Assembly of (−)-Cylindrocyclophanes A and F via Remarkable Olefin Metathesis Dimerizations

Amos B. Smith, III,* Sergey A. Kozmin, Christopher M. Adams, and Daniel V. Paone

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center University of Pennsylvania, Philadelphia, Pennsylvania 19104

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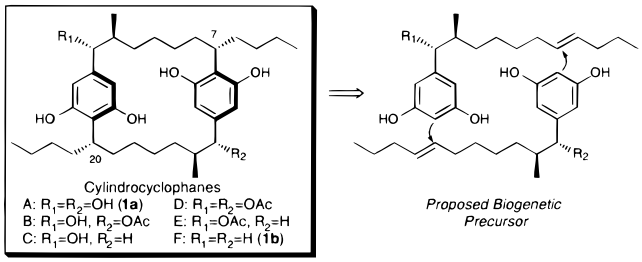
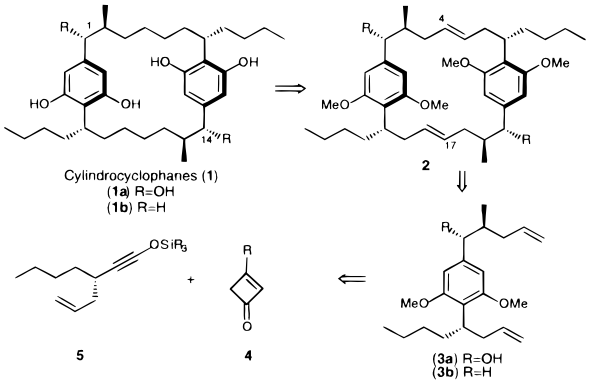
A fascinating array of architecturally complex natural products arise via dimerization.[1] The vast majority of these structures involve assembly via carbon−heteroatom linkages (e.g., ester, amide, etc.), giving rise to macrocyclic lactones and lactams often possessing C_2-symmetry. Dimerization via carbon−carbon bond formation, a relatively rare event, not surprisingly furnishes particularly attractive synthetic targets. The cylindrocyclophanes A−F represent such a case.[2] These unique naturally occurring 22-membered carbocyclic [7,7]-paracyclophanes,[3] isolated by Moore and co-workers from *Cylindrospermum licheniforme*,[2b] are postulated to arise biosynthetically via dimerization involving electrophilic aromatic substitution at C(2) of a 5-substituted resorcinol with an olefin appropriately positioned in the side chain.[2c]



From the retrosynthetic perspective, exploitation of the above biomimetic strategy, 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 olefin metathesis[4] to close the [7,7]-paracyclophane skeleton.[5] This approach led to cylindrocyclophane F (**1b**), the first member of the family to succumb to total synthesis. Encouraged by the high efficiency of the ring-closing metathesis (RCM) process, we recently explored the feasibility of assembling the C_2-symmetric cyclophane skeletons for both cylindrocyclophanes A and F via olefin metathesis dimerization, a tactic not previously exploited in natural product total synthesis.[4] The plan called for disconnection of macrocycle **2** at C(4−5) and C(17−18); incorporation of the requisite terminal olefins revealed diene **3** (Scheme 1). Assembly of **3** would again rely on Danheiser

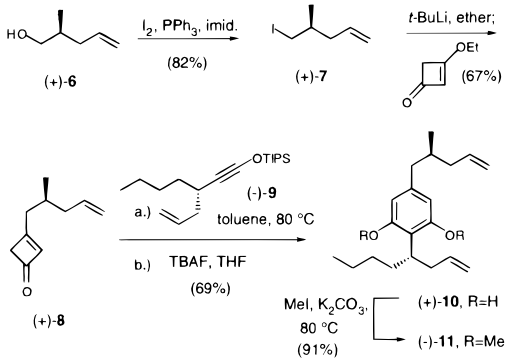
Scheme 1



annulation,[6] in this case involving cyclobutenone **4** and siloxy acetylene **5**, the latter prepared in our first-generation synthesis.[5] We envisioned this approach to hold considerable promise for significant improvement in overall efficiency.

