite resorcinol fragments were readily constructed utilizing a combination of the Kowalski chain homologation and Danheiser annulation. Assembly of the

(47) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

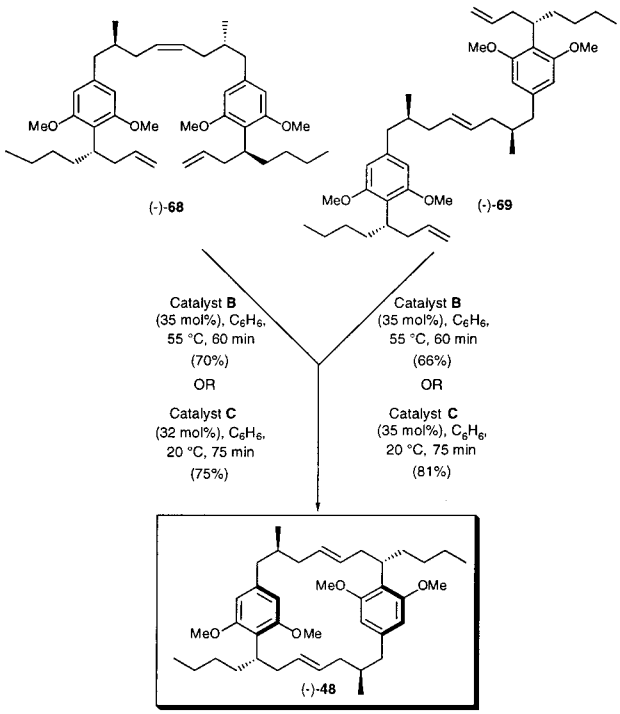
(48) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(49) To simplify calculations, the butyl chains in isomers **48** and **62**−**67** were replaced with methyl groups.

(50) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

(51) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

Scheme 27



macrocycle was performed by olefin metathesis. Having secured initial access to the [7,7]-paracyclophane skeleton by ring-closing metathesis, we discovered a remarkably efficient cross metathesis dimerization process which culminated in the efficient total syntheses of both (−)-cylindrocyclophane A (16 steps) and (−)-cylindrocyclophane F (11 steps). Importantly, the conversion of (−)-**68** and (−)-**69** to (−)-**48** establishes that the cross metathesis dimerization process can lead selectively to the thermodynamically most stable member of a set of structurally related isomers. This self-editing process has important strategic implications for the design and implementation of future synthetic strategies.

Experimental Section[52]

Second-Generation Synthesis of (−)-Cylindrocyclophane F (1f). Ethyl Ester (−)-11. Potassium carbonate (45.6 g, 330 mmol) and iodoethane (42 mL, 528 mmol) were added to a solution of acid (−)-**10** (20.65 g, 132 mmol) in acetone (380 mL) and water (20 mL), and the mixture was heated to 75 °C. After 3 h, the reaction was cooled to room temperature, diluted with water (600 mL) and 10% HCl (50 mL), extracted with dichloromethane (3 × 500 mL), washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to provide (−)-**11** (23.2 g, 96% yield) as a yellow oil: $[\alpha]^{20}_D$ −8.8° (*c* 1.21, $CHCl_3$); IR ($CHCl_3$) 3020 (s), 2960 (m), 2940 (m), 2860 (w), 1730 (s), 1510 (w), 1470 (w), 1445 (w), 1380 (w), 1205 (s), 1185 (s), 1030 (m), 920 (m), 720 (s), 670 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 17.2, 10.2, 7.0, 7.0 Hz, 1 H), 5.05 (dd, J = 17.1, 1.8 Hz, 1 H), 5.00 (dd, J = 10.2, 1.1 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 2.43−2.32 (m, 2 H), 2.25−2.19 (m, 1 H), 1.65−1.58 (m, 1 H), 1.51−1.44 (m, 1 H), 1.33−1.23 (m, 4 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.68, 135.64, 116.48, 60.03, 45.34, 36.49, 31.53, 29.44, 22.55, 14.31, 13.87; high-resolution mass spectrum (CI, NH_3) *m*/*z* 185.1547 [(M + H)$^+$; calcd for $C_{11}H_{21}O_2$, 185.1541].

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.53; H, 10.62.

Dibromoketone (+)-13. A solution of ester (−)-**11** (1.29 g, 7.00 mmol) and dibromomethane (3.04 g, 17.5 mmol) in THF (30 mL) was cooled to −78 °C. In a separate flask, a solution of 2,2,6,6-tetramethylpiperidine (TMP) (3.18 mL, 18.9 mmol) in THF (30 mL) was cooled to 0 °C and treated with *n*-BuLi (2.5 M in hexanes; 6.72 mL, 16.8 mmol), and this yellow LiTMP solution was immediately added dropwise via an addition funnel to the ester solution over a 25 min period. After 20 min, the reaction was quenched by slow addition to a 1.2 M aqueous solution of HCl (50 mL), extracted with hexanes (2 × 50 mL), washed with water (30 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on silica gel (hexanes/Et_2O, 50:1; 20:1) to afford 1.76 g (80% yield) of the desired dibromoketone as a light yellow oil: $[\alpha]^{20}_D$ +22.3 (*c* = 3.00, $CHCl_3$); IR ($CHCl_3$) 3080 (w), 2960 (s), 2930 (m), 2940 (s), 2860 (m), 1735 (s), 1640 (w), 1470 (w), 1440 (w), 1150 (w), 920 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1 H), 5.74 (dddd, J = 17.7, 14.5, 7.3, 7.3 Hz, 1 H), 5.08 (m, 2 H), 3.10 (dddd, J = 7.5, 7.5, 6.0, 6.0 Hz, 1 H), 2.41 (ddd, J = 14.7, 7.3, 7.3 Hz, 1 H), 2.29 (ddd, J = 12.8, 6.1, 6.1 Hz, 1 H), 1.73 (m, 1 H), 1.53 (m, 1 H), 1.30 (m, 4 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 134.6, 117.8, 46.9, 43.4, 37.2, 31.9, 29.3, 22.6, 13.8.

Siloxyalkyne (−)-12. A solution of dibromoketone (1.50 g, 4.78 mmol) in THF (27 mL) was cooled to −78 °C. In a separate flask, a solution of hexamethyldisilazane (HMDS) (1.21 mL, 5.70 mmol) in THF (27 mL) was cooled to 0 °C and treated with *n*-BuLi (2.5 M in hexanes; 2.0 mL, 5.0 mmol), and this colorless LHMDS solution was immediately added dropwise via addition funnel to the dibromoketone solution over a 25 min period. The reaction mixture was stirred for 20 min at −78 °C and treated with *n*-BuLi (2.5 M in hexanes; 4.2 mL, 10.5 mmol) via syringe. After 30 min, freshly distilled TIPSOTf (1.39 mL, 5.18 mmol) was added. The reaction mixture was allowed to warm to 0 °C, cooled to −78 °C, quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with hexanes (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by bulb-to-bulb distillation (0.1 mmHg, oven temperature 80−120 °C) to afford 1.48 g (100% yield) of (−)-**12** as a colorless oil: $[\alpha]^{25}_D$ −6.2° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 2960 (m), 2280 (s), 1640 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.1, 10.1, 7.0, 7.0 Hz, 1 H), 5.03 (dd, J = 17.1, 2.1 Hz, 1 H), 5.00 (dd, J = 10.1, 1.1 Hz, 1 H), 2.31−2.26 (m, 1 H), 2.16−2.12 (m, 2 H), 1.48−1.21 (m, 9 H), 1.12 (d, J = 7.3 Hz, 18 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 115.5, 88.2, 40.7, 35.4, 33.6, 30.5, 29.6, 22.6, 17.4, 14.1, 11.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 309.2624 [(M + H)$^+$; calcd for $C_{19}H_{37}OSi$, 309.2613].

