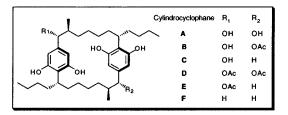
# Total Synthesis of (-)-Cylindrocyclophane F

## Amos B. Smith, III,\* Sergey A. Kozmin, and Daniel V. Paone

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

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The cylindrocyclophanes A-F, recently isolated by Moore and co-workers from Cylindrospermum licheniforme,<sup>1</sup> comprise a unique family of natural products possessing a 22-membered [7,7]-paracyclophane ring. Although a wide variety of cyclophanes have been prepared<sup>2,3</sup> since their initial synthesis by Cram and Steinberg in 1951,<sup>4</sup> the cylindrocyclophanes represent the first examples isolated from a natural source. Structural assignments, including complete relative and absolute stereochemistry, were based on extensive NMR studies<sup>1b</sup> in conjunction with CD spectroscopy and X-ray crystallography.<sup>1a</sup> In addition to their novel architecture, the cylindrocyclophanes display in vitro cytotoxicity against the KB and LoVo tumor cell lines.1a Captivated both by the structure and the promising biological profile, we initiated a program directed at their synthesis. Herein, we disclose the first total synthesis of (-)-cylindrocyclophane F (1).



From the outset we planned to take advantage of the  $C_2$  symmetry of the cylindrocyclophane skeleton (Scheme 1). Disconnection at the C(4–5) and C(17–18)  $\sigma$  linkages revealed resorcinol **4** as a possible common advanced intermediate for iodide **2** and tosyl hydrazone **3**. For cyclophane assembly we envisioned a two-step process,<sup>5</sup> involving union of **2** and **3** via reductive alkylation a la Myers,<sup>6</sup> followed by a ring-closing metathesis (RCM).<sup>7</sup> Resorcinol **4**, possessing the requisite stereogenic centers securely installed, would, in turn, be constructed from fragments **5** and **6** via a Danheiser benzannulation.<sup>8</sup>

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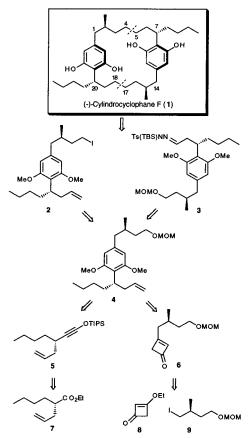
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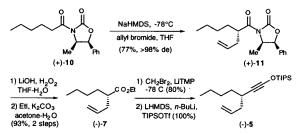
### Scheme 1



Application of two versions of the Kowalski ester chain homologation<sup>9,10</sup> (vide infra) would provide access to siloxy acetylene **5** and iodide **9**; the latter, in turn, would be coupled with known ethoxycyclobutenone  $8^{11}$  to furnish **6**.

Our point of departure entailed alkylation of (+)-10<sup>12</sup> (>98% de) with allyl bromide (Scheme 2),<sup>13</sup> followed by removal of the

### Scheme 2



chiral auxiliary and conversion to ester (-)-7<sup>14</sup> (72% yield, three steps). Best results for the initial Kowalski ester homologation<sup>9</sup>

(9) (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.

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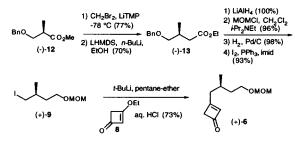
(12) Imide (+)-10 was prepared in 97% yield from (1*S*,2*R*)-(+)-norephedrine derived oxazolidinone and hexanoyl chloride (*n*-BuLi, THF, -78 °C).
(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. J. Am. Chem. Soc. 1982, 104, 1737.

