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$FeCl_3$ Catalyzed Prins-Type Cyclization for the Synthesis of Highly Substituted Indenes: Application to the Total Synthesis of (±)-Jungianol and *epi*-Jungianol

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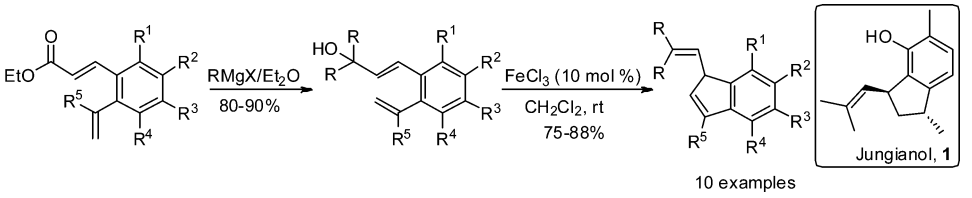
ABSTRACT



A novel approach was developed for the synthesis of highly substituted indene derivatives, using an $FeCl_3$ catalyzed Prins-type cyclization reaction which was further applied in the total synthesis of jungianol and *epi*-jungianol.

Indanes are compounds of great interest as they are encountered in many biologically active natural products[1] and are also used as building blocks for pharmaceutical[2] and material chemistry[3] (Figure 1). Thus development of new pentannulation reactions of aromatic rings remains to be an important quest in synthetic organic chemistry.[4]

The development of new methodologies to gain access to various indene derivatives has steadily increased in recent years. There are various methods reported in the literature for the synthesis of indenes; recently Sarpong,[4b] Nolan,[4e] and Wang[4g] independently reported the metal catalyzed cyclopentannulation of aromatic rings. In fact the past decade has witnessed a variety of synthetic methods for the formation of indene rings.[5] Very recently Tian and co-workers[4n] have reported the $FeCl_3$ catalyzed synthesis of indenes from arylallenes.

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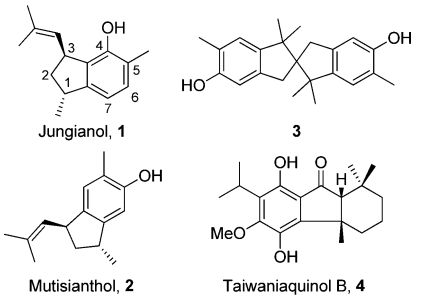
