Natural Product Synthesis

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Asymmetric Total Synthesis of Cylindrocyclophanes A and F through Cyclodimerization and a Ramberg–Bäcklund Reaction**

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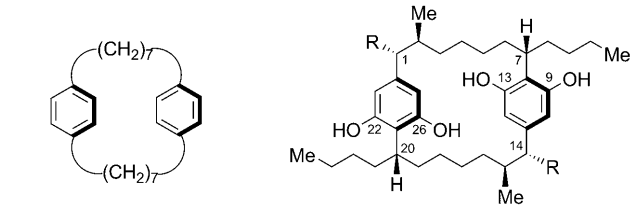
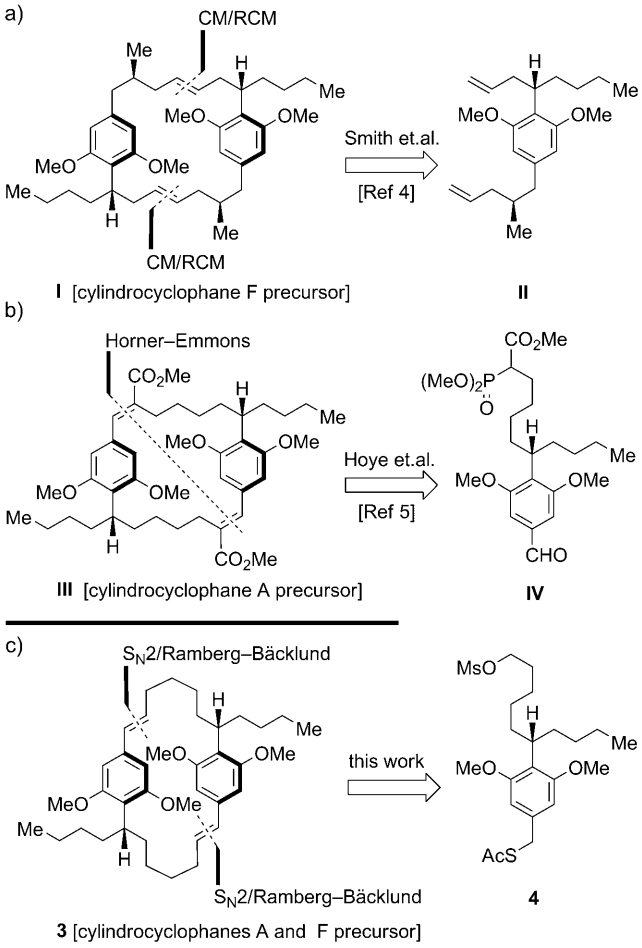
With their appealing architectures and unique chemical and physical properties, the bridged class of aromatic compounds known as cyclophanes (e.g. parent [7.7]paracyclophane, Scheme 1) have been inspiring chemists ever since their introduction by Cram and Steinberg almost 60 years ago.[1] To the designed cyclophanes[2] were later added naturally occurring compounds, beginning in 1990 when Moore et al. reported the isolation of cylindrocyclophane A (**1**, Scheme 1) and its siblings from a blue–green algae belonging to *Cylindrospermum licheniforme* Kützing (ATTC 29204).[3a] Two years later, the same research group isolated cylindrocyclophane F (**2**) from the same algae.[3b] These 22-membered [7.7]paracyclophanes exhibit potent cytotoxicity against the KB and LoVo tumor cell lines ($IC_{50} = 2$–$10\ \mu g\,mL^{-1}$).



Scheme 1. Structures of parent [7.7]paracyclophane and cylindrocylophanes A (**1**) and F (**2**).

The unique molecular architectures and important biological properties of the cylindrocyclophane natural products elicited considerable research activities directed toward their total synthesis,[4–6] with two total syntheses of such molecules, both employing head-to-tail cyclodimerizations.[4,5] The total synthesis of cylindrocyclophanes A (**1**) and F (**2**) by Smith et al.[4] involved an elegant cross metathesis/ring-closing metathesis (CM/RCM) dimerization to cast the molecule's [7.7]paracyclophane framework (see bis(olefin) **I** and its precursor **II**, Scheme 2a). The total synthesis of cylindrocyclophane A by Hoye et al.[5] exploited a dimerization based on a double Horner–Emmons reaction to construct a [7.7]paracyclophane intermediate from a suitable precursor (structures **III** and **IV**, Scheme 2b). Herein we describe our own head-to-tail dimerization approach to access this class of compounds based on the Ramberg–Bäcklund olefination reaction to generate [7.7]paracyclophane intermediate **3** from



Scheme 2. Cyclodimerization approaches to cylindrocyclophanes: a) Smith et. al.;[4] b) Hoye et. al.;[5] c) this work.

