Transition Metal Catalyzed Cycloadditions: An Intramolecular [4 + 4] Cycloaddition Strategy for the Efficient Synthesis of Dicyclopenta[*a,d*]cyclooctene 5−8−5 Ring Systems

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The dicyclopenta[a,d]cyclooctene 5−8−5 ring system is the structural core of numerous diterpenes such as the fusicoccins[1] and sesterterpenes such as the ophiobolins (e.g., **1**, Scheme 1)[2] and ceroplastins (e.g., **2**).[3] The wide range of biological and phytological activities[4] exhibited by these compounds coupled with the paucity of information on their mode of action and the novelty of their structures have stimulated the development of several creative approaches to their core ring system,[5] including total syntheses reported by the groups of Kato and Takeshita,[6] Kishi,[7] Boeckman,[8] and Paquette.[9] In addressing the central eight-membered ring, these approaches collectively illustrate the utility of three of the four fundamental concepts for ring construction (acyclic closure, ring expansion or contraction, and polycycle fragmentation). We describe herein an example of the fourth fundamental approach to the 5−8−5 ring system in which the eight-membered ring[10] is formed through a direct cycloaddition reaction.

We previously introduced a versatile strategy for accessing eight-membered carbocycles based on an intramolecular Ni(0)-catalyzed [4 + 4] cycloaddition of bis-dienes.[11] In theory, this method could be applied in two ways to the 5−8−5 problem (Figure 1), differing principally by whether the third ring is introduced before or after the [4 + 4] cycloaddition. While the former strategy (route A) has thus far been difficult to reduce to practice,[12] the latter (route B), as described below, has now been developed into a concise and flexible synthetic route to 5−8−5 ring systems.

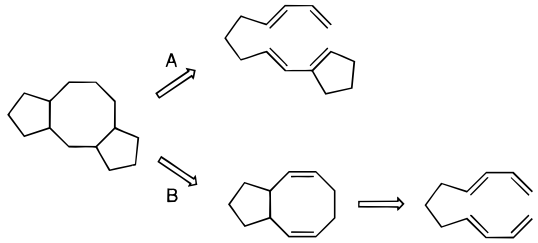
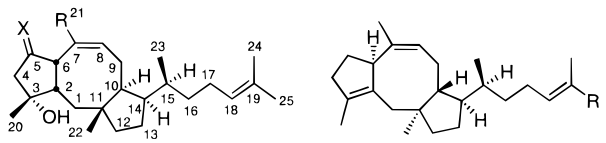


Figure 1.

Scheme 1



1a X= O; R=CHO Ophiobolin C
1b X=H,H; R=Me Ophiobolin F

2a R=CO_2H Albolic acid
2b R=CH_2OH Ceroplastol II

Our preparation of the bis-diene (**4**) required for the investigation of this cycloaddition strategy (route B) started with commercially available cyclopropyl methyl ketone, which was converted in three steps and in 50% yield to the dienyl aldehyde **3** (3:1 = *E*:*Z*) following literature procedures[13] (Scheme 2). Conversion of **3** to bis-diene **4**[14] was then accomplished on a multigram scale by lithium vinylacetylide addition to the carbonyl group (99%), E-selective reduction of the resultant alkyne with Red-Al (91%),[15] and alcohol silylation (99%). This vinylacetylide addition and alkyne reduction sequence has been found to serve as a general, practical, and efficient (ca. 90% overall) method for the nucleophilic introduction of terminal dienes into our cycloaddition precursors.

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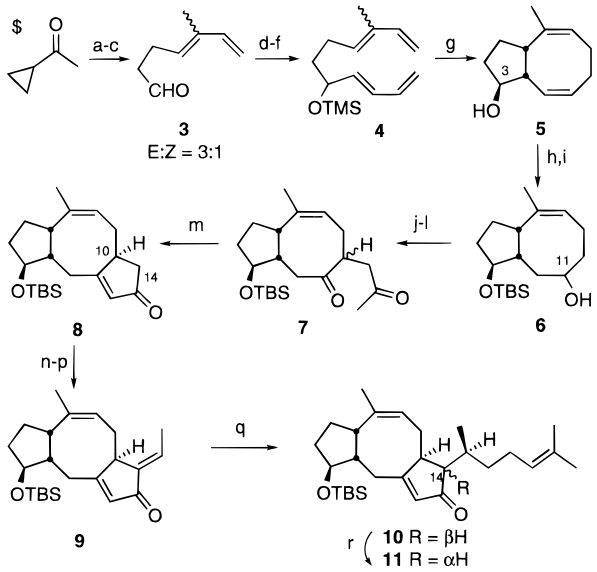
Scheme 2[a]



