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Asymmetric Total Synthesis of Cyliindrocyclophanes A and F Through Cyclodimerization and Ramberg–Bäcklund Reaction

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Abstract

A Ramberg–Bäcklund reaction was employed to form the macrocyclic carbon skeleton of the marine natural products cylindrocyclophanes A and F in an asymmetric synthesis of these target molecules.

Keywords

paracyclophanes; Ramberg–Bäcklund reaction; total synthesis

Due to their appealing architectures and unique chemical and physical properties, the bridged class of aromatic compounds known as cyclophanes (e.g. parent [7.7]-paracyclophane, Figure 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, beginning in 1990 when Moore and co-workers reported the isolation of cylindrocyclophane A (**1**, Figure 1) and its siblings from a blue-green algae belonging to *Cylindrospermum licheniforme* Kützinger (ATTC 29204).[3a] Two years later, the same 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 (IC₅₀ = 2–10 µg/mL).

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, already reported.[4,5] The total synthesis of cylindrocyclophanes A (**1**) and F (**2**) by the Smith group[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**, Figure 2a), while the total synthesis of cylindrocyclophane A by the Hoye group[5] exploited a double Horner–Emmons based dimerization to construct a [7.7]-paracyclophane intermediate from a suitable precursor (see structures **III** and **IV**, Figure 2b). Herein we describe our own head-to-tail dimerization

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approach to this class of compounds based on the Ramberg–Bäcklund olefination reaction to generate [7.7]-paracyclophane intermediate **3** from precursor **4** (see Figure 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 Figure 3. Disassembly of **5** led to bifunctional monomeric unit **4**, which was traced back to aryl bromide **6** through asymmetric functionalization.

The enantioselective construction of the bifunctional precursor **4** commenced with bromide **6**[7] and proceeded as depicted in Scheme 1. 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), followed by PDC-mediated oxidative allylic transposition of the resulting allylic alcohol, gave vinyl ketone **9** (64% over the 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* (*dr*>20:1). Deoxygenation of the latter intermediate was achieved through its mesylate which reacted with Super-H to generate, after desilylation (TBAF), benzylic alcohol **11** in 73% overall yield. Mitsunobu reaction of **11** with AcSH (Ph_3P , DIAD) followed by desilylation (*p*TsOH, AcOH, H_2O) and mesylation (MsCl , Et_3N) led to the desired thioacetate mesylate **4** in 76% overall yield.

With the monomeric precursor **4** in hand, its dimerization to a [7.7]-paracyclophane **3** and further functionalization to the targeted cylindrocyclophanes became possible, and indeed was realized as demonstrated in Scheme 2. The much anticipated cyclodimerization of **4** was brought about by treatment with NaOMe in MeOH at ambient temperature to afford the corresponding macrocyclic bithioether, whose oxidation with H_2O_2 in the presence of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$ furnished macrocyclic bis-sulfone **5** in 51% overall yield. Treatment of sulfone **5** with alumina-impregnated KOH ($\text{KOH}/\text{Al}_2\text{O}_3$) in the presence of CF_2Br_2 in $\text{CH}_2\text{Cl}_2/t\text{BuOH}$ (1:1) at $0 \rightarrow 23^\circ\text{C}$ led to the expected bis-olefin **3** in 70% yield (ca. 12:1 *EE/EZ* before complete isomerisation to *EE*-**3** with $\text{Pd}[\text{CH}_3\text{CN}]_2\text{Cl}_2$).[10] Dihydroxylation of the latter compound with AD-mix β (MeSO_2NH_2 , $t\text{BuOH}:\text{H}_2\text{O}$, ambient temperature)[11] efficiently generated the corresponding tetraol, which was selectively deoxygenated to diol **12** under Barton conditions (*n* Bu_3SnH , AIBN)[12] of its bis-thionocarbonate (prepared by exposure to 1,1'-thiocarbonyldiimidazole), leading to dihydroxy compound **12** (50% overall yield for the three steps). Methylation of **12** (MsCl ; then AlMe_3),[13] followed by deprotection of the 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 $[\text{Fe}(\text{acac})_3]$,[14] led to bis-olefin **13** (74% yield, single geometrical isomer). The latter compound served as a precursor in Hoyer'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 described chemistry 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 followed by a hydroxyl-directed hydrogenation employing the Crabtree catalyst and deoxygenation. The crucial macrocyclodimerization was achieved

through the use of the Ramberg–Bäcklund reaction, whose application to the synthesis of complex molecules is on the rise.[15]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of parent [7.7]-paracyclophane and cylindrocyclophanes A (1) and F (2).