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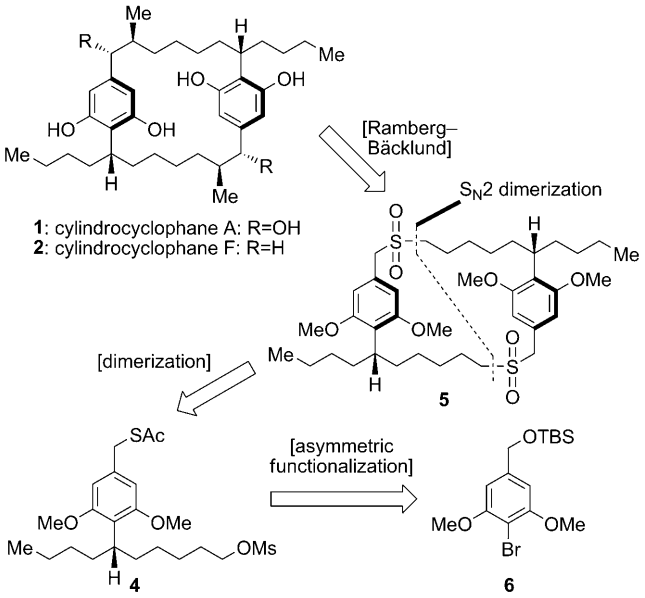
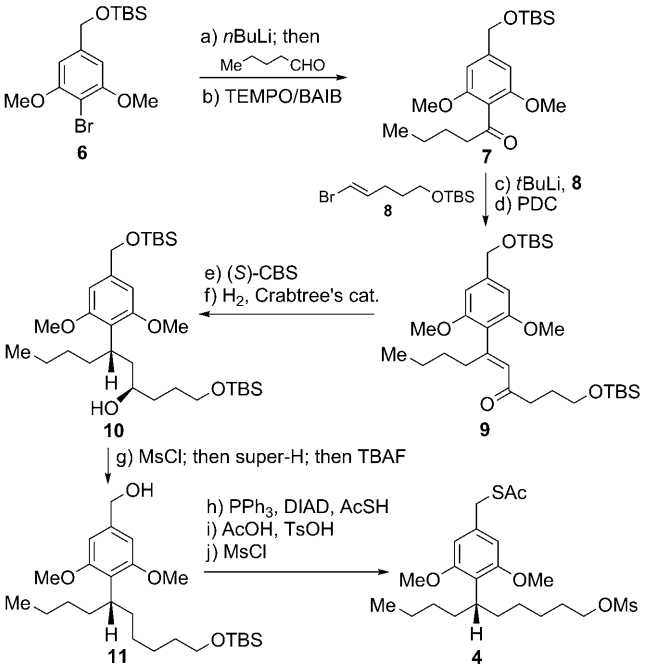
precursor **4** (Scheme 2c) that culminated in asymmetric total syntheses of cylindrocyclophanes A (**1**) and F (**2**).

From a strategic perspective, it would be most desirable to construct the C_2-symmetric cyclophane structural motif of these molecules through dimerization, preferably head-to-tail, of two identical fragments. To this end, our approach envisioned a Ramberg–Bäcklund reaction of sulfone **5** as shown retrosynthetically in Scheme 3. Disassembly of **5** led to bifunctional monomeric unit **4**, which was traced back to aryl bromide **6** through asymmetric functionalization.



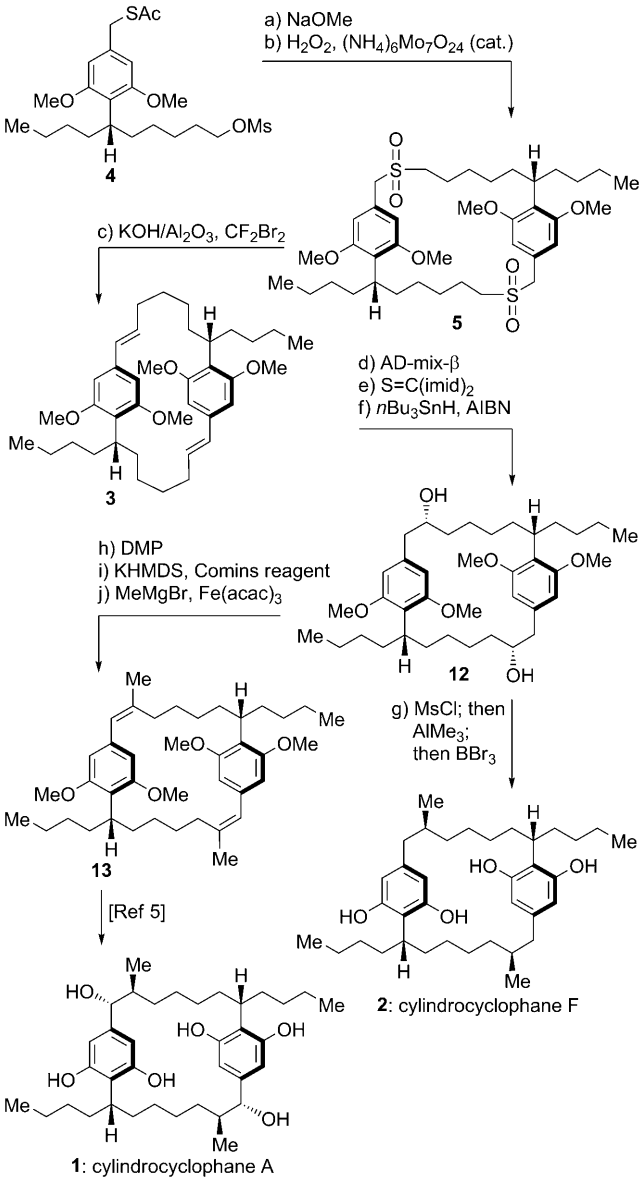
Scheme 3. Retrosynthetic analysis of cylindrocyclophanes A (**1**) and F (**2**). Ac = acetyl, TBS = *tert*-butyldimethylsilyl.

