

Total Synthesis of Pareitropone via Radical Anion Coupling

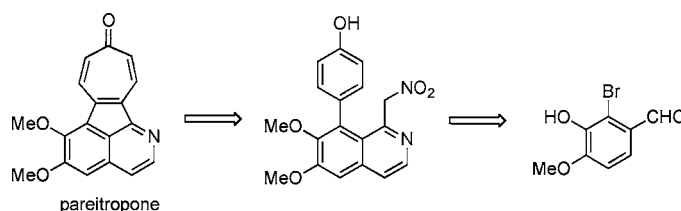
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ABSTRACT



A concise (9-step) synthesis of the tropoloisoquinoline alkaloid pareitropone has been achieved starting from 2-bromoisovanillin. The key step features oxidative cyclization of a readily available phenolic nitronate for the convenient construction of the fused troponone ring. This work underscores the synthetic utility of intramolecular oxidative coupling reactions of phenolic nitronates.

Pareitropone (**1**), isolated from the roots of *Cissampelos pareira* (*Menispermaceae*), was reported to display the most potent cytotoxicity (against P388 cells) among a small family of naturally occurring tropoloisoquinolines.¹ These alkaloids are structurally similar to the mitotic inhibitor colchicine. Although deceptively simple, they pose considerable synthetic challenges. Among a small number of total syntheses documented in the literature,^{2–4} there has been only one synthesis of **1** by Feldman, which features an elegant application of alkynyl-iodonium chemistry.⁵ Prompted by the scarcity and promising bioactivity of **1**, we report herein its concise synthesis.⁶

Extension of the [4 + 3] oxyallyl cycloaddition approach would require furan **2**, which differs from a previously utilized cycloaddition substrate in the substitution pattern, for the regioselective installation of the troponone (Scheme 1).^{4c} Instead of developing a new route to **2**, we decided to pursue an alternate approach based on oxidative cyclization of phenolic nitronates, which had been developed by Kende.⁷ Kende's elegant method for preparing fused tropones features radical anion coupling of **4** and subsequent norcaradiene rearrangement of the presumed intermediate **3a**. This approach could provide an efficient and scalable route to the target alkaloid under mild conditions.

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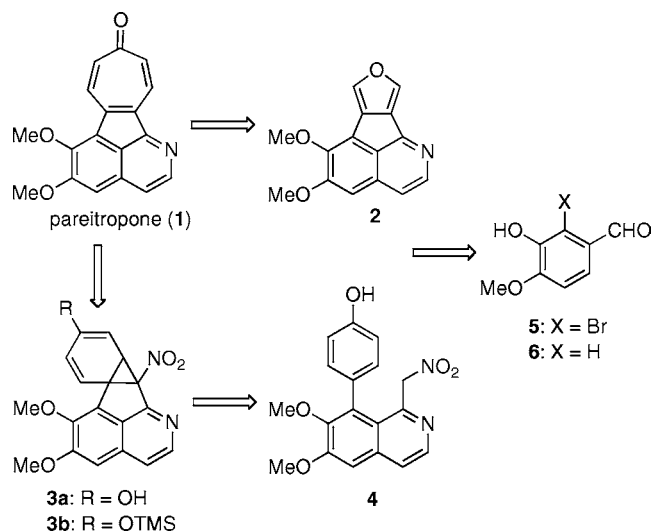
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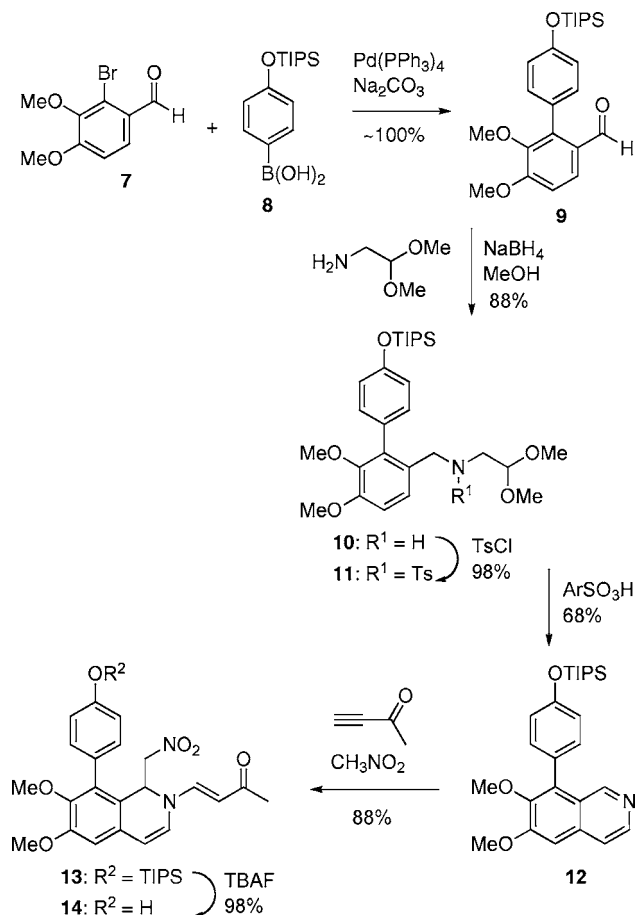
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Scheme 1. Retrosynthetic Analysis



Our synthesis began with *O*-methylation of **5**⁸ (97%) to give known 2-bromoveratraldehyde (**7**). The Suzuki coupling of **7** with **8**⁹ gave the biaryl adduct **9** in quantitative yield (Scheme 2).¹⁰ The isoquinoline ring was next installed by

