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Synthetic Progress toward Azadirachtins. 1. Enantio- and Diastereoselective Synthesis of the Left-Wing Fragment of 11-*epi*-Azadirachtin I

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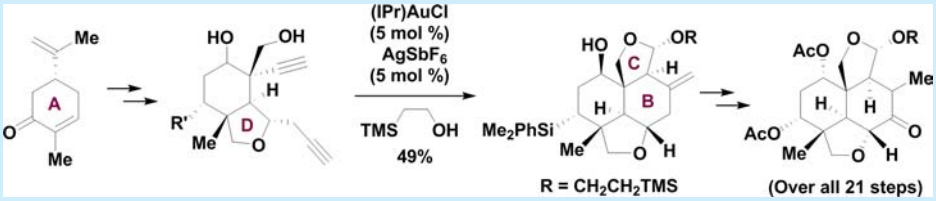
Supporting Information



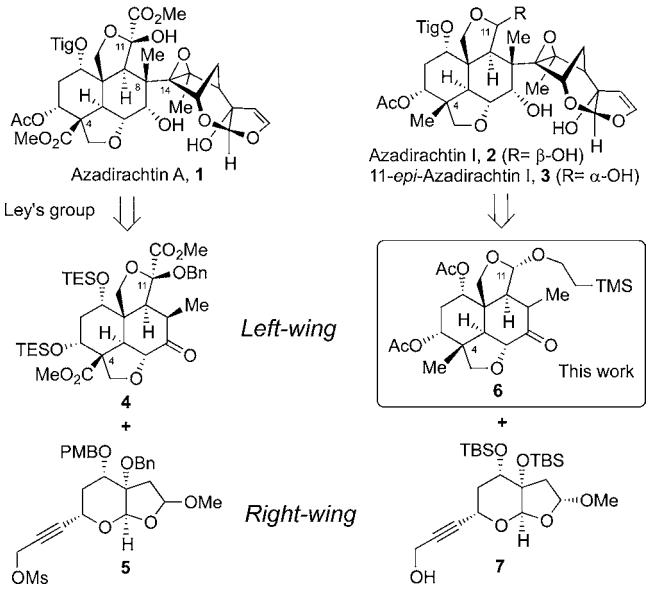
ABSTRACT: A highly enantio- and diastereoselective synthesis of the left-wing fragment of 11-*epi*-azadirachtin I characterized with the pairwise use of palladium- and gold-catalyzed cascade reactions is presented. By enlisting a sequence of stereocontrolled transformations, our 21-step route established the stereocenters of the left-wing fragment from one chiral starting material, (−)-carvone, which would significantly facilitate the synthetic studies of the azadirachtin-type limonoids.

Azadirachtin A (**1**, Scheme 1) is a highly oxygenated tetranortriterpenoid isolated from the neem tree *Azadirachta indica A.* Juss (Meliaceae).[1] Azadirachtin A is a powerful insect repellent with low mammalian toxicity; however, there is limited structure−activity relationship information, and it has an elusive mechanism of action.[2] Various azadirachtin congeners possess remarkable antifeedant activity; for example, azadirachtin I (**2**) acts against *Spodoptera litura* with potency similar to that of azadirachtin A.[3] The anti-insect properties of these azadirachtin-type limonoids are less well studied, partially due to limited availability.[4]

Azadirachtin A possesses a number of intriguing structural elements, such as a highly oxygenated scaffold, 16 contiguous chiral centers including seven quaternary ones, and a crowded C8−C14 bond. These fascinating and highly complex structural features have challenged as well as inspired synthetic chemists for decades,[5] culminating in the "relay total synthesis" of azadirachtin A by Ley et al.[6] One key to Ley's success is the strategic disconnection of the C8−C14 bond, leading to the left- and right-wing (**4** and **5**) fragments (Scheme 1).[7]

Inspired and motivated by the aforementioned studies, we aimed to establish a practical approach to access the azadirachtin family of natural products as well as a wide variety of analogues to probe their chemical biology. On the basis of our hypothesis that azadirachtin I (**2**) interconverts with its C11 diastereomer, 11-*epi*-azadirachtin I (**3**),[8] through the