Our point of departure for cylindrocyclophane F (**1b**) involved conversion of known alcohol (+)-**6**[7] to iodide (+)-**7**[8] (Scheme 2). Treatment of this iodide with *t*-BuLi in ether at −78 °C,

Scheme 2



followed by addition of the resultant organolithium to ethoxy cyclobutenone,[9] furnished cyclobutenone (+)-**8**[8] in 62% yield. Danheiser annulation[6] was then achieved by heating a solution of (+)-**8**[8] and siloxy acetylene (−)-**9**[5] for 2 h at 80 °C. Treatment of the reaction mixture with TBAF, followed after chromatography by methylation (MeI, K_2CO_3, 2-butanone), led to diene (−)-**11**.[8]

For cylindrocyclophane A (**1a**), Danheiser annulation of stannyl cyclobutenone **12**[10] with siloxyacetylene (−)-**9**,[5] followed by iododestannylation and desilylation, furnished resorcinol (+)-**13**;[8] methylation then gave iodide (−)-**14**.[8] The iodide was next metalated with *t*-BuLi and the lithium alkoxide obtained from

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(8) The structural assignment to each new compound is in accord with its IR, ^{1}H and ^{13}C NMR, and mass spectroscopic analysis.

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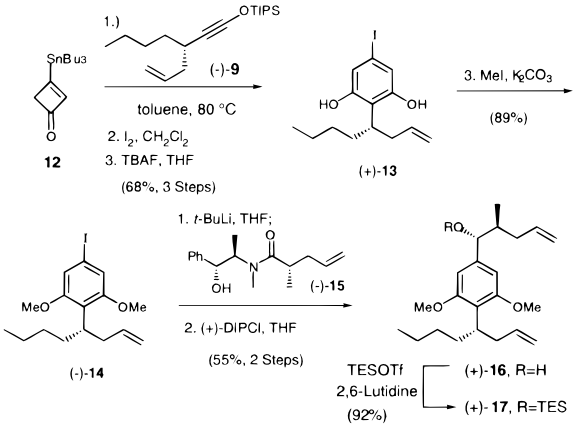
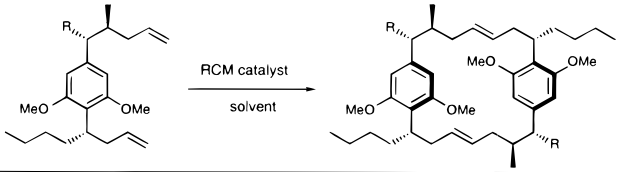
the Myers amide (−)-**15**[11] added to furnish, as anticipated, a ketone which was reduced with (+)-*B*-chlorodiisopinocampheylborane (dr = 19:1)[12] to give alcohol (+)-**16**.[8] Protection of the benzylic hydroxyl (TESOTf, 2,6-lutidine) completed construction of diene (+)-**17** (Scheme 3).[8]

Scheme 3



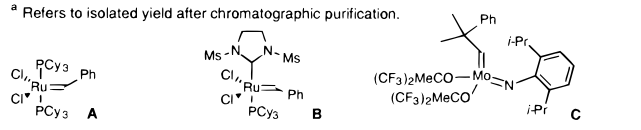
With both (−)-**11** and (+)-**17** in hand, we turned to the required dimerizations. Treatment of diene (−)-**11** with Grubbs catalyst **A**[13a] (15 mol %; Table 1) for 25 h at ambient temperature led to paracyclophane (−)-**18**[8] in 55% yield. Interestingly, only the *E*,*E* isomer was observed. With 20 mol % of catalyst and a longer reaction time (72 h; entry 2) (−)-**18** was produced in 61% yield. The perhydroimidazolidine catalyst (**B**), recently introduced by Grubbs,[13b] also promoted the dimerization with similar efficiency at 40 °C for 4 h in benzene. The Schrock catalyst (**C**)[13c] proved most reactive, furnishing (−)-**18** in 72% in 2 h at 20 °C. Even higher efficiency (77% yield, entry 6) was obtained when the latter conditions were applied to diene (+)-**17**, required for cylindrocyclophane A (**1a**). It is noteworthy that the alternative "head-to-head" dimerization products were not detected in these experiments, presumably indicative of the reversible nature of the metathesis reaction and the low-energy nature of the *all-trans* "head-to-tail" dimer.[14]