(14) The structural assignment given to each new pure compound is in accord with its IR, <sup>1</sup>H, and <sup>13</sup>C NMR, and high-resolution mass spectra.

were obtained via a modified two-step sequence, in which the initial dibromoketone was isolated and then subjected to rearrangement at -78 °C. This protocol, leading to siloxy acetylene (-)-**5**<sup>14</sup> in 80% yield,<sup>15</sup> proved superior to the one-pot process.<sup>9a</sup>

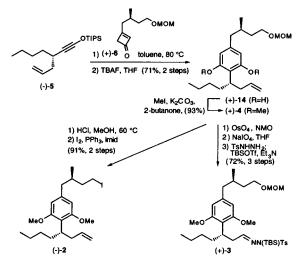
A second Kowalski homologation was employed for the preparation of cyclobutenone 6 (Scheme 3). In this case, ester (-)-12<sup>16</sup> was chain extended to (-)-13.<sup>14</sup> Conversion to iodide (+)-9 was then achieved by reduction of (-)-13, protection of the resulting alcohol (MOMCl, Hünig's base), hydrogenolysis of the benzyl ether, and iodination (I2, PPh3, imidazole). Generation of the organolithium reagent from iodide (+)-9 [t-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 benzannulation<sup>8</sup> (Scheme 4). Heating (-)-5 and (+)-6 at 80 °C for 2 h in toluene and then treating with TBAF afforded (+)-14<sup>14</sup> in 71% yield. Methylation (MeI, K<sub>2</sub>CO<sub>3</sub>, 2-butanone) then furnished (+)-4,<sup>14</sup> the common precursor for coupling partners (-)-2 and (+)-3.

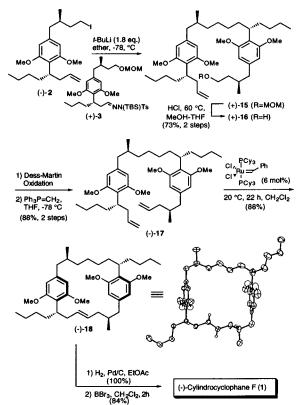
Scheme 4



To set the stage for paracyclophane assembly, removal of the MOM group from (+)-4 and iodination (I<sub>2</sub>, PPh<sub>3</sub>, imidazole) led to (-)-2;<sup>14</sup> alternatively, oxidative cleavage of the olefin (OsO<sub>4</sub>, NMO; NaIO<sub>4</sub>) afforded the corresponding aldehyde, which was converted to labile TBS-protected tosyl hydrazone (+)-3 (TsNHNH<sub>2</sub>, THF; TBSOTf, Et<sub>3</sub>N, THF)<sup>6</sup> in 72% yield for 3 steps.

Elaboration of the paracyclophane skeleton began with the Myers reductive coupling<sup>6</sup> of hydrazone (+)-3 employing the organolithium reagent generated from iodide (-)-2 (Scheme 5); coupled product (+)-15<sup>14</sup> was obtained in 73% yield. Removal of the MOM group (HCl, MeOH-THF, 60 °C), followed by Dess-Martin oxidation<sup>17</sup> 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, CH<sub>2</sub>-Cl<sub>2</sub>, 20 °C) with the Grubbs ruthenium catalyst<sup>7</sup> (6 mol %) furnished the desired paracyclophane  $(-)-18^{14}$  in 88% yield. Interestingly, only the  $\vec{E}$  isomer was observed (>95%). That (-)-18 possessed the [7,7]-paracyclophane skeleton was established via X-ray crystallographic analysis. The solid-state confomation of (-)-18 features a highly ordered [7,7]-paracyclophane ring system with the aromatic rings parallel and separated by  $\sim 7.65$ Å.<sup>18</sup> Hydrogenation of (-)-18 (Pd/C, EtOAc), followed by BBr<sub>3</sub> liberation<sup>19</sup> of the phenolic hydroxyl groups, afforded (-)cylindrocyclophane F (1), identical in all respects [500 MHz <sup>1</sup>H and 125 MHz <sup>13</sup>C NMR, HRMS, optical rotation, and  $R_f$  (TLC; three solvent systems)] to the natural material.<sup>20</sup>

#### 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.

Acknowledgment support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM 29028. This article is dedicated to Professor Virgil Boekelheide, colleague and friend, on the occasion of his 80th birthday.

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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<sup>(20)</sup> We thank Professor Moore (University of Hawaii) for a generous