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# Total Synthesis of Ivorenolide A Following a Base-Induced Elimination Protocol

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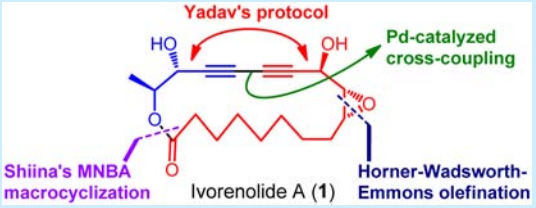
Supporting Information

**ABSTRACT:** A concise and stereocontrolled first total synthesis of Ivorenolide A (**1**) is reported in 16 longest linear steps with a 13.4% overall yield starting from (+)-diethyl tartrate (DET). Key features are base-induced elimination protocol for the construction of chiral propargyl alcohols in both fragments, Pd-catalyzed cross-coupling of terminal acetylenes, and Shiina's 2-methyl-6-nitrobenzoic anhydride (MNBA) mediated macrolactonization.




Macrolactones with polyacetylene moieties represent a unique family of natural products endowed with impressive biological properties such as immunosuppressive activities. Usually, immunosuppressive agents are used in the treatment of organ grafts and also for autoimmune chronic inflammatory disorders. In the past few decades, the discovery of cyclosporin (CsA)[1] and tacrolimus (FK506)[2] enabled successful transplantation of the major organs in humans. However, neither drug can be used for managing transplantation tolerance for the long-term.[3,4] Recently discovered immunosuppressants such as tetranactin,[5] didemnin B,[6] and discodermolide[7] all seem to have related but unique modes of action, suggesting that these compounds have discrete intracellular target mechanisms. In addition, the search for new immunosuppressants that possess better therapeutic effects or those which can be combined with currently used drugs for longer time maintenance and reduced side effects is of great interest. Traditional Chinese medicines (TCM) have been used for centuries in China to treat various immune-mediated disorders.[8] The search for immunosuppressants from TCM has led to the isolation of many limonoids from an antirheumatic Chinese herb *Khaya ivorensis* A. Chev. (Meliaceae), which has shown cytotoxic, anti-inflammatory, and antimalarial activities.[9]

Very recently, Ivorenolide A (**1**) and B (**2**) were isolated by Yue et al. from the stem bark of *K. ivorensis*.[10] These natural products contain conjugated acetylenic bonds including five and four oxygenated centers embedded in 18- and 17-membered macrolides, respectively (Figure 1). Ivorenolide A has been reported to exhibit significant inhibition of ConA-induced T-cell proliferation and LPS-induced B-cell proliferation. Owing to their interesting biological properties and intriguing structural motifs, the Ivorenolides have attracted the attention of synthetic chemists.

Herein, a full account of our work is presented which culminated in the first total synthesis of Ivorenolide A, using our own developed protocol for the construction of chiral propargyl alcohols,[11] metal-catalyzed cross-coupling to construct a diacetylenic moiety,[12] and Shiina's MNBA macrolactonization[13] as a pivotal step.

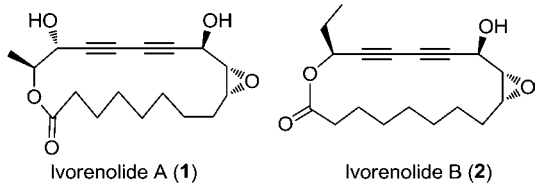



**Figure 1.** Structures of Ivorenolide A (**1**) and B (**2**).

The initial disconnection in the retrosynthesis involved cleavage of the macrolactone linkage at C1 to provide a diyne system (Scheme 1). This diyne could be accessible from an alkyne and a bromoalkyne through a Sonogashira coupling strategy. The alkyne and bromoalkyne fragments could be easily accessible from (+)-DET and known aldehyde **8**[16] respectively, by utilizing sequences which relied on the implementation of a chiral propargyl alcohol construction protocol.

The synthesis of alkyne fragment **5** is delineated in Scheme 2, which was prepared in a stereoselective manner commenced with the primary alcohol **7** which was in turn obtained from (+)-DET.[14] TBS protected primary alcohol **7** was oxidized with Dess-Martin periodinane (DMP)[15] and subjected to a Wittig reaction with bromo(9-((4-methoxybenzyl)oxy)nonyl)-triphenyl phosphorane in the presence of LHMDS to afford olefin **9** as an exclusive *Z*-isomer in 78% yield. The TBS group was deprotected using TBAF to afford **10** in 97% yield. The primary alcohol was converted to chloride **11** using $CCl_4$−$Ph_3P$ under reflux conditions, which was subjected to our protocol[11] of a base-induced elimination reaction to provide the chiral acetylenic alcohol **12**, with *n*-BuLi at −78 °C, in 87% yield. The product was converted to its corresponding MOM ether **5**

