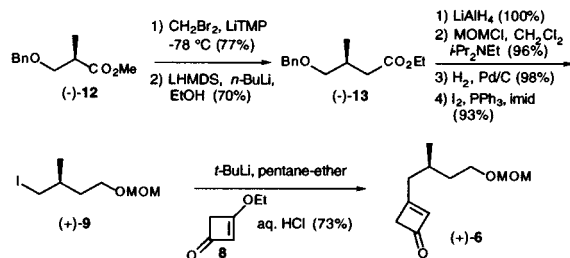


were obtained via a modified two-step sequence, in which the initial dibromoketone was isolated and then subjected to rearrangement at $-78\text{ }^{\circ}\text{C}$. This protocol, leading to silyloxy acetylene ($-$)-**5**¹⁴ in 80% yield,¹⁵ proved superior to the one-pot process.^{9a}

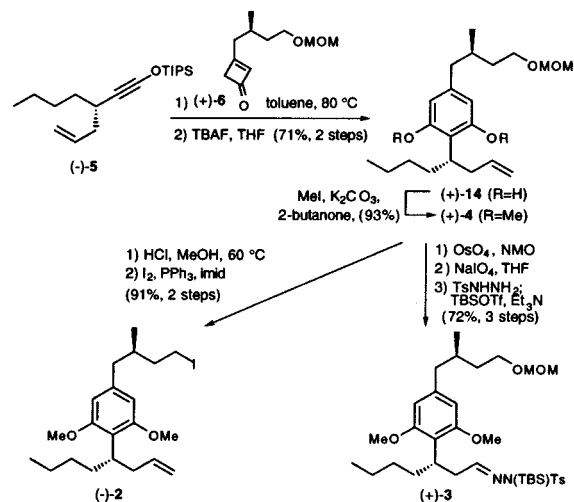
A second Kowalski homologation was employed for the preparation of cyclobutenone **6** (Scheme 3). In this case, ester ($-$)-**12**¹⁶ was chain extended to ($-$)-**13**.¹⁴ Conversion to iodide ($+$)-**9** was then achieved by reduction of ($-$)-**13**, protection of the resulting alcohol (MOMCl, Hünig's base), hydrogenolysis of the benzyl ether, and iodination (I_2 , PPh_3 , imidazole). Generation of the organolithium reagent from iodide ($+$)-**9** [$t\text{-BuLi}$ (2 equiv), ether-pentane] and addition to ethoxycyclobutenone **8**,¹¹ afforded cyclobutenone ($+$)-**6**¹⁴ in 73% yield after acidic workup.

Scheme 3



To construct the tetrasubstituted resorcinol **4**, we turned to the Danheiser benzannulation⁸ (Scheme 4). Heating ($-$)-**5** and ($+$)-**6** at $80\text{ }^{\circ}\text{C}$ for 2 h in toluene and then treating with TBAF afforded ($+$)-**14**¹⁴ in 71% yield. Methylation (MeI, K_2CO_3 , 2-butanone) then furnished ($+$)-**4**,¹⁴ the common precursor for coupling partners ($-$)-**2** and ($+$)-**3**.

Scheme 4



To set the stage for paracyclophane assembly, removal of the MOM group from ($+$)-**4** and iodination (I_2 , PPh_3 , imidazole) led to ($-$)-**2**;¹⁴ alternatively, oxidative cleavage of the olefin (OsO_4 , NMO; NaIO_4) afforded the corresponding aldehyde, which was converted to labile TBS-protected tosyl hydrazone ($+$)-**3** (TsNHNH_2 , THF; TBSOTf, Et_3N , THF)⁶ in 72% yield for 3 steps.

(15) The integrity of the chiral center in ($-$)-**5** was established rigorously. Paone, D. V. Ph.D. Dissertation, University of Pennsylvania, 1998.

(16) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292.

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

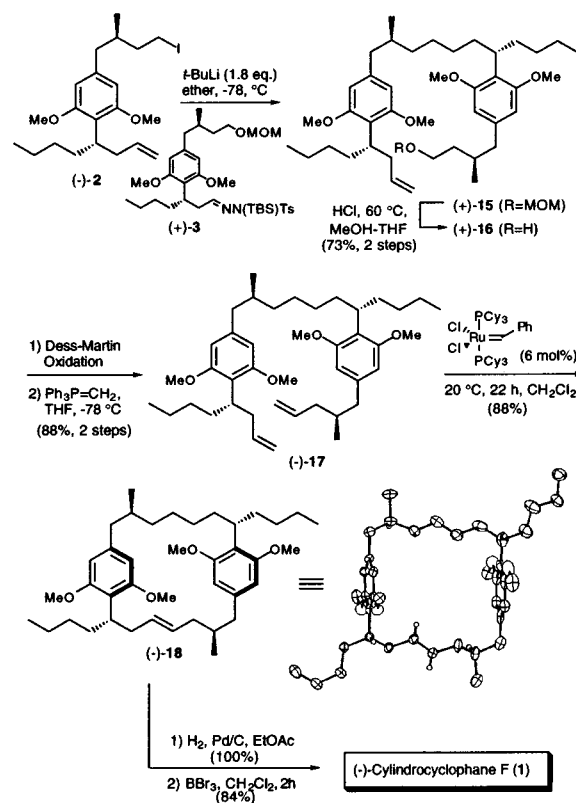
(18) Carroll, P. J. University of Pennsylvania, unpublished results.

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

(20) We thank Professor Moore (University of Hawaii) for a generous sample of authentic ($-$)-cylindrocyclophane F.

Elaboration of the paracyclophane skeleton began with the Myers reductive coupling⁶ of hydrazone ($+$)-**3** employing the organolithium reagent generated from iodide ($-$)-**2** (Scheme 5); coupled product ($+$)-**15**¹⁴ was obtained in 73% yield. Removal of the MOM group (HCl, MeOH-THF, $60\text{ }^{\circ}\text{C}$), followed by Dess–Martin oxidation¹⁷ and Wittig methylenation, then afforded ($-$)-**17**, the substrate for the ring-closing metathesis. To our delight, treatment of a dilute solution of ($-$)-**17** (0.004 M, $\text{CH}_2\text{-Cl}_2$, $20\text{ }^{\circ}\text{C}$) with the Grubbs ruthenium catalyst⁷ (6 mol %) furnished the desired paracyclophane ($-$)-**18**¹⁴ in 88% yield. Interestingly, only the *E* isomer was observed (>95%). That ($-$)-**18** possessed the [7,7]-paracyclophane skeleton was established via X-ray crystallographic analysis. The solid-state conformation of ($-$)-**18** features a highly ordered [7,7]-paracyclophane ring system with the aromatic rings parallel and separated by $\sim 7.65\text{ \AA}$.¹⁸ Hydrogenation of ($-$)-**18** (Pd/C, EtOAc), followed by BBr_3 liberation¹⁹ of the phenolic hydroxyl groups, afforded ($-$)-cylindrocyclophane F (**1**), identical in all respects [500 MHz ^1H and 125 MHz ^{13}C NMR, HRMS, optical rotation, and R_f (TLC; three solvent systems)] to the natural material.²⁰

Scheme 5



In summary, the first total synthesis of ($-$)-cylindrocyclophane F has been achieved in 20 steps and 8.3% overall yield. Progress toward the synthesis of other members of this family of natural cyclophanes will be reported in due course.

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Supporting Information Available: Spectroscopic data for **1–18** and X-ray data for ($-$)-**18** as well as representative experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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