Iodide (+)-52. To a solution of known alcohol (+)-**51**[35] (1.05 g, 10.5 mmol) in Et_2O (20 mL) and acetonitrile (6 mL) at 0 °C were added triphenylphosphine (2.88 g, 11 mmol), imidazole (748 mg, 11

(52) **Materials and Methods.** Reactions were carried out in oven- or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene, and diisopropylamine were freshly distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Anhydrous pyridine, dimethylformamide, and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium and *tert*-butyllithium were purchased from Aldrich and standardized by titration with diphenylacetic acid. Except as indicated otherwise, reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040−0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Melting points were determined on a Bristoline heated-stage microscope or Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded with a Perkin-Elmer model 283B spectrometer with polystyrene as external standard. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer. Carbon-13 NMR spectra were recorded on a Bruker AM-500. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00), chloroform (δ 7.24), methanol (δ 3.34), or dimethyl sulfoxide (δ 2.54) for ^1H and either chloroform (δ 77.0), benzene (δ 128.0), or methanol (δ 49.9) for ^{13}C. Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a VG Micromass 70/70H or a VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, NJ. Single-crystal X-ray structures were determined at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer. High-performance liquid chromatography (HPLC) was performed with a Ranin component analytical/semipreparative system.

mmol), and iodine in three portions (2.67 g, 10.5 mmol in total). The reaction was allowed to reach room temperature and stirred for 2 h, passed through a pad of silica (pentane/Et_2O 5:1), and concentrated via rotary evaporation (bath temperature 15 °C). Bulb-to-bulb distillation (oven temperature 50−80 °C, 20 mmHg) afforded (+)-**52** (1.8 g, 82% yield): $[\alpha]^{25}_D$ +6.3° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3060 (w), 2960 (s), 2800 (s), 1640 (m), 1450 (m), 2800 (s), 1440 (m), 1380 (m), 1320 (m), 1190 (s), 990 (s), 910 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, J = 17.2, 10.1, 7.1, 7.1 Hz, 1 H), 5.08 (m, 2 H), 3.23 (dd, J = 5.1, 9.6 Hz, 1 H), 3.15 (dd, J = 6.0, 9.6 Hz, 1 H), 2.14 (ddd, J = 13.9, 6.8, 6.8 Hz, 1 H), 2.03 (ddd, J = 13.9, 6.9, 6.9 Hz, 1 H), 1.58 (m, 1 H), 1.0 (d, J = 6.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 116.9, 40.6, 34.6, 20.3, 16.6.

Cyclobutenone (+)-50. A solution of iodide (+)-**52** (210 mg, 1.00 mmol) in Et_2O (2 mL) was cooled to −78 °C and treated slowly with *t*-BuLi (1.7 M in pentane, 1.0 mL, 1.7 mmol). The resulting white suspension was stirred for 45 min and then treated with ethoxy cyclobutenone (90 mg, 0.8 mmol) in Et_2O (2 mL). The reaction mixture was allowed to warm to 20 °C and quenched with 1.2 M aqueous HCl (15 mL). The resulting mixture was diluted with Et_2O (40 mL), transferred into a separatory funnel, and vigorously shaken for 2 min. The aqueous layer was extracted with Et_2O (50 mL). Combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on silica gel (pentane/Et_2O, 3:1) to afford 81 mg (67% yield) of (+)-**50** as a colorless oil: $[\alpha]^{25}_D$ +15 ° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 1760 (s), 1580 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1 H), 5.74 (m, 1 H), 4.98−5.20 (m, 2 H), 3.12 (m, 2 H), 2.57 (ddd, J = 16.3, 5.8, 1.0 Hz, 1 H), 2.36 (ddd, J = 16.3, 7.9, 1.0 Hz, 1 H), 2.10−2.05 (m, 1 H), 2.04−1.97 (m, 1 H), 1.93−1.85 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 180.1, 136.0, 135.1, 116.8, 50.9, 41.0, 38.7, 30.9, 19.6; low-resolution mass spectrum (CI, CH_4) *m*/*z* 151 [(M + H)$^+$; calcd for $C_{10}H_{15}O$, 151.1].

Resorcinol (+)-53. A solution of siloxyalkyne (−)-**12** (385 mg, 1.25 mmol) and cyclobutenone (+)-**50** (220 mg, 1.47 mmol) in toluene (2 mL) was heated to 100 °C. After 2 h, the reaction mixture was cooled to 0 °C, diluted with THF (10 mL), and treated with TBAF (1.5 mL, 1.0 M in THF). The resulting solution was stirred for 15 min at ambient temperature and quenched with 1.2 M HCl (1.5 mL), diluted with water (50 mL), and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated, and purified by flash chromatography on silica gel (hexanes/Et_2O, 2:1) to afford 261 mg (69% yield) of (+)-**53** as a colorless oil: $[\alpha]^{25}_D$ +3.0° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3600 (s), 3300 (m), 2960 (m), 1620 (s), 1580 (s), 1420 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 2 H), 5.7−5.82 (m, 2 H), 4.98−5.03 (m, 2 H), 4.90 (br d, J = 20.1 Hz, 1 H), 4.74 (s, 2 H), 3.18−3.12 (m, 1 H), 2.60 (m, 1 H), 2.50−2.42 (m, 2 H), 2.22 (dd, J = 13.4, 8.1 Hz, 1 H), 2.1 (m, 1 H), 1.93−1.85 (m, 2 H), 1.80−1.65 (m, 2 H), 1.35−1.10 (m, 4 H), 0.85 (d, J = 6.7 Hz, 3 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 140.6, 138.3, 137.3, 115.9, 115.1, 114.7, 109.4, 42.5, 40.9, 38.1, 36.0, 34.5, 32.9, 30.4, 22.8, 19.3, 14.0; high-resolution mass spectrum (CI, CH_4) *m*/*z* 303.2318 [(M + H$^+$); calcd for $C_{20}H_{31}O_2$, 303.2324].