Table 1

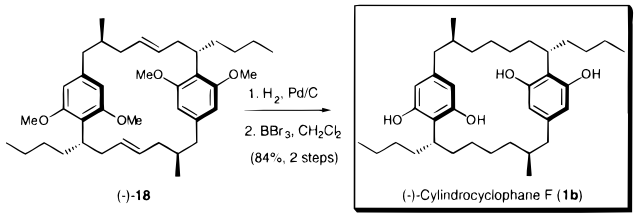


Entry	Substrate	Catalyst (mol%)	Solvent	Rxn Time, Temp.	Product[a] (% yield)
1	(-)-**11**	**A** (15%)	CH_2Cl_2	25h, 20 °C	(-)-**18** (55)
2	(-)-**11**	**A**(20%)	CH_2Cl_2	72 h, 20 °C	(-)-**18** (61)
3	(-)-**11**	**B**(15%)	CH_2Cl_2	4 h, 40 °C	(-)-**18** (48)
4	(-)-**11**	**B** (15%)	C_6H_6	27 h, 40 °C	(-)-**18** (58)
5	(-)-**11**	**C** (30%)	C_6H_6	2 h, 20 °C	(-)-**18** (72)
6	(+)-**17**	**C** (34%)	C_6H_6	1 h, 20 °C	(+)-**19** (77)

[a] Refers to isolated yield after chromatographic purification.



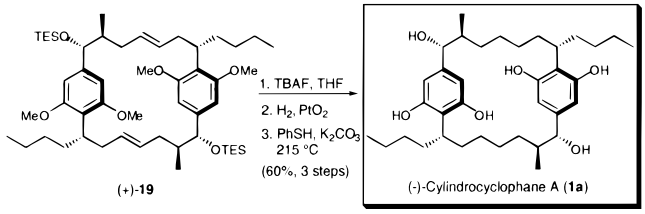
Scheme 4



completed the synthesis of (−)-cylindrocyclophane F (**1b**), which was identical in all respects [500-MHz ^{1}H and 125-MHz ^{13}C NMR, HRMS, optical rotation, and TLC (three solvent systems)] with an authentic sample.[15] As anticipated, the second-generation synthesis of (−)-cylindrocyclophane F (**1b**) proved more efficient (11 steps; 22% overall yield) compared to our first synthesis (20 steps; 8.3% overall yield), which employed a stepwise construction of the cyclophane skeleton.[5]

Completion of (−)-cylindrocyclophane A (**1a**) was next achieved via desilylation (TBAF, THF) of (+)-**19**, hydrogenation (Adams' catalyst), and cleavage of methyl ethers (PhSH, K_2CO_3, NMP, 215 °C) (Scheme 5).[16] The synthesis required 16 steps and

Scheme 5



proceeded in 8.1% overall yield.[17] (−)-Cylindrocyclophane A (**1a**) was identical in all respects with the literature spectral data [500-MHz ^{1}H and 125-MHz ^{13}C NMR, HRMS] and chiroptic properties.[2b,17]

In summary, dimerization via the ring-closing metathesis provides a remarkably efficient tactic for assembly of the cylindrocyclophane [7,7]-paracyclophane skeleton.

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Supporting Information Available: Spectroscopic data for **1**−**19**, as well as representative experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.
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