Scheme 1. Structure Disconnection



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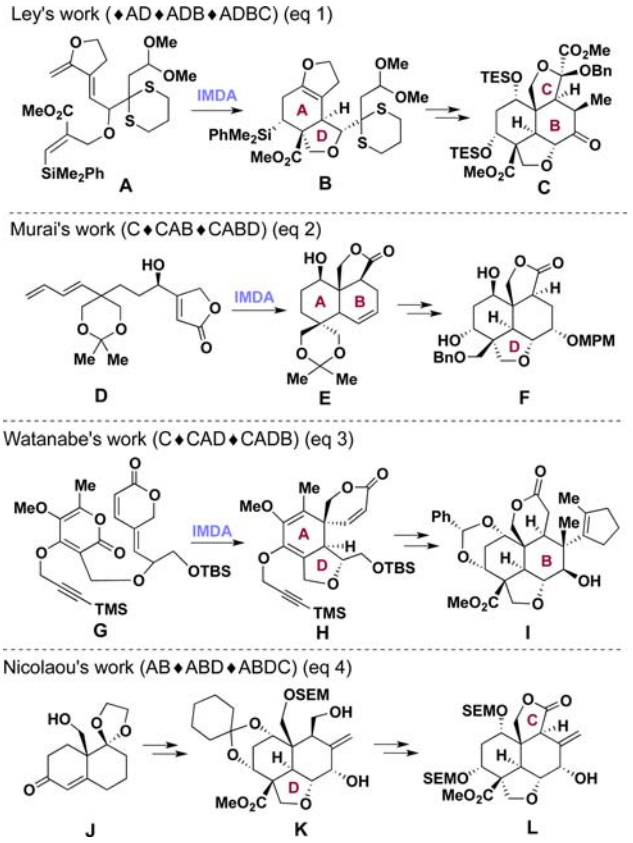
epimerization of the hemiacetal, the first stage for their total synthesis would be the preparation of one left-wing fragment, tetracycle **6**, in enantiopure form.

The major differences between **6** and Ley's left-wing fragment **4** are the substituents at C4 and C11. Herein, we report the enantioselective synthesis of *trans*-decalin **6**, which contains nine contiguous stereocenters. The majority of the previously published synthetic approaches to the functionalized ABCD ring frameworks were based on the Diels–Alder reaction, which served as a key step (typical examples, eqs 1–3, Scheme 2).[9] Nicolaou developed a stepwise ring

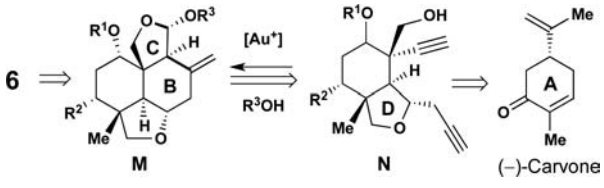
Scheme 2. Selected Examples of the Synthetic Study toward the Left Wing of Azadirachtin



cyclization strategy to access the left fragment **L** from ketone **J**.[5h,i] To our knowledge, there is no report of one-step BC rings formation in the synthetic study toward azadirachtin.

Given widely functional group tolerance and high efficiency in multiple bond formations, gold-catalyzed tandem cyclizations enabled preparation of densely functionalized natural products is interest in our laboratory.[10] We envisioned that the fully functionalized *trans*-decalin **6** could be derived from precursor **M** through suitable elaboration (Scheme 3). The tetracycle **M**

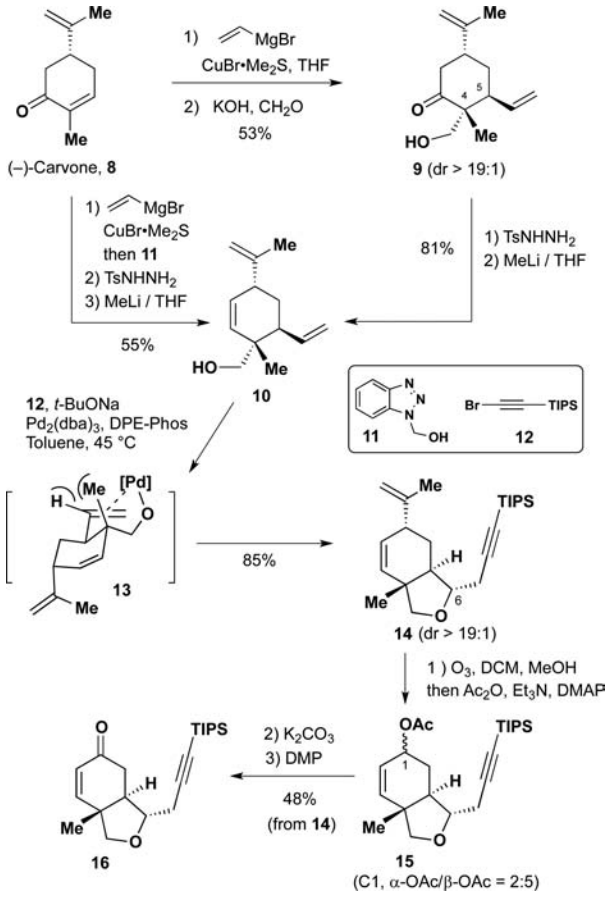
Scheme 3. Retrosynthetic Analysis



was reasoned to arise by our recently developed gold-catalyzed tandem reaction[10a] of 1,7-diyne **N**, which in turn could be made from the commercially available (−)-carvone. If developed, we would provide the first concise access to the densely functionalized left-wing fragment starting from the A ring (A → AD → ADCB).