[a] Key: (a) $H_2C{=}CHMgBr$ then HBr, −10 °C (70%); (b) NaCN, 60 °C (98%); (c) DIBAL-H (72%); (d) $LiC{\equiv}CCH{=}CH_2$, −78 °C (99%); (e)Red-Al (91%); (f) TMS-Imid (99%); (g) $Ni(COD)_2$, 10 mol %, PPh_3, 20 mol %, 60 °C then nBu_4NF (60%); (h) TBSCl, imidazole (99%); (i) 9-BBN, 60 °C then H_2O_2, NaOH (86%); (j) PCC (92%); (k) KHMDS, −78 °C, BEt_3 then $CH_2{=}CHCH_2I$; (l) $PdCl_2$, H_2O, CuCl, O_2 (88% for two steps); (m) 1 N KOH/ethanol (85%); (n) KHMDS, LiBr, −78 °C then CH_3CHO (86%); (o) MsCl, DMAP; (p) Et_3N, DMAP, 40 °C (68% for two steps); (q) $(CH_3)_2C{=}CHCH_2CH_2$-MgBr, CuBr·DMS, −78 to 0 °C then acetic acid, −78 °C (97%); (r) LDA, acetic acid, −78 °C (45%).

The key cycloaddition was accomplished by treatment of bis-diene **4** with 10 mol % $Ni(COD)_2$ and 20 mol % triphenylphosphine in toluene at 60 °C, giving after desilylation the cycloadduct **5** in 60% yield along with its C3 epimer (8%).[16] The *cis* ring fusion and exo orientation of the silyloxy group of **5** are consistent with previously reported mechanistic models and were confirmed by X-ray analysis of a derivative (*vide infra*) and independent preparation from **4** by photosensitized intramolecular [2 + 2] cycloaddition followed by Cope rearrangement of the [2 + 2] cycloadduct.[12]

The further development of this route to 5−8−5 rings systems required at this point the chemo- and regioselective transformation of the Δ-1,11 alkene of **5** into a functional group suitable for annelative introduction of the remaining five-membered ring. For this purpose, **5** was first silylated (99%) and the product treated with 9-BBN (1.5 equiv, slow addition)[17] to give, after heating and standard basic peroxide workup, alcohol **6** as a single diastereomer in 86% yield. This alcohol was then oxidized with PCC (92%), and the resulting ketone was treated with KHMDS, triethylborane, and allyl iodide[18] to provide after Wacker oxidation[19] diketones **7** in 88% yield (two steps) as an inconsequential mixture (7:1) of epimers. Treatment of this mixture with a 1 N solution of KOH in ethanol[20] gave in 85% yield tricycle **8**, which incorporates the core 5−8−5 ring system of the natural products noted above.

As a consequence of its differential functionalization, tricycle **8** represents a potentially general precursor to a number of naturally occurring 5−8−5 ring systems and their analogs. Differing principally by the side chain at C14, several of these targets could potentially be accessed from **8** through the use of an alkylidination, conjugate addition, and protonation sequence.[21] Illustrative of this strategy, tricycle **8** was regioselectively deprotonated with KHMDS and quenched with acetaldehyde (86%) to provide after mesylation and elimination (Et_3N/ DMAP) the cross-conjugate enone **9** (68%) along with its Z-isomer (15%). Copper-catalyzed conjugate addition of the Grignard reagent derived from 5-bromo-2-methyl-2-pentene to enone **9** followed by kinetically controlled quenching with acetic acid provided in 97% yield the C14 epimers **10** and **11** (1:1). The effective yield of either epimer can be enhanced as needed through base treatment of the undesired isomer and separation of the resultant epimers. The structure of **10** (and by chemical correlation its C14 epimer **11**) was confirmed by X-ray crystallography.[22] Tricycle **11** is thus seen to possess 5 of the 7 stereogenic centers of ophiobolin F. Access to other stereoisomers should be possible through variations on this sequence.

In summary, this study provides a fundamentally new approach to the 5−8−5 ring system of several di- and sesterterpene families. In this approach, two of the three rings are assembled from commercially available starting materials in seven steps and in 27% overall yield, based on a Ni(0)-catalyzed [4 + 4] cycloaddition. The third ring is attached with stereocontrol through a five-step annelation sequence proceeding in 59% overall yield. Introduction and control of side-chain stereochemistry is achieved through an alkylidination−conjugate addition sequence. Further studies on the development and application of this new strategy are in progress.

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Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds (6 pages).

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