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First total synthesis of medicinally important 3,4,7-trimethoxy-9, 10-dihydrophenanthrene-1,5-diol

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ABSTRACT

The first total synthesis was successfully achieved for biologically active 9,10-dihydrophenanthrene-1,5-diol. The key features of our synthetic approach are Perkin condensation, followed by bromination, palladium mediated intramolecular C-C bond coupling, and selective isopropyl ether cleavage. Synthesized compounds were purified and characterized by IR, ^{1}HNMR, ^{13}CNMR and HRMS/LC-MS.

Introduction

A new class of 9,10-dihydrophenanthrene, namely 3,4,7-trimethoxy-9,10-dihydrophenanthrene-1,5-diol **1**[1] was isolated from Dendrobium moniliforme, which is a class of Orchidaceae plant widely occurring in India and Japan. The core structure 9,10-dihydrophenanthrene is a framework of many natural products that have shown significant biological properties. To date, various biological activities of phenanthrene derivatives have been reported, such as spasmolytic, antiplatelet aggregation, phytotoxic, antimicrobial, anti-inflammatory, cytotoxic and anti-allergic activities.[2]

Due to the vital role of these biological properties in regular life, this class of 9,10-dihydrophenanthrene derivatives has gain importance in recent years. Phenanthrenes are considered to be a class of aromatic metabolites, which are generally formed by oxidative or C—C bond coupling of appropriate stilbene precursors. Based on connectivity, phenanthrenes are divided into three types, i.e., mono-, di- and tri-phenanthrenes.[2] Some 9,10-dihydrophenanthrenes show ability of scavenging DPPH free radical.[3] A large number of substituted phenanthrenes that have been reported in the literature and showing different biological activities[2] are shown in Fig. 1.

Due to its promising biological activity and the impressive structural features, 3,4,7-trimethoxy-9,10-dihydrophenanthrene 1,5-diol **1** seems to be an attractive synthetic target. In this communication, to the best of our knowledge, we report the first total synthesis of dihydrophenanthrene **1**. As outlined in the Scheme 1, our initial synthetic strategy for the target compound **1** was designed to proceed from two building blocks **4** and **8.** We envisioned that the olefin segment **9** (precursor to **10**) arise from aryl bromide **4** and alkene **8** via Heck cross-coupling C—C bond-forming

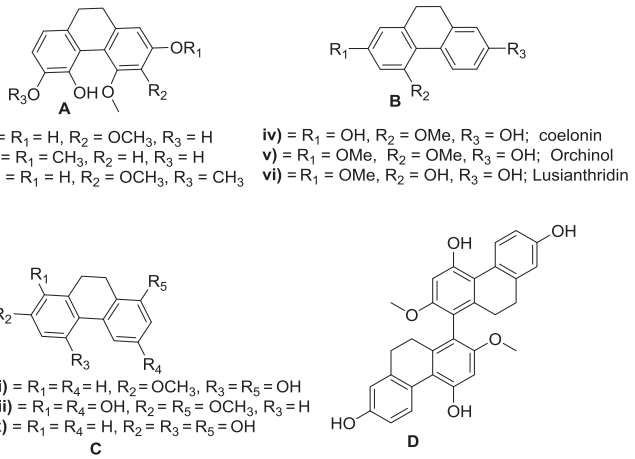

Figure 1. Structures of 9,10-dihydrophenanthrene derivatives[2].

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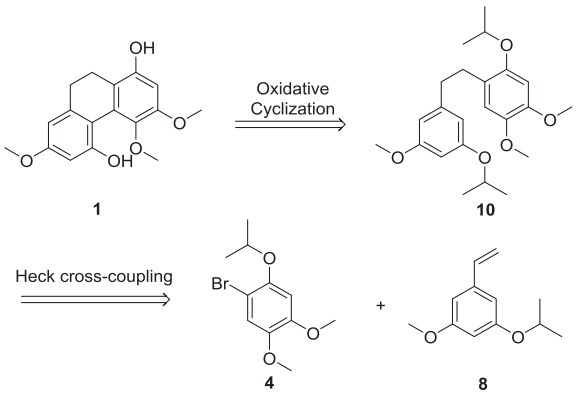
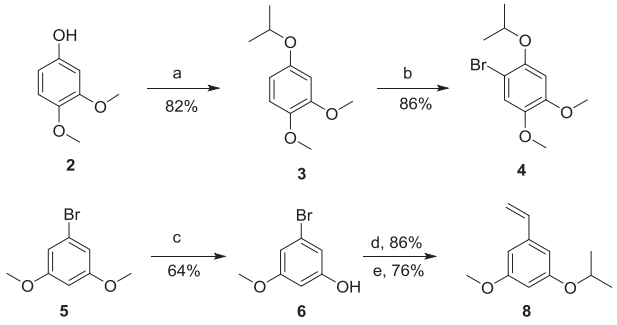


Scheme 1. Proposed Synthetic Strategy.