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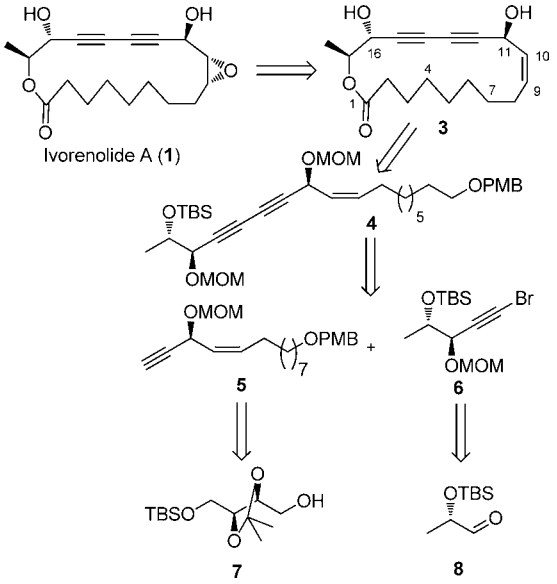
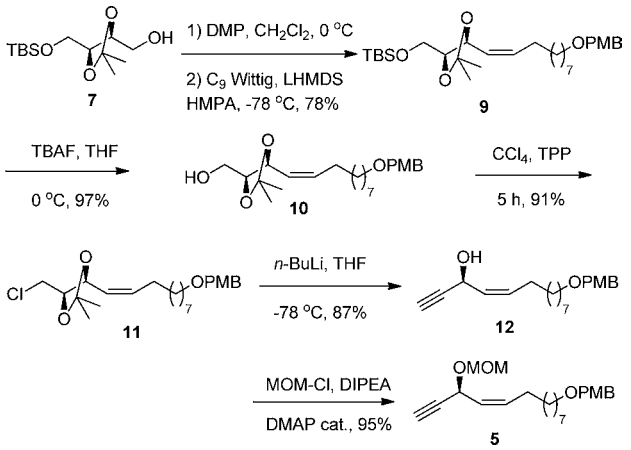
**Scheme 1. Retrosynthetic Analysis**




**Scheme 2. Synthesis of Alkyne 5**

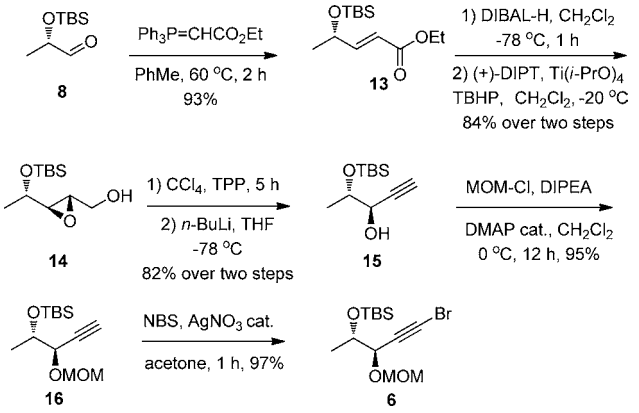



using MOM-Cl and DIPEA in the presence of a catalytic amount of DMAP in 95% yield.

The focus was then shifted toward the synthesis of chiral subunit **6**, which was achieved in good yield and optical purity when compared to the previous route.[10a] For this, the known aldehyde **8**[16] was transformed to unsaturated ester **13** through two carbon homologation in 93% yield. Reduction of **13** with DIBAL-H gave the allylic alcohol, which was subjected to the Sharpless asymmetric epoxidation[17] to obtain epoxy alcohol **14** as the sole product in 84% yield over two steps (Scheme 3). This set the stage for the base-induced elimination protocol for the second time. The epoxy alcohol **14** was converted to a chloro product with $CCl_4$−$Ph_3P$ under reflux conditions, followed by base-induced elimination with *n*-BuLi at −78 °C affording chiral propargylic alcohol **15** in 82% yield over two steps. This secondary alcohol was protected as its MOM-ether with MOM-Cl, in the presence of *N*,*N*-diisopropylethyl amine (DIPEA) to afford compound **16** in 95% yield. The terminal acetylene **16** on treatment with NBS and a catalytic amount of $AgNO_3$[18] furnished bromo alkyne **6** in 97% yield.