Diene (−)-49. To a solution of (+)-**53** (205 mg, 0.68 mmol) in 2-butanone (2.0 mL) was added K_2CO_3 (1.0 g, 7.2 mmol) and methyl iodide (1.74 mL, 27.9 mmol). The reaction was heated at reflux for 21 h, diluted with Et_2O (40 mL), filtered, and concentrated. Flash chromatography (hexanes/Et_2O, 5:1) afforded (−)-**49** (203 mg, 91% yield) as a colorless oil: $[\alpha]^{25}_D$ −2.8 ° (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) 2960 (m), 1600 (s), 1580 (s), 1120 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 2 H), 5.73 (m, 1 H), 5.60 (dddd, J = 17.0, 10.0, 6.9, 6.9 Hz, 1 H), 4.92 (m, 2 H), 4.81 (d, J = 17.0 Hz, 1 H), 4.72 (d, J = 10.0 Hz, 1 H), 3.66 (s, 6 H), 3.24 (m, 1 H), 2.50 (dd, J = 13.4, 6.2 Hz, 1 H), 2.47−2.40 (m, 1 H), 2.35−2.27 (m, 1 H), 2.24 (dd, J = 13.4, 8.1 Hz, 1 H), 2.07−2.00 (m, 1 H), 1.86−1.65 (m, 3 H), 1.54−1.47 (m, 1 H), 1.25−0.90 (m, 5H), 0.79 (d, J = 6.6 Hz, 3 H), 0.73 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.0, 139.2, 137.4, 118.8, 115.8, 114.0, 105.5, 56.0, 43.6, 41.0, 38.3, 35.0, 34.8, 32.9, 30.4, 22.8, 19.3, 14.1; high-resolution mass spectrum (CI, CH_4) *m*/*z* 331.2625 [(M + H)$^+$; calcd for $C_{22}H_{35}O_2$, 331.2637].

Macrocycle (−)-48. General Procedure for Metathesis Dimerization. A degassed solution (ca. 0.02 M) of diene (−)-**49** (0.05 mmol) was treated with the metathesis catalyst (15−34 mol %). The resulting homogeneous solution was stirred at ambient temperature for the time period indicated in Table 1; concentration under reduced pressure led to the product that was purified by flash chromatography on silica gel. For (−)-**48**: $[\alpha]^{25}_D$ −91° (*c* 0.80, C_6H_6); IR ($CHCl_3$) 2960 (m), 1600 (s), 1580 (s), 1450 (m), 1100 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 2 H), 6.00 (s, 2 H), 5.15 (br dd, J = 14, 10 Hz, 2 H), 5.09 (br dd, J = 14, 9 Hz, 2 H), 3.77 (s, 6 H), 3.73 (s, 6 H), 3.40 (m, 2 H), 2.61 (ddd, J = 12.6, 12.6, 10.4 Hz, 2 H), 2.27 (m, 2 H), 2.00 (m, 2 H), 1.78 (m, 2 H), 1.63−1.55 (m, 4 H), 1.50−1.42 (m, 1 H), 1.40−1.08 (m, 14 H), 0.80 (dd, J = 13.5, 11.4 Hz, 2 H), 0.83 (t, J = 7.0 Hz, 6 H), 0.57 (d, J = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.1, 141.7, 131.9, 129.5, 117.9, 107.1, 104.2, 56.5, 55.1, 41.6, 41.5, 36.9, 35.2, 35.1, 33.6, 30.7, 22.9, 19.9, 14.1; high-resolution mass spectrum (CI, CH_4) *m*/*z* 605.4552 [(M + H)$^+$; calcd for $C_{40}H_{61}O_4$, 605.4569].

(−)-Cylindrocyclophane F. A solution of macrocycle (−)-**48** (38 mg, 0.062 mmol) in ethyl acetate (6 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) under 1 atm of hydrogen for 20 h. Filtration of the reaction mixture through a plug of silica gel, followed by removal of volatiles under reduced pressure, afforded 38 mg of the desired product (quantitative yield) as a white solid. A solution of the hydrogenation product (5.5 mg, 0.009 mmol) in CH_2Cl_2 (150 μL) was treated slowly with BBr_3 (1.0 M in CH_2Cl_2, 60 μL, 0.06 mmol) at 20 °C. The resulting dark red solution was stirred for 2.5 h, diluted with CH_2Cl_2 (5 mL), and quenched with water (1 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 4:1) to afford 4.2 mg (84%) of (−)-cylindrocyclophane F (**1f**) as an amorphous solid identical in all respects to a sample of the natural material[33] [500 MHz ^1H NMR and 125 MHz ^{13}C NMR, HRMS, optical rotation, and TLC (three solvent systems)]: $[\alpha]^{25}_D$ −70° (*c* 0.2, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 6.00 (br s, 2 H), 5.97 (br s, 2 H), 3.14−3.06 (m, 2 H), 2.57 (dd, J = 13.1, 3.8 Hz, 2 H), 2.00−1.88 (m, 4 H), 1.82 (dd, J = 13.1, 11.4 Hz, 2 H), 1.60−1.54 (m, 2 H), 1.52−0.90 (m, 22 H), 0.80−0.73 (m, 4 H), 0.93 (d, J = 6.6 Hz, 6 H), 0.81 (t, J = 7.1 Hz, 6 H), 0.64 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.3, 157.1, 140.9, 116.2, 110.0, 108.1, 45.8, 36.8, 36.7, 36.7, 35.5, 34.9, 31.7, 30.6, 30.1, 23.9, 20.8, 14.5; high-resolution mass spectrum (CI, NH_3) *m*/*z* 553.4235 [(M + H)$^+$; calcd for $C_{36}H_{57}O_4$, 553.4256].

Synthesis of (−)-Cylindrocyclophane A (1a). Resorcinol (+)-56. A degassed solution of siloxyalkyne (−)-**12** (375.0 mg, 1.22 mmol) and cyclobutenone **18** (542.0 mg, 1.52 mmol) in toluene (2.9 mL) was heated to 100 °C for 2 h. The resulting dark brown mixture was cooled to ambient temperature, diluted with Et_2O (50 mL), washed twice with saturated aqueous $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Flash chromatography (hexanes/ethyl acetate, 60:1) using deactivated silica gel [prepared by thoroughly mixing silica (90 g) and water (18 mL)] gave the desired monosilylated aryl stannane as an oil (691.0 mg, 85% yield). A solution of stannane (355 mg) prepared as described above in CH_2Cl_2 (8.5 mL) was treated dropwise with iodine (7.0 mL, 0.075 M in CH_2Cl_2) until the starting material was consumed. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ (5 mL) and water (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried with $MgSO_4$, filtered, and concentrated to give an oil. Flash chromatography on silica gel (1% → 6% ethyl acetate in hexanes) afforded the unstable monoprotected aryl iodide as an oil (184.4 mg, 77% overall yield for two steps) which was used immediately in the next step.