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

Figure 3.
Retrosynthetic analysis of cylindrocyclophanes A (1) and F (2).

Scheme 1.

Enantioselective construction of bifunctional monomeric unit **4**. Reagents and conditions: a) $n\text{BuLi}$ (1.3 equiv), THF, $-78 \rightarrow -30$ °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% for the two steps; c) vinyl bromide **8** (2.0 equiv), $t\text{BuLi}$ (4.1 equiv), Et_2O , $-78 \rightarrow 23$ °C, 0.5 h, ketone **7**, $-78 \rightarrow 0$ °C, 0.5 h; d) PDC (3.0 equiv), 4 Å MS, CH_2Cl_2 , 23 °C, 3 h, 48% (64% brsm) over the two steps; e) (*S*)-CBS (0.3 equiv), catecholborane (2.0 equiv), toluene, $-78 \rightarrow 0$ °C, 12 h; f) Crabtree's catalyst (9 mol %), H_2 (50 atm), CH_2Cl_2 , 23 °C, 4 h, 65% yield over the two steps, 93% *ee*, *dr* > 20:1; g) MsCl (1.1 equiv), Et_3N (1.2 equiv), THF, 0 °C, 0.5 h; then LiBEt_3H (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) *p*TsOH (0.2 equiv), AcOH:H₂O (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% for the three steps. TBS = *tert*-butyldimethylsilyl, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, BAIB = bis(acetoxyiodo)benzene, CBS = Corey–Bakshi–Shibata reagent, Ms = mesyl, Super-H = LiBEt_3H , TBAF = tetrabutylammonium fluoride, DIAD = diisopropyl azodicarboxylate, Ac = acetyl, *p*Ts = *para*-toluenesulfonyl, THF = tetrahydrofuran

Scheme 2.

Construction of [7.7]-paracyclophane **3** and its conversion to cylindrocyclophanes A (**1**) and F (**2**). Reagents and conditions: a) NaOMe (5.0 equiv), MeOH, 23 °C, 36 h; b) $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ (0.3 equiv), H_2O_2 (aq., 35% w/w, 10.0 equiv), EtOH, 23 °C, 12 h, 51% over the two steps; c) CF_2Br_2 (5.0 equiv), $\text{KOH}/\text{Al}_2\text{O}_3$ (15% w/w, 2 g per mmol), $\text{CH}_2\text{Cl}_2/t\text{BuOH}$ (1:1), 0→23 °C, 2 h; then $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (0.3 equiv), 40 °C, 4 h, 70%; d) AD-mix- β , MeSO_2NH_2 (1.0 equiv), $t\text{BuOH}/\text{H}_2\text{O}$ (2:1), 23 °C, 12 h; e) 1,1'-thiocarbonyldiimidazole (10.0 equiv), toluene, 125 °C, 5 h; f) AIBN (2.0 equiv), $n\text{Bu}_3\text{SnH}$ (10.0 equiv), toluene, 100 °C, 1.5 h, 50% for the 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) $\text{Fe}(\text{acac})_3$ (0.3 equiv), MeMgBr (10.0 equiv), THF/NMP(20:1), 0 °C, 1 h, 74% for the three steps; for **13**→**1** see ref [5]. imid = imidazole, AIBN = 2,2'-azobis(2-methylpropionitrile), DMP = Dess–Martin periodinane, KHMDS = potassium hexamethyldisilazide, acac = acetylacetonate.