The enantioselective construction of the bifunctional precursor **4** commenced with bromide **6**[7] and proceeded as depicted in Scheme 4. Thus, addition of lithiated **6** (*n*BuLi) to pentanal and subsequent oxidation of the resulting alcohol with TEMPO/BAIB furnished benzylic ketone **7** in 76% overall yield. Reaction of the latter compound with the vinyl lithium derived from **8** (*t*BuLi) and subsequent PDC-mediated oxidative allylic transposition of the resulting allylic alcohol gave vinyl ketone **9** (64% yield over two steps).[8] Enantioselective reduction of **9** with (*S*)-CBS furnished the expected chiral allylic alcohol (95% *ee*), which underwent hydroxy-directed hydrogenation (CH_2Cl_2, 50 atm of H_2) in the presence of Crabtree's catalyst (9 mol%)[9] to afford alcohol **10** in 65% yield and 93% *ee* (d.r. > 20:1). Deoxygenation of the latter intermediate was achieved through its mesylate, which reacted with superhydride (super-H = $LiBEt_3H$) to generate, after desilylation (TBAF), benzylic alcohol **11** in 73% overall yield. Mitsunobu reaction of **11** with AcSH (Ph_3P, DIAD) and subsequent desilylation (TsOH, AcOH, H_2O) and mesylation (MsCl, Et_3N) led to the desired thioacetate mesylate **4** in 76% overall yield.



Scheme 4. Enantioselective construction of bifunctional monomeric unit **4**. Reagents and conditions: a) *n*BuLi (1.3 equiv), THF, −78→−30°C, 0.5 h, pentanal (2.0 equiv), 0°C, 1 h; b) TEMPO (0.15 equiv), BAIB (1.2 equiv), CH_2Cl_2, 23°C, 12 h, 76% over two steps; c) vinyl bromide **8** (2.0 equiv), *t*BuLi (4.1 equiv), Et_2O, −78→23°C, 0.5 h, ketone **7**, −78→0°C, 0.5 h; d) PDC (3.0 equiv), M.S. (4 Å), CH_2Cl_2, 23°C, 3 h, 48% (64% brsm) over two steps; e) (*S*)-CBS (0.3 equiv), catecholborane (2.0 equiv), toluene, −78→0°C, 12 h; f) Crabtree's catalyst (9 mol%), H_2 (50 atm), CH_2Cl_2, 23°C, 4 h, 65% yield over two steps, 93% *ee*, d.r. > 20:1; g) MsCl (1.1 equiv), Et_3N (1.2 equiv), THF, 0°C, 0.5 h; then super-H (4.0 equiv), THF, 80°C, 4 h; then TBAF (3.0 equiv), THF, 0°C, 1 h, 73%; h) PPh_3 (1.8 equiv), DIAD (1.8 equiv), THF, 0°C, 20 min; then AcSH (1.7 equiv) and alcohol **11**, 0°C, 1 h; i) TsOH (0.2 equiv), AcOH/H_2O (7:1), 23°C, 1 h; j) MsCl (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0°C, 0.5 h, 76% over three steps. BAIB = bis(acetoxyiodo)benzene, brsm = based upon recovered starting material, CBS = Corey–Bakshi–Shibata catalyst, DIAD = diisopropyl azodicarboxylate, Ms = mesyl, M.S. = molecular sieves, PDC = pyridinium dichromate, TBAF = tetrabutylammonium fluoride, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, THF = tetrahydrofuran, super-H = $LiBEt_3H$, Ts = *para*-toluenesulfunyl.