A solution of the iodide prepared above (165 mg, 0.328 mmol) in THF (3.3 mL) was cooled to 0 °C. In a separate flask, tetrabutylammonium fluoride (TBAF) (1.0 M in THF; 1.28 mL, 1.28 mmol) was added to glacial acetic acid (75.0 μL, 1.30 mmol) and stirred for 5 min. The aryl iodide solution was then treated with the TBAF solution (0.957 M in AcOH/THF, 0.45 mL, 0.41 mmol). After 15 min at 0 °C, the reaction mixture was allowed to warm to ambient temperature over a 10 min period, quenched with saturated aqueous NH_4Cl (20 mL) and

water (5 mL), extracted with ethyl acetate (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (2% → 5% ethyl acetate in hexanes) gave (+)-**56** (98 mg, 88% yield) as a pale yellow oil: $[\alpha]^{20}_D$ +4.87° (*c* 0.575, $CHCl_3$); IR ($CHCl_3$) 3560 (s), 3285 (m), 2945 (s), 2925(s), 2845 (s), 1760 (w), 1635 (w), 1595 (s), 1405 (s), 1320 (m), 1135 (m), 1015 (s), 940 (w), 910 (m), 825 (s), 570 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl^3$) δ 6.67 (s, 2 H), 5.69 (dddd, J = 17.1, 10.1, 7.1, 7.1 Hz, 1 H), 4.97 (d, J = 17.1 Hz, 1 H), 4.87 (d, J = 10.1, 1 H), 4.73 (s, 2 H), 3.13 (dddd, J = 9.4, 9.4, 6.0, 6.0 Hz, 1 H), 2.56 (m, 1 H), 2.40 (m, 1 H), 1.84 (dddd, J = 13.4, 9.9, 9.9, 5.3 Hz, 1 H), 1.63 (m, 1 H), 1.20 (complex m, 4 H), 0.82 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.78, 137.83, 117.87, 117.57, 115.48, 89.47, 37.78, 36.01, 32.60, 30.36, 22.74, 14.03; high-resolution mass spectrum (CI, CH_4) *m*/*z* 347.0508 [$(M + H)^+$; calcd for $C_{14}H_{20}O_2I$, 347.0508].

Aryl Iodide (−)-57. To a solution of resorcinol (+)-**56** (130 mg, 0.375 mmol) in 2-butanone (1.2 mL) were added K_2CO_3 (520 mg, 3.76 mmol) and methyl iodide (2.0 mL, 32.1 mmol). This solution was vigorously stirred and heated at 64 °C for 22.5 h. The reaction was then allowed to cool to room temperature and diluted with Et_2O (25 mL) and water (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were then washed with brine (15 mL), dried over $MgSO_4$, and concentrated. Purification via flash chromatography (0% → 2.5% ethyl acetate in hexanes) gave (−)-**57** (125 mg, 0.334 mmol, 89% yield) as a colorless oil: $[\alpha]^{20}_D$ −2.54° (*c* 0.59 $CHCl_3$); IR ($CHCl_3$) 3060 (w), 2990 (m). 2950 (s), 2840 (s), 1635 (w), 1570 (s), 1460 (s), 1400 (s), 1365 (m), 1300 (w), 1275 (w), 1230 (m), 1170 (m), 1130 (s), 1100 (s), 990 (w), 950 (w), 905 (m), 810 (s), 570 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 2 H), 5.62 (dddd, J = 17.1, 10.1, 7.1, 7.1 Hz, 1 H), 4.88 (d, J = 17.1 Hz, 1 H), 4.79 (d, J = 10.1 Hz, 1 H), 3.74 (s, 6 H), 3.31 (dddd, J = 9.3, 9.3, 6.4, 6.4 Hz, 1 H), 2.47 (m, 1 H), 2.35 (m, 1 H), 1.75 (dddd, J = 13.2, 9.9, 9.9, 5.2 Hz, 1 H), 1.55 (m, 1 H), 1.22 (m, 2 H), 1.10 (m, 1 H), 1.00 (m, 1 H), 0.79 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.42, 138.59, 121.32, 114.46, 114.11, 90.32, 55.91, 37.90, 35.05, 32.58, 30.30, 22.76, 14.05; high-resolution mass spectrum (CI, CH_4) *m*/*z* 375.0804 [$(M + H)^+$; calcd for $C_{16}H_{24}O_2I$, 375.0821].

Ketone (+)-59. To a solution of known amide (−)-**58** (259 mg, 0.991 mmol) in THF (1.9 mL) at −78 °C was added *tert*-butyllithium (1.7M in pentane, 0.585 mL, 0.994 mmol). In a separate flask, to a solution of aryl iodide (−)-**57** (141 mg, 0.377 mmol) in THF (2.2 mL) at −78 °C was added *tert*-butyllithium (1.7M in pentane, 0.455 mL, 0.774 mmol). The amide solution was then transferred dropwise via cannula to the aryl iodide solution and allowed to stir for 7 min at −78 °C. The reaction was then brought to −20 °C for 10 min, and then to 0 °C for 7 min, at which time diisopropylamine (0.50 mL, 3.57 mmol) was added and allowed to stir for 5 min. The reaction was then quenched with 10% v/v aqueous acetic acid (5 mL) and diluted with Et_2O (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with 50% aqueous $NaHCO_3$ (2 × 10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (1% ethyl acetate in hexanes) gave (+)-**59** (88 mg, 0.255 mmol, 68% yield) as a colorless oil: $[\alpha]^{20}_D$ +23.7° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3060 (w), 2960 (s), 2840 (m), 1670 (s), 1635 (m), 1570 (s), 1455 (s), 1410 (s), 1370 (m), 1300 (s), 1230 (m), 1190 (m), 1130 (s), 985 (m), 940 (w), 910 (m), 850 (w), 565 (br, w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 2 H), 5.79 (dddd, J = 17.1, 10.1, 6.9, 6.9 Hz, 1 H), 5.63 (dddd, J = 17.1, 10.1, 7.1, 7.1 Hz, 1 H), 5.05 (d, J = 17.1 Hz, 1 H), 5.01 (d, J = 10.1 Hz, 1 H), 4.89 (d, J = 17.1 Hz, 1 H), 4.79 (d, J = 10.1 Hz, 1 H), 3.82 (s, 6 H), 3.44 (complex m, 2 H), 2.54 (m, 2 H), 2.41 (ddd, J = 6.9, 13.9, 6.9 Hz, 1 H), 2.19 (ddd, J = 7.4, 14.4, 7.4 Hz, 1 H), 1.81 (dddd, J = 13.3, 9.9, 9.9, 5.2 Hz, 1 H), 1.60 (dddd, J = 13.1, 10.5, 5.8, 5.8 Hz, 1 H), 1.24 (complex m, 2 H), 1.20 (d, J = 6.9 Hz, 3 H), 1.13 (m,1 H), 1.01 (m,1 H), 0.80 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.25, 159.28, 138.66, 136.27, 135.49, 127.60, 116.86, 114.81, 104.55, 56.04, 40.65, 38.09, 38.04, 35.73, 32.77, 30.57, 22.98, 17.50, 14.25; high-resolution mass spectrum (CI, CH_4) *m*/*z* 345.2426 [$(M + H)^+$; calcd for $C_{22}H_{33}O_3$, 345.2430].