The stereogenic center at C5 was secured by the diastereoselective copper(I)-catalyzed 1,4-addition of vinyl Grignard reagent to the enone functionality of (−)-carvone (**8**) (Scheme 4). The resulting cyclohexanone condensed with

Scheme 4. Preparation of Enantiopure Enone 16



formaldehyde in the presence of KOH to afford **9** as a single diastereomer in 53% isolated yield over two steps.[11] Subsequently, **9** was converted to the *p*-toluenesulfonyl hydrazone derivative, which then underwent the Shapiro reaction to provide highly substituted cyclohexene **10** in 81% yield over two steps.

Alternatively, the enolate formed from the 1,4-addition of **8** could be trapped in situ by formaldehyde generated from reagent **11**.[12] This afforded **9** in one pot as a pair of inseparable diastereomers (C4, α-Me/β-Me = 3:10). Subsequently, **10** was isolated as a single diastereomer by following the previously adopted procedure. This route gave rise to **10** in 55% yield over three steps. Importantly, both routes to enantiopure **10** proceeded smoothly on a multigram scale, setting the stage for the palladium-catalyzed oxyalkynylation.[13] Gratifyingly, [6,5]-bicycle **14** was synthesized from **10** in 85% yield under optimized reaction conditions. This cascade transformation was highly chemo- and regioselective and also highly diastereoselective at the new stereogenic center (C6). This could be

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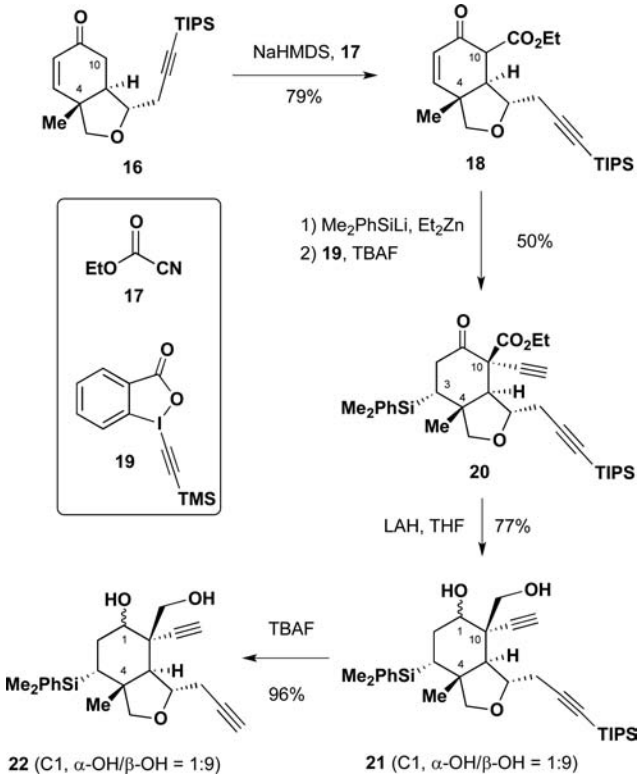
attributed to the minimized *syn*-pentane interaction between the methyl and vinyl group in the transition state **13**. Ozonolysis, followed by acetylation and the Criegee rearrangement,[14] converted the propenyl group in **14** into an acetate, giving **15** as a pair of inseparable diastereomers (dr = 2:5).[15] The epimerization of C1 could be rationalized by involving the allyl cation intermediate during the Criegee rearrangement. Hydrolysis of acetate **15** followed by oxidation yielded **16** as a single diastereomer. This three-step sequence converted **14** to **16** on a gram scale in 48% overall yield.

We next worked on the synthesis of the key intermediate 1,7-diyne **22** (Scheme 5). To this end, the C10 in **16** was first