With the monomeric precursor **4** in hand, its dimerization to [7.7]paracyclophane **3** and further functionalization to the targeted cylindrocylophanes became possible, and indeed was realized as demonstrated in Scheme 5. The much anticipated cyclodimerization of **4** was brought about by treatment with NaOMe in MeOH at ambient temperature and afforded the corresponding macrocyclic bis(thioether), whose oxidation with H_2O_2 in the presence of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ furnished macrocyclic bis(sulfone) **5** in 51% overall yield. Treatment of sulfone **5** with alumina-impregnated KOH (KOH/Al_2O_3) in the presence of CF_2Br_2 in CH_2Cl_2/*t*BuOH (1:1) at 0→23°C led to the expected bis(olefin) **3** in 70% yield (ca. *EE*/*EZ* = 12:1 before complete isomerization to *EE*-**3** with [Pd-$(CH_3CN)_2Cl_2$]).[10] Dihydroxylation of the latter compound with AD-mix-β ($MeSO_2NH_2$, *t*BuOH/H_2O (2:1), ambient temparature)[11] efficiently generated the corresponding



Scheme 5. Construction of [7.7]paracyclophane **3** and its conversion into cylindrocylophanes A (**1**) and F (**2**). Reagents and conditions: a) NaOMe (5.0 equiv), MeOH, 23 °C, 36 h; b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.3 equiv), H_2O_2 (aq, 35% w/w, 10.0 equiv), EtOH, 23 °C, 12 h, 51% over two steps; c) CF_2Br_2 (5.0 equiv), KOH/Al_2O_3 (15% w/w, 2 g per mmol), CH_2Cl_2/*t*BuOH (1:1), 0→23 °C, 2 h; then $[Pd(CH_3CN)_2Cl_2]$ (0.3 equiv), 40 °C, 4 h, 70%; d) AD-mix-β, $MeSO_2NH_2$ (1.0 equiv), *t*BuOH/H_2O (2:1), 23 °C, 12 h; e) 1,1′-thiocarbonyldiimidazole (10.0 equiv), toluene, 125 °C, 5 h; f) AIBN (2.0 equiv), nBu$_3$SnH (10.0 equiv), toluene, 100 °C, 1.5 h, 50% over three steps; g) MsCl (5.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; then $AlMe_3$ (5.0 equiv), 0 °C, 10 min; then BBr_3 (10.0 equiv), 23 °C, 5 h, 71% one pot; h) DMP (5.0 equiv), $NaHCO_3$ (10.0 equiv), CH_2Cl_2, 23 °C, 1 h; i) KHMDS (6.0 equiv), Comins reagent (6.0 equiv), THF, −78 °C, 1 h; j) Fe(acac)$_3$ (0.3 equiv), MeMgBr (10.0 equiv), THF/NMP (20:1), 0 °C, 1 h, 74% over three steps; for **13**→**1** see Ref. [5]. acac = acetylacetonate, AIBN = 2,2′-azobis(2-methylpropionitrile), DMP = Dess–Martin periodinane, imid = imidazole, HMDS = hexamethyldisilazide.

tetraol, which was selectively deoxygenated to diol **12** under Barton conditions (nBu$_3$SnH, AIBN)[12] of its bis(thionocarbonate) (prepared by exposure to 1,1′-thiocarbonyldiimidazole), and led to dihydroxy compound **12** (50% yield over three steps). Methylation of **12** (MsCl; then $AlMe_3$),[13] and subsequent removal of the methyl groups to reveal phenolic groups (BBr_3), all in one pot, secured cylindrocyclophane F (**2**) in 71% overall yield. Oxidation of common intermediate **12** (DMP), followed by enol triflate formation (KHMDS, Comins reagent) and subsequent Kumada-type coupling with MeMgBr in the presence of $[Fe(acac)_3]$,[14] led to bis(olefin) **13** (74% yield over three steps, single geometrical isomer). The latter compound served as a precursor in Hoye's total synthesis of cylindrocyclophane A (hydroboration/deprotection).[5] The physical properties of synthetic **2** and **13** were in accord with those previously reported in the literature.[3b,5]

The chemistry described here constitutes a short and efficient total synthesis of cylindrocyclophane F (**2**) and a formal total synthesis of cylindrocyclophane A (**1**) in their naturally occurring enantiomeric forms. The asymmetry was introduced through a CBS reduction of an enone and subsequent hydroxy-directed hydrogenation employing the Crabtree catalyst and deoxygenation. The crucial macrocyclodimerization was achieved through the use of a Ramberg–Bäcklund reaction, whose application to the synthesis of complex molecules is on the rise.[15]

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