Alcohol (+)-55. To neat (+)-*B*-chlorodiisopinocampheylborane [(+)-DIPCl] (103 mg, 0.321 mmol) was added a solution of (+)-**59** (57 mg, 0.166 mmol) in THF (0.30 mL). Once the solution became homogeneous by stirring, the reaction was placed at 0 °C for 10 h and then allowed to warm to room temperature. After 86 h at room temperature, the reaction was diluted with Et_2O (5.5 mL) and transferred to a larger flask. The solution was them stirred vigorously, and diethanolamine (100 mg, 0.952 mmol) was added to yield a white precipitate. After 1 h, 45 min, the reaction was filtered through a pad of Celite, diluted with Et_2O (25 mL) and washed with 1 N NaOH (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (3% → 7% ethyl acetate in hexanes) gave (+)-**55** (43 mg, 0.124 mmol, 81% yield, dr 19:1) as a colorless oil: $[\alpha]^{20}_D$ +5.4° (*c* 0.725, $CHCl_3$); IR ($CHCl_3$) 3585 (m), 3065 (m), 2940 (s), 2925 (s), 2835 (m), 1635 (m), 1605 (m),1580 (s), 1455 (s), 1420 (s), 1360 (m), 1310 (w), 1230 (w), 1190 (w), 1130 (s), 990 (m), 980 (w), 910 (s), 820 (w), 620 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.47 (s, 2 H), 5.94 (dddd, J = 17.1, 10.1, 7.0 Hz, 1 H), 5.74 (dddd, J = 17.1, 10.2, 7.1, 7.1 Hz, 1 H), 5.10 (d, J = 17.0 Hz, 1 H), 5.00 (m, 2 H), 4.94 (d, J = 10.2 Hz, 1 H), 4.32 (dd, J = 2.8, 4.6 Hz, 1 H), 3.78 (dddd, J = 9.1, 9.1, 6.1, 6.1 Hz, 1 H), 3.42 (s, 6 H), 2.88 (m,1 H), 2.68 (m,1 H), 2.21 (m,1 H), 2.15 (m,1 H), 1.86 (complex m, 3 H), 1.40 (m, 2 H), 1.31 (m, 2 H), 1.22 (d, J = 3.01 Hz, 1 H), 1.01 (d, J = 6.4 Hz, 3 H), 0.85 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 159.57, 143.73, 139.26, 137.64, 120.87, 115.93, 114.50, 103.21, 77.82, 55.50, 40.83, 38.98, 38.46, 35.84, 33.58, 31.01, 23.20, 14.39, 14.18; high-resolution mass spectrum (CI, CH_4) *m*/*z* 345.2424 [$(M - H)^+$; calcd for $C_{22}H_{33}O_3$, 345.2430].

Triethyl Silyl Ether (+)-60. To a solution of (+)-**55** (33 mg, 0.095 mmol) in CH_2Cl_2 (2.1 mL) at 0 °C was added 2,6-lutidine (60 μL, 0.609 mmol), followed by triethylsilyl trifluoromethanesulfonate (TESOTf) (54 μL, 0.238 mmol). After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (18 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated to a clear oil. Purification via flash chromatography (1% Et_2O in hexanes) gave (+)-**60** (40 mg, 0.087 mmol, 92% yield) as a colorless oil: $[\alpha]^{20}_D$ +29.7° (*c* 0.525, $CHCl_3$); IR ($CHCl_3$) 3060 (w), 2930 (s), 2850 (s), 1635 (m), 1605 (m), 1570 (s), 1460 (s), 1420 (s), 1375 (m), 1305 (m), 1235 (m), 1185 (w), 1135 (s), 1095 (s), 1000 (m), 910 (s), 835 (m), 805 (w); ^1H NMR (500 MHz, C_6D_6) δ 6.56 (s, 2 H), 5.92 (dddd, J = 17.1, 10.1, 7.1, 7.1 Hz, 1 H), 5.78 (dddd, J = 17.2, 10.2, 7.3, 7.3 Hz, 1 H), 5.05 (m, 3 H), 4.94 (d, J = 10.1 Hz, 1 H), 4.50 (d, J = 5.1 Hz, 1 H), 3.77 (dddd, J = 9.2, 9.2, 6.1, 6.1 Hz, 1 H), 3.46 (s, 6 H), 2.87 (m, 1 H), 2.67 (m, 1 H), 2.30 (m, 1 H), 2.16 (dddd, J = 14.2, 9.8, 9.8, 4.8 Hz, 1 H), 1.88 (complex m, 3 H), 1.38 (m, 2 H), 1.28 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.86 (t, J = 6.9 Hz, 3 H), 0.59 (q, J = 7.8 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 159.4,143.9, 139.2, 137.9, 120.9, 115.8, 114.4, 103.8, 79.7, 55.5, 42.2, 39.0, 38.3, 35.9, 33.5, 31.0, 23.2, 15.0, 14.2, 7.0, 5.6; high-resolution mass spectrum (CI, CH_4) *m*/*z* 459.3284 [$(M - H)^+$; calcd for $C_{28}H_{47}O_3Si$, 459.3294].

Macrocycle (+)-54. To a solution of (+)-**60** (28 mg, 0.0608 mmol) in degassed benzene (5.0 mL) was added a solution of Schrock's catalyst (0.1 M in benzene, 1.3 mL, 0.0205 mmol), yielding a brown solution. After 1.25 h, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), diluted with Et_2O (20 mL), washed consecutively with saturated aqueous NH_4Cl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (0.25% → 1% ethyl acetate in hexanes) gave (+)-**54** (20 mg, 0.023 mmol, 77% yield) as a white solid: mp 176−178 °C, $[\alpha]^{20}_D$ +22.0° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2940 (s), 2870 (s), 2350 (w), 1730 (m), 1610 (m), 1590 (s), 1450 (s), 1420 (s), 1380 (m), 1300 (w), 1240 (s), 1140 (s), 1115 (s), 1100 (s), 1000 (m), 965 (w), 905 (m), 845 (m), 820 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.50 (s, 2 H), 6.05 (s,2 H), 5.01 (complex m, 4 H), 4.13 (d, J = 5.3 Hz, 2 H), 3.7 (s,6 H), 3.65 (s,6 H), 3.28 (m, 2 H), 2.52 (ddd, J = 8.1, 12.5, 12.5 Hz, 2 H), 2.14 (ddd, J = 12.9, 4.5, 4.5 Hz, 2 H), 1.81 (m,2 H), 1.64 (m,2 H), 1.51 (m,2 H), 1.17 (complex m,10 H), 1.00 (m, 2 H), 0.79 (q, J = 8.0 Hz, 18 H), 0.61 (d, J = 5.6 Hz, 6 H), 0.43 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 157.7, 143.0, 131.0, 128.9, 119.4, 104.0, 102.9, 80.4, 56.5, 55.3, 42.3, 36.8,

36.7, 35.7, 33.4, 30.6, 22.8, 14.3, 14.1, 6.8, 4.9; high-resolution mass spectrum (ES+) *m/z* 887.6025 [(M + Na)$^+$; calcd for $C_{52}H_{88}O_6NaSi_2$, 887.6017].