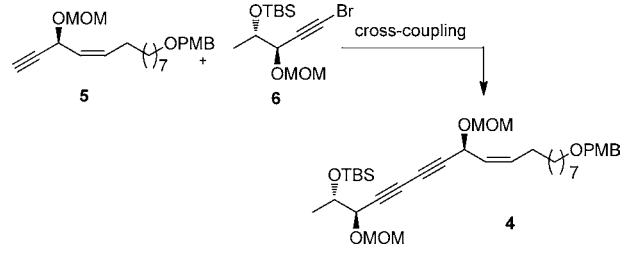
With the requisite fragments in hand, the coupling reaction between **5** and **6** was carried out next. However, an ensuing investigation revealed that the modified Sonogashira conditions

**Scheme 3. Synthesis of Bromo Alkyne 6**




$(Pd(PPh_3)_2Cl_2$, CuI, *i*-$Pr_2NH$, THF)[12] gave the required cross-coupling product **4** in 74% yield along with homocoupling of excess bromoalkyne as the byproduct. Further investigation gave an inferior result with (CuI, $PPh_3$, $K_2CO_3$, EtOH) in 61% yield (Table 1).[19] The coupled product was subjected to

**Table 1. Cross-Coupling of Alkyne and Bromoalkyne**




| entry | reaction conditions | time | yield (%)[a] |
|---|---|---|---|
| 1 | $Pd(PPh_3)_2Cl_2$, CuI, *i*-$Pr_2NH$, THF | 1 h | 74 |
| 2 | CuI, $PPh_3$, $K_2CO_3$, EtOH | 6 h | 61 |

[a]Isolated yield.

deprotection of the TBS group with TBAF to afford **17** in 97% yield. Treatment of compound **17** with DDQ in the presence of pH 7 buffer in $CH_2Cl_2$ afforded diol **18** in 92% yield. Selective oxidation of the primary alcohol with (diacetoxyiodo)benzene (BAIB) in the presence of TEMPO and subsequent oxidation of the aldehyde with $NaClO_2$ in the presence of $NaH_2PO_4$ as the buffer furnished **19** in 91% yield over two steps.

With a seco acid in hand, the attention was turned toward macrolactonization to complete the synthesis of Ivorenolide A. Recently, in a related transformation,[13b] it was found that Shiina's lactonization protocol (MNBA, DMAP, PhMe) appeared to be an excellent method for macrolactonization owing to its remarkable efficiency and simple operation. On treating with MNBA and DMAP in toluene at room temperature, the seco acid smoothly provided the macrolide **20** in 84% yield (Scheme 4). Treatment of compound **20** with 3 N HCl in ethanol afforded **3** in 74% yield. Oxidation of **3** (*Z*-form) with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded **1** as the sole product in 81% yield assuming that the *m*-CPBA approached the double bond from the sterically less hindered face of the molecule as reported earlier.[10a] The spectral and analytical data {$[\alpha]_D^{27}$ = +49.6 (*c* 0.43, MeOH); lit.[10a] $[\alpha]_D^{23}$ = −50.9 (*c* 0.157, MeOH)} for the synthetic molecule was in good agreement with the data reported for the natural product.[10a]



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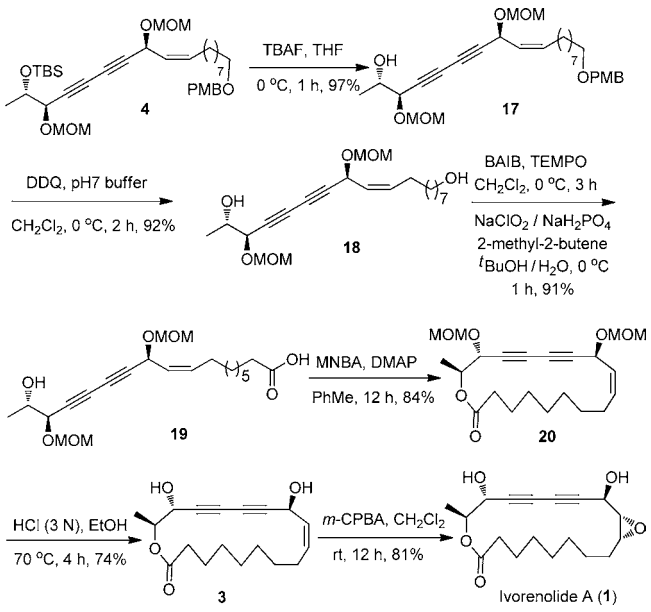
**Scheme 4. Accomplishment of the First Total Synthesis of Ivorenolide A (1)**




In summary, the investigation described above has resulted in the first total synthesis of Ivorenolide A (**1**) in 16 longest linear steps with a 13.4% overall yield. Highlights of the synthetic sequence include a base-induced elimination protocol for the construction of both fragments in a concise and stereoselective manner and Pd-catalyzed cross-coupling to construct a diyne system. For the macrocyclization, the MNBA-mediated lactonization for its high efficiency and simple operation has been demonstrated. Further studies toward the total synthesis of Ivorenolide B (**2**) are currently underway in our laboratory and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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