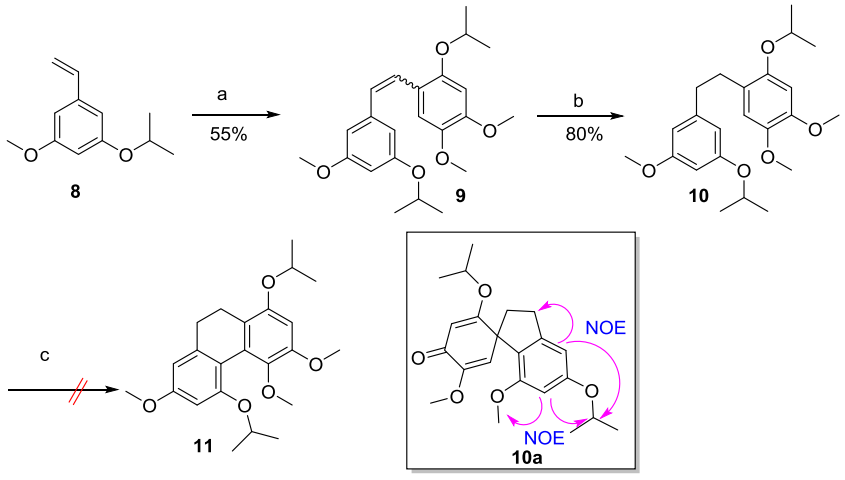
Scheme 2. Synthesis of building blocks bromo **4** and alkene **8**. *Reagents and conditions*; (a) K_2CO_3, *i*PrI, CH_3CN, 60 °C, 24 h; (b) NBS, SiO_2, CCl_4, rt, 16 h; (c) BBr_3, CH_2Cl_2, 0 °C-rt, 20 h; (d) Cs_2CO_3, *i*PrI, CH_3CN, 65 °C, 24 h; (e) Tri-*n*-butyl(vinyl)tin, $Pd(PPh_3)_4$, DMF, 80 °C, 6 h.

reaction, which on reduction to **10** followed by oxidative cyclization would give the desired product **1**.

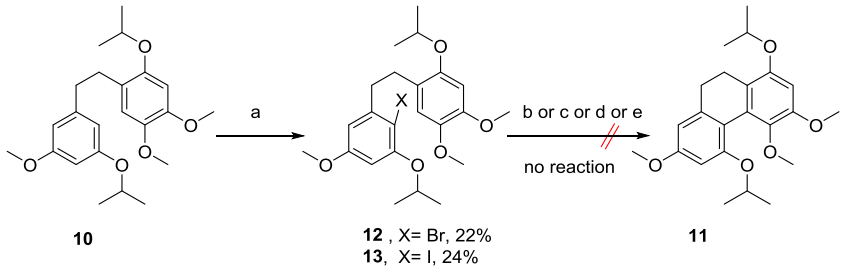
Our synthetic approach is depicted in scheme 2 to access the key building blocks **4** and **8**. The first synthesis commenced with commercially available 3,4-dimethoxy phenol **2**, which was converted to isopropyl ether **3** with *i*PrI and K_2CO_3, followed by bromination using NBS and silica-gel[4] in CCl_4 at ambient temperature delivered bromo precursor **4** in excellent yield. Next, boron-mediated (BBr_3) selective mono demethylation of **5** in CH_2Cl_2 to phenol **6** (64% yield),[5] followed by cesium carbonate assisted etherification (*i*PrI, 86% yield) and palladium catalyzed Stille cross-coupling with tri-*n*-butyl(vinyl)tin afforded olefin **8** in 76% yield.

After having required building blocks in hand, we then exposed bromo **4** and alkene **8** to catalytic quantities of $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine under optimized Heck cross-coupling conditions provided alkene **9** in 55% yield. The reduction of alkene **9** with 10% Pd on charcoal at 50 psi of H_2 in methanol gave ethane derivative **10**, which is the building block for oxidative cyclization (Scheme 3). Now, we performed oxidative cyclization with different Lewis acids to furnish desired 1,6-cyclized product **11**, albeit 1,5-cyclized dihydrospiro dienone[7] **10a** yielded majorly, which was well characterized by NOE (see Fig. 2 in SI for plausible mechanism and NOE). Unfortunately, several attempts to this oxidative cyclization using a number of conditions[6a–h] failed to derive the desired product **11** (see SI: Table 1).

In order to circumvent the problem, we thought it appropriate to introduce halo group at a right position to construct intramolecular C—C bond via Pd-mediated cyclization. The desired halo compounds **12** & **13** were synthesized from **10** although in low yields (22% and 24%) due to the formation of other separable regioisomers. However further cyclization of **12** and **13** with palladium



Scheme 3. First synthetic attempt for cyclized precursor **11**. *Reagents and conditions:* (a) **4**, Tri(*o*-tolyl)phosphine, $Pd(OAc)_2$, $(Et)_3N$, 120 °C, 48 h; (b) 10% Pd-C/H_2, 50 psi, MeOH, rt, 16 h; (c) Conditions of all attempts were tabulated. See Table 1 in SI.



Scheme 4. Second synthetic attempt for cyclized precursor **11**. *Reagents and conditions:* (a) NBS, CH_2Cl_2, rt for **12**, 8 h; NIS, $CHCl_3$, cat. TFA for **13**, 50 °C, 8 h; (b) $Pd(OAc)_2$, $(Cy)_3P$, Cs_2CO_3, DMA, 120 °C, 24 h; (c) $Pd(OAc)_2$, *t*$Bu_3PH{\cdot}BF_4$, Cs_2CO_3, DMF, 100 °C, 48 h; (d) Pd(II)TFA, $(Cy)_3P$, KOAc, DMF, 100 °C, 48 h; (e) Bu_3SnH, azobis (cyclohexane carbonitrile), toluene, 120 °C, 10 h.