Diol (−)-61. To a solution of (+)-**54** (13.5 mg, 0.0156 mmol) in THF (0.65 mL) at 0 °C was added a solution of TBAF (1.0 M in THF, 105 μL, 0.105 mmol). The reaction was brought to room temperature after 30 min, and after 90 min the reaction was quenched with NH_4Cl (5 mL), extracted with ethyl acetate (4 × 10 mL), dried over $MgSO_4$, filtered, and concentrated to a yellow solid. Purification via flash chromatography (10% → 15% ethyl acetate in hexanes) gave (−)-**61** (7 mg, 0.011 mmol 71% yield) as a white solid: mp 144−126 °C; $[\alpha]^{20}_D$ −131.4° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3560 (m), 3000 (m), 2950 (s), 1605 (s), 1585 (s), 1460 (s), 1415 (s), 1385 (m), 1310 (m), 1235 (m), 1185 (m),1140 (s), 1115 (s), 1100 (s), 970 (s), 815 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 2 H), 5.86 (s, 2 H), 5.28 (m, 2 H), 5.10 (m, 2 H), 3.78 (s, 6 H), 3.76 (s, 6 H), 3.47 (m, 2 H), 3.18 (m, 2 H), 2.62 (app q, *J* = 12.3 Hz, 2 H), 2.31 (m, 2 H), 1.89 (m, 4 H), 1.81 (m, 2 H), 1.61 (m, 2 H), 1.41 (m, 2 H), 1.24 (m, 6 H), 1.11 (m, 2 H), 0.82 (t, *J* = 7.0, 2 H), 0.78 (d, *J* = 4.8, 2 H), 0.52 (d, *J* = 6.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.25, 158.51, 145.17, 132.65, 128.67, 118.86, 101.79, 101.05, 71.74, 56.34, 55.12, 39.50, 37.61, 36.86, 35.13, 33.22, 30.68, 22.86,14.10, 12.58; high-resolution mass spectrum (ES+) *m/z* 659.4301 [(M + Na)$^+$; calcd for $C_{40}H_{60}O_6Na$, 659.4288].

(−)-Cylindrocyclophane A (1a). A solution of diol (−)-**61** (6.5 mg, 0.010 mmol) in ethanol (2.1 mL) was hydrogenated in the presence of a catalytic amount of PtO_2 under 1 atm of H_2 gas for 75 min. The resulting mixture was diluted with ethyl acetate (25 mL), filtered through a pad of Celite, and concentrated, to give the expected hydrogenated product (6.5 mg, 0.010 mmol, quantitative yield) as a white powder: mp 195−197 °C; $[\alpha]^{20}_D$ −8.44° (*c* 0.32, $CHCl_3$); IR 3690 (m), 2930 (s), 2855 (m), 1654 (w), 1603 (s), 1458 (m), 1420 (w), 1375 (w), 1136 (m), 979 (w), 838 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 2 H), 6.25 (s, 2 H), 3.96 (dd, *J* = 2.3, 9.4 Hz, 2 H) 3.73 (s, 6 H), 3.70 (s, 6 H), 3.19 (m, 2 H), 1.82 (d, *J* = 2.6 Hz, 2 H) 1.77 (m, 4 H), 1.54 (m, 4 H), 1.35 (m, 4 H), 1.23 (m, 4 H), 1.13 (m, 2 H), 1.07 (d, *J* = 6.4 Hz, 6 H), 1.01 (m, 2 H), 0.82 (m, 4 H), 0.80 (t, *J* = 7.1 Hz, 6 H), 0.58 (complex m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.07, 158.13, 142.68, 121.42, 106.06, 101.51, 81.24, 56.75, 55.58, 41.33, 35.62, 34.29, 33.70, 33.52, 30.60, 29.38,28.52, 22.86, 16.37, 14.09; high-resolution mass spectrum (ES$^+$) *m/z* 663.4600 [(M + Na)$^+$; calcd for $C_{40}H_{64}O_6Na$, 663.4601].

To a solution of the hydrogenation product (4.0 mg 0.00624 mmol) in 1-methyl-2-pyrrolidinone (0.80 mL) was added anhydrous K_2CO_3 (4.5 mg, 0.033 mmol) followed by thiophenol (0.190 mL, 1.84 mmol). The reaction vessel was sealed and heated to 215 °C for 6 h, at which time it was diluted with ethyl acetate (15 mL) and pH 4 buffer (10 mL) The layers were separated, and the aqueous layer was saturated with NaCl and extracted with ethyl acetate (4 × 15 mL), followed by 5% MeOH in CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The solvent and excess of thiophenol were removed by bulb-to-bulb distillation (60 °C, 2 mmHg), leaving behind a yellow solid. Purification via flash chromatography on silica gel (5% → 7% methanol in CH_2Cl_2) gave 3.1 mg (85% yield) of (−)-cylindrocyclophane A (**1a**) as a white solid. The spectroscopically pure sample was obtained upon reverse-phase HPLC purification (70% MeCN/30% H_2O) to yield (−)-cylindrocyclophane A (**1a**) as a white solid (2.9 mg, 79% yield) that was identical in all respects to the reported literature data [500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR, HRMS]: mp 276−278 °C; $[\alpha]^{20}_D$ −20.7° (*c* 0.14, MeOH); ^{1}H NMR (500 MHz, DMSO) δ 8.55 (s, 2 H), 8.52 (s, 2 H), 6.16 (s, 2 H), 5.94 (s, 2 H), 4.83 (d, *J* = 1.9 Hz, 2 H), 3.56 (dd, *J* = 9.5, 3.7 Hz, 2 H) 3.06 (m, 2 H), 1.89 (m, 2 H), 1.81 (m, 2 H), 1.44 (m, 2 H), 1.36 (m, 2 H), 1.30 (m, 2 H), 1.26 (m, 2 H),1.23 (m, 2 H), 1.16 (m, 2 H), 1.09 (m, 2 H), 1.02 (m, 2 H), 0.97 (d, *J* = 6.4 Hz, 6 H), 0.86 (m, 2 H), 0.77 (t, *J* = 7.2 Hz, 6 H), 0.70 (m, 2 H), 0.62 (m, 2 H), 0.57 (complex m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.9, 157.0, 143.9, 117.8, 109.0, 105.1, 81.9, 42.1, 36.9, 35.5, 35.3, 34.9, 31.7, 30.7, 29.9, 23.9, 17.0, 14.5; high-resolution mass spectrum (ES+) *m/z* 607.3956 [(M + Na)$^+$; calcd for $C_{36}H_{56}O_6Na$, 607.3975].