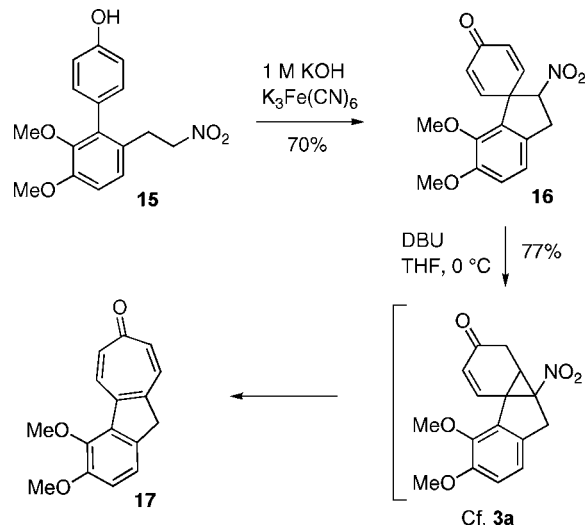
Scheme 2. Preparation of Cyclization Substrate **14**



the Pomeranz–Fritsch method.^{2b,4c,11} Thus, reductive amination of **9** with aminoacetaldehyde dimethylacetal and subsequent tosylation of **10** delivered the ring-closure substrate **11** in good yield. Cyclization of **11** by the action of 2,4-dinitrobenzenesulfonic acid gave the desired isoquinoline **12** in 68% yield, whereas the use of 6 M HCl produced the corresponding desilylated phenol. The next task was the introduction of the requisite nitromethyl group onto the isoquinoline ring, which proved to be challenging. After considerable experimentation, an attractive solution was found in a slight modification of Yadav's procedure.¹² Addition of nitromethane to **12** took place in the presence of 3-butyne-2-one to yield the Reissert-type adduct **13** in 88% yield. Desilylation of **13** furnished the phenol **14** to set the stage for the Kende cyclization.

The Kende annulation for the preparation of a fused tropone was first implemented in model studies (**15** → **16** → **17** in Scheme 3).^{13,14}

Scheme 3. Model Study of Radical Anion Coupling



Similarly, exposure of a solution of **14** in 1 M aqueous KOH to an excess amount of $K_3Fe(CN)_6$ resulted in oxidative cyclization and concomitant removal of the butenone moiety to afford the spiro dienone **18** in 76% yield (Scheme 4). With **18** in hand, the final conversion to the tropone only remained.

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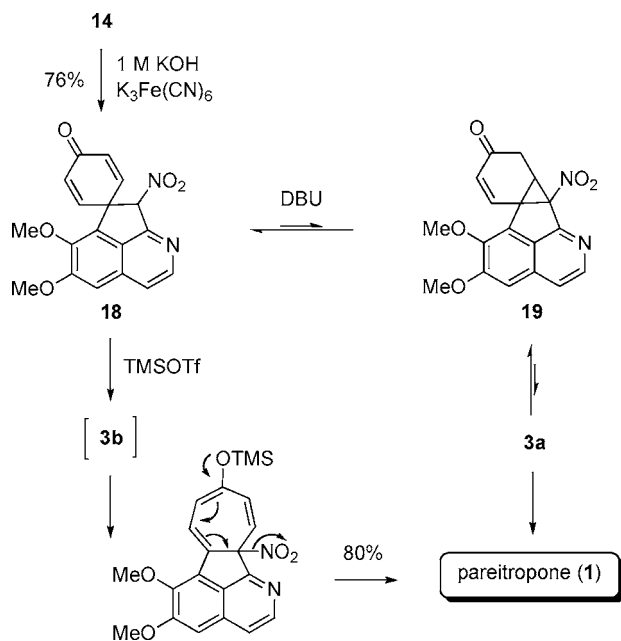
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(13) Compound **15** was prepared from **9** by standard methods in good yield.

(14) Although Kende and Koch employed dilute base (0.01 M KOH),^{7a} a 1 M KOH solution was used for the generation of the requisite phenolic nitronate in the present work due to the solubility issue. A complex reaction mixture was observed when a 0.01 M KOH solution was used for cyclization of **14**.

Scheme 4. Completion of a Total Synthesis of **1**



In marked contrast to clean conversion of **16** to **17**, reaction of **18** with DBU was unsatisfactory and gave only poor (up to 15%) yields of **1**. Other bases, such as triethylamine, morpholine, *N*-methylmorpholine, etc., were screened, but none were effective. We hypothesized that the chief hurdles arose from the energetically unfavorable cyclopropane formation due to the high strain present in **19**, coupled with inauspicious competition of norcaradiene rearrangement of **3a** with the retro-Michael reaction.¹⁵ A possible solution was devised to promote the conjugate addition by the use of

TMSOTf or TMSCl. Additionally, in situ trapping of the Michael adduct as a silylenol ether (e.g., **3b**) would help drive the reaction toward electrocyclic ring opening rather than the retro-Michael reaction. Treatment of **18** with an excess of TMSOTf indeed afforded pareitropone (**1**) in excellent (80%) yield.¹⁶ The spectral data (1H , ^{13}C NMR, and UV spectra, along with HRMS) of the final target were in excellent agreement with those reported in the literature.^{1,5}

In conclusion, a concise synthesis of pareitropone (**1**) has been achieved from commercially available 2-bromoisovanillin in 9 steps and 30% overall yield. The brevity is made possible by the under-utilized oxidative cyclization of phenolic nitronates. SAR studies of **1** will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data (1H NMR, ^{13}C NMR, and HRMS) for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) (a) Interestingly, TMSOTf alone was more effective than the use of TMSOTf and Et_3N . The latter conditions gave **1** in 50% yield. (b) Subsequent to electrocyclic ring opening of **3b**, the loss of "TMSONO" would be more likely than that of "HONO" in the presence of an excess of TMSOTf.