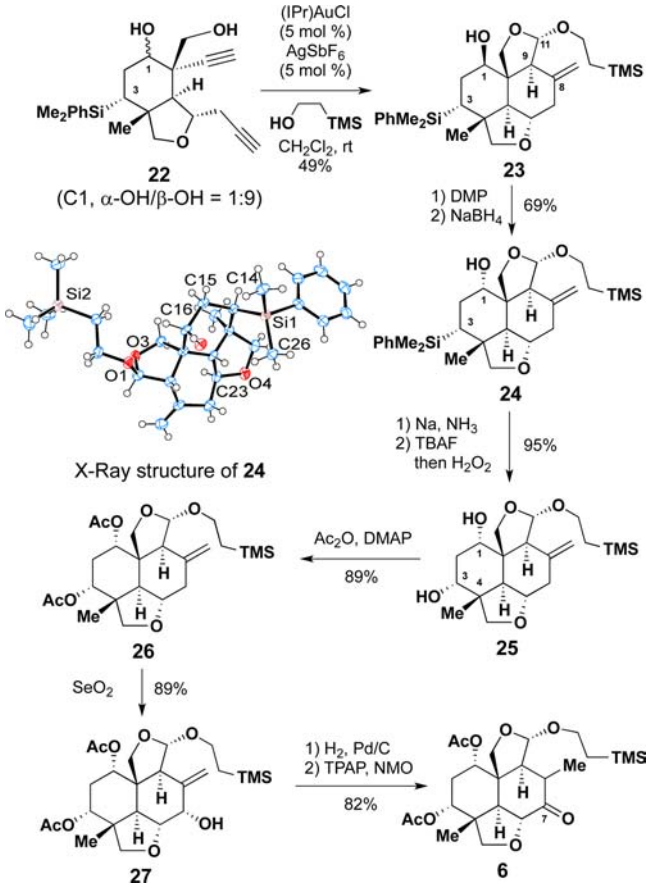
Scheme 5. Synthesis of 1,7-Diyne 22



acetylated using Mander's reagent **17** in the presence of NaHDMS to give **18**. Serving as a masked form of the hydroxyl group, the phenyldimethylsilyl group was then attached at C3 by stereoselective 1,4-addition using the reagents $PhMe_2SiLi$/Et_2Zn.[17] Further treatment of the resultant β-keto ester with iodonium reagent **19** afforded **20** as a single diastereoisomer in 50% yield over two steps.[18] Both the phenyldimethylsilyl and alkyne groups were introduced in a diastereoselective manner, presumably due to the influence of the axial methyl group at C4. To complete the synthesis of diyne **22**, β-keto ester **20** was first reduced with $LiAlH_4$, and the resultant diol **21** as a pair of inseparable diastereomers (C1, α-OH/β-OH = 9:1) was treated with TBAF to remove its TIPS group to afford 1,7-diyne **22** in 74% yield over two steps.

The stage was set for the gold-catalyzed cascade reaction (Scheme 6). Under the optimized reaction conditions,[10a] treatment of **22** with (IPr)AuCl (5 mol %) and $AgSbF_6$ (5 mol %) in dichloromethane (CH_2Cl_2) at room temperature in the presence of 2-(trimethylsilyl)ethanol as the nucleophile gave the fully functionalized *trans*-decalin **23** as a single stereoisomer in 49% yield by forming two rings with two chiral

Scheme 6. Synthesis of Left-Wing Fragment 6



centers at C9 and C11. To reverse its stereochemistry of the hydroxyl group at C1, substrate **23** was then oxidized with Dess–Martin periodinane (DMP) followed by reduction with $NaBH_4$ to give alcohol **24**. The structure of **24** was confirmed by single-crystal X-ray analysis.[16]

To convert the C3 silyl group in **24** into its corresponding hydroxyl group in **25**, substrate **24** was first subjected to a Birch reduction, followed by treatment with TBAF/H_2O_2 to give diol **25** in excellent yield over two steps.[19] Diol **25** was then acetylated with Ac_2O/DMAP to produce diacetate **6**, which subsequently underwent allylic oxidation with SeO_2 introducing the hydroxyl group at C7 in **27**. The stereochemistry at the C7 of **27** was deduced by coupling constant analysis and molecular modeling (see the Supporting Information for details). Hydrogenation of the alkene and oxidation of the C7 hydroxyl group in **27** then led to **6** as a pair of diastereomers (C8, α-Me/β-Me = 10:3) in 82% yield over two steps.[7c] The stereochemistry of α-Me **6** was confirmed by extensive 2D-NMR experiments (see the Supporting Information for details).

In summary, we have synthesized the left-wing fragment of azadirachtin-type limonoids with minimal use of protecting groups. The fully functionalized *trans*-decalin **6** (left-wing fragment of azadirachtins) was prepared from (−)-carvone in **21** linear steps. Notably, a single stereocenter in the starting material dictates the stereochemical outcomes of all nine stereocenters in the product. Key steps in our synthesis are the palladium-catalyzed intramolecular oxyalkynylation of an olefin and the gold-catalyzed cascade cyclization of a 1,7-diyne. The work reported herein serves as a milestone in our program toward understanding and synthesizing azadirachtin-type

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limonoids as environmentally friendly insecticides. Further studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and other characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00829.

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Notes

The authors declare no competing financial interest.

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(15) The dr of **15** was variable from batch to batch (see the Supporting Information for details).

(16) CCDC944023 (**24**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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