The Cross Olefin Metathesis Dimerization Process: Aldehyde (+)-70. To a solution of the alcohol dervied from acidic hydrolysis of (+)-**36** (35 mg, 0.105 mmol) in CH_2Cl_2 (1.9 mL) was added pyridine (50 μL, 0.620 mmol). The reaction was placed at 0 °C, and Dess−Martin periodinane (103 mg, 0.242 mmol) was added. The reaction as placed at room temperature and stirred for 2.5 h, at which time it was quenched with saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous Na_2SO_3 (1 mL), diluted with CH_2Cl_2 (10 mL), washed consecutively with saturated aqueous $NaHCO_3$ (4.0 mL) and brine (4.0 mL), and then dried over $MgSO_4$. Purification via flash chromatography (47% Et_2O in hexanes) gave (+)-**70** (31 mg, 91% yield) as a yellow oil: $[\alpha]^{20}_D$ + 9.7° (*c* 0.48, C_6H_6); IR ($CHCl_3$) 2950 (s), 2930 (s), 2840 (w), 1715 (s), 1600 (w), 1570 (m), 1450 (m), 1410 (m), 1125 (m), 1110 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (t, *J* = 1.7 Hz, 1 H), 6.23 (s, 2 H), 5.91 (dddd, *J* = 17.1, 10.2, 7.2, 7.2 Hz, 1 H), 5.08 (m, 1 H), 4.92 (m, 1 H), 3.73 (dddd, *J* = 9.2, 9.2, 6.2, 6.2 Hz, 1 H), 3.43 (s, 6 H), 2.84 (m, 1 H), 2.66 (m, 1 H), 2.34 (ddd, *J* = 0, 1.2, 7.2 Hz, 1 H), 2.25 (ddd, *J* = 0, 13.3, 7.3 Hz, 1 H), 2.13 (m, 2 H), 2.00 (ddd, *J* = 16.5, 5.6, 1.6 Hz, 1 H), 1.84 (m, 1 H), 1.78 (m, 1 H), 1.35 (m, 4 H), 0.84 (t, *J* = 7.0 Hz, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.5, 159.5, 139.32, 139.27, 119.4. 114.7, 105.6, 55.3, 50.4, 43.8, 39.0, 35.6, 33.5, 31.2, 31.0, 30.5, 30.2, 23.4, 23.3, 20.1, 20.0, 14.3; high-resolution mass spectrum (CI, CH_4) *m/z* 333.2415 [(M + H)$^+$; calcd for $C_{21}H_{33}O_3$, 333.2430].

Wittig Salt (−)-71. To a solution of iodide (+)-**37** (10.0 mg, 0.0225 mmol) in acetonitrile (0.75 mL) was added triphenylphosphine (71 mg, 0.27 mmol). The reaction was heated at reflux for 7.5 h and then cooled to room temperature and purified directly via flash chromatography (5% → 10% ethyl acetate in hexanes to 5% MeOH in CH_2Cl_2), which gave (−)-**71** (15.0 mg, 94% yield) as a yellow amorphous solid: $[\alpha]^{20}_D$ −13.6° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2950 (s), 2850 (m), 1610 (w), 1585 (m), 1465 (m), 1440 (s), 1240 (m), 1120 (s), 1000 (w), 910 (w), cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (m, 9 H), 7.67 (m, 6 H), 6.31 (s 2 H), 5.61 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1 H), 4.87 (dd, *J* = 1.5, 17.1 Hz, 1 H), 4.71 (dd, *J* = 1.3, 10.1 Hz, 1 H), 3.72 (m, 1 H), 3.70 (s, 6 H), 3.56 (m, 1 H), 3.27 (ddd, *J* = 15.1, 8.8, 6.5 Hz, 1 H), 2.56 (m, 1 H), 2.44 (m, 2 H), 2.36 (m, 1 H), 2.24 (m, 1 H), 1.64 (m, 3 H), 1.41 (m, 1 H), 1.21 (m, 4 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.76 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 158.8, 139.1, 139.0, 135.0, 133.7, 133.6, 132.1, 132.0, 131.88, 130.5, 130.4, 128.5, 128.4, 119.0, 118.6, 117.9, 117.8, 114.1, 105.5, 56.1, 43.3, 38.2, 35.2, 35.1, 34.9, 32.8, 30.4, 28.81, 28.77, 22.8, 21.4, 21.0, 19.9, 14.0; high-resolution mass spectrum (CI, CH_4) *m/z* 579.3403 [(M − I)$^+$; calcd for $C_{39}H_{48}O_2P$, 579.3391].

***Z*-Dimer (−)-68.** To a solution of Wittig salt (−)-**71** (56 mg, 0.089 mmol) in THF (1.30 mL) at −78 °C was added KHMDS (0.5 M in toluene; 177 μL, 0.089 mmol). The resulting bright orange solution was brought to 0 °C for 8 min and then returned to −78 °C. A solution of aldehyde (+)-**70** (22 mg, 0.067 mmol) in THF (0.70 mL) was then added dropwise via cannula to the ylide. After 1.5 h, the reaction was brought to 0 °C for 5 min, quenched with saturated aqueous $NaHCO_3$ (5.0 mL), extracted with Et_2O (3 × 7 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (1% → 5% Et_2O in hexanes) gave (−)-**68** (35 mg, 88% yield, *E/Z* > 15:1) as a colorless oil: $[\alpha]^{20}_D$ −19.0° (*c* 0.78, $CHCl_3$); IR (film) 3072 (w), 2955 (s), 2913 (s), 2860 (m), 1637 (w), 1605 (m), 1573 (s), 1456 (m), 1414 (m), 1371 (w), 1212 (m), 1132 (s), 1110 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 4 H), 5.67 (dddd, *J* = 17.3, 10.1, 7.4, 7.4 Hz, 2 H), 5.48 (dd, *J* = 4.7, 4.7 Hz, 2 H), 4.91 (app d, *J* = 17.2 Hz, 2 H), 4.79 (app d, *J* = 10.1 Hz, 2 H), 3.73 (s, 12 H), 3.31 (m, 2 H), 2.58 (dd, *J* = 13.4. 6.2 Hz, 2 H), 2.50 (dddd, *J* = 13.9, 7.0, 7.0, 7.0 Hz, 2 H), 2.39 (m, 2 H), 2.28 (m, 2 H), 2.04 (app dt, *J* = 10.0, 4.7, 4.7 Hz, 2 H), 1.87 (m, 2 H), 1.77 (m, 4 H), 1.57 (m, 2 H), 1.22 (m, 6 H), 1.04 (m, 2 H), 0.85 (d, *J* = 6.6 Hz, 6 H), 0.80 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 159.6, 140.6, 139.4, 129.6, 119.6, 114.5, 106.0, 55.5, 44.3, 39.1, 36.0, 35.8, 34.9, 33.6, 31.0, 23.2, 19.8, 14.2; high-resolution mass spectrum (CI, CH_4) *m/z* 633.4883 [(M + H)$^+$; calcd for $C_{42}H_{65}O_4$, 633.4870].

Sulfone (−)-72. To a solution of the alcohol derived from acidic hydrolysis of (+)-**36** (15.0 mg, 0.045 mmol) in THF (0.50 mL) was added 1-phenyl-1*H*-tetrazole-*S*-thiol (16 mg, 0.091 mmol). The reaction was placed at 0 °C, and then triphenylphosphine was added (18.0 mg, 0.069 mmol), followed by diethyl azodicarboxylate (13 μL, 0.082

mmol). The resulting yellow solution was brought to 20 °C and after 20 min diluted with Et_2O (10 mL) and brine (5 mL), extracted with Et_2O (2 × 7 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (20% Et_2O in hexanes) afforded the thioether (0.21 mg, 95% yield) as a yellow oil: $[\alpha]^{20}_D$ − 24.0° (*c* 0.20, C_6H_6); IR ($CHCl_3$) 3000 (m), 2950 (s), 2860 (m), 1640 (w), 1610 (s), 1590 (s), 1500 (s), 1465 (s), 1425 (s), 1280 (w), 1250 (m), 1130 (s), 1015 (w), 750 (s), 680 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 6 H), 6.28 (s, 2 H), 5.65 (dddd, J = 17.3, 10.0, 7.4, 7.4 Hz, 1 H), 4.88 (app d, J = 17.7 Hz, 1 H), 4.77 (app d, J = 10.1 Hz, 1 H), 3.72 (s, 6 H), 3.46 (m, 1 H), 3.33 (m, 2 H), 2.59 (m, 1 H), 2.49 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 1 H), 2.38 (m, 2 H), 1.87 (m, 1 H), 1.75 (m, 1 H), 1.67 (m, 1H), 1.56 (m, 1 H), 1.22 (m, 2 H), 1.13 (m, 1 H), 1.02 (m, 1 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.78 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 63 °C) δ 159.6, 154.2, 139.8, 139.3, 134.6, 129.6, 127.54, 124.0, 119.8, 114.5, 106.0, 55.6, 43.9, 39.0, 36.6, 35.8, 34.5, 33.6, 31.7, 31.0, 23.2, 19.5, 14.2; high-resolution mass spectrum (CI, CH_4) m/z 495.2794 [$(M + H)^+$; calcd for $C_{28}H_{39}O_2N_4S$, 495.2784].

To a solution of the thioether (11.0 mg, 0.022 mmol) in EtOH (1.5 mL) at 0 °C was added a solution of aqueous hydrogen peroxide and ammonium heptamolybdate tetrahydrate [25.0 μL of a stock solution of $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$ (240 mg, 0.19 mmol) in 30% w/v aqueous hydrogen peroxide (1.0 mL)]. The reaction was allowed to warm to 20 °C and after 18.5 h was quenched with water (3.0 mL), extracted with ethyl acetate (3 × 5.0 mL), dried with $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (10% ethyl acetate in hexanes) gave (−)-**72** (10.0 mg, 87% yield) as a yellow oil: $[\alpha]^{20}_D$ −21.3° (*c* 0.15, $CDCl_3$); IR (film) 2983 (s), 2915 (s), 2859 (w), 1603 (m), 1573 (w), 1495 (w), 1456 (s), 1420 (m), 1339 (s), 1149 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32 (m, 2 H), 6.88 (m, 3 H), 6.21 (s, 2 H), 5.93 (dddd, J = 17.1, 10.1, 7.0, 7.0 Hz, 1 H), 5.10 (app d, J = 17.6 Hz, 1 H), 4.95 (app d, J = 10.2 Hz, 1 H), 3.76 (dddd, J = 9.1, 9.1, 6.0, 6.0 Hz, 1 H), 3.48 (s, 6 H), 3.38 (m, 1 H), 3.26 (m, 1 H), 2.88 (m, 1 H), 2.68 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1 H), 2.29 (dd, J = 13.5, 6.6 Hz, 1 H), 2.14 (m, 2 H), 1.86 (m, 2 H), 1.66 (m, 1 H), 1.60 (m, 1 H), 1.35 (m, 4 H), 0.85 (t, J = 6.9 Hz, 3 H), 0.63 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, 63 °C) δ 159.4, 154.0, 138.9, 138.8, 133.4, 130.6, 129.1, 125.0, 119.7, 114.2, 105.5, 55.2, 54.4, 43.2, 38.6, 35.4, 33.6, 33.2, 30.6, 28.6, 22.9, 19.9, 13.8; high-resolution mass spectrum (CI, CH_4) m/z 549.2488 [$(M + Na)^+$; calcd for $C_{28}H_{38}O_4N_4SNa$, 549.2511].

***E*-Dimer (−)-69.** To a solution of sulfone (−)-**72** (18.0 mg, 0.034 mmol) in THF (0.90 mL) at −78 °C was added KHMDS (0.5 M in toluene; 87 μL, 0.034 mmol), resulting in a bright yellow solution. After 30 min, aldehyde (+)-**70** (12.0 mg, 0.036 mmol), predissolved in THF (0.70 mL), was added dropwise via cannula to the reaction mixture and allowed to stir for 2 h, after which the reaction was brought to 20 °C and allowed to stir for 19 h, quenched with H_2O (1.0 mL), diluted with Et_2O (10 mL), washed successively with saturated aqueous NH_4Cl (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (2% Et_2O in hexanes) gave (−)-**69** (16.0 mg, 74% yield, *E*/*Z* > 15:1) as a colorless oil: $[\alpha]^{20}_D$ −12.8° (*c* 0.40, $CDCl_3$); IR (film) 2955 (s), 2923 (s), 2859 (m), 1637 (w), 1605 (m), 1573 (s), 1456 (m), 1419 (m), 1371 (w), 1212 (m), 1132 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.34 (s, 4 H), 5.93 (dddd, J = 17.2, 10.1, 7.2, 7.2 Hz, 2 H), 5.50 (app t, J = 4.1 Hz, 2 H), 5.10 (app d, J = 16.3 Hz, 2 H), 4.94 (app d, J = 10.1 Hz, 2 H), 3.76 (dddd, J = 9.1, 9.1, 6.6, 6.6 Hz, 2 H), 3.44 (s, 12 H), 2.86 (m, 2 H), 2.70 (m, 4 H), 2.34 (dd, J = 13.3, 8.2 Hz, 2 H), 2.14 (m, 4 H), 1.95 (m, 2 H), 1.86 (m, 4 H), 1.36 (complex m, 8 H), 0.95 (d, J = 6.6 Hz, 6 H), 0.85 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 159.6, 140.6, 139.4, 130.7, 119.6, 114.5, 106.0, 55.5, 44.1, 40.4, 39.1, 35.8, 35.7, 33.6, 31.0, 23.2, 19.7, 14.2; high-resolution mass spectrum (CI, CH_4) m/z 655.4677 [$(M + Na)^+$; calcd for $C_{42}H_{64}O_4Na$, 655.4702].

Macrocycle (−)-48 from Trienes (−)-68 and (−)-69. General Procedure for Metathesis Reaction. A degassed solution (ca. 0.02 M) of triene (−)-**69** (4.5 mg, 0.007 mmol) in degassed benzene (0.70 mL) was treated with the metathesis catalyst (32−35 mol %). The resulting homogeneous solution was stirred for 60−75 min; concentration under reduced pressure led to the product, which was purified by preparative TLC. All spectroscopic and chirooptic properties are identical to those reported above for macrocycle (−)-**48**.

Acknowledgment. Support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM-29028. In addition, we thank Professor Grubbs (California Institute of Technology) for a generous sample of ruthenium complex **B**, and Drs. George T. Furst, Patrick J. Carroll, and Rakesh Kohli of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra, respectively. Finally, we thank Professor Hoye for the exchange of spectral data and Professor Kozlowski for useful advice and comments regarding molecular modeling.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for compounds **1a**, **1f**, **9**−**13**, **19**, **20**, **22**−**25**, **27**, **29**−**34**, **36**−**41**, **43**−**53**, **54**−**57**, **59**−**61**, **68**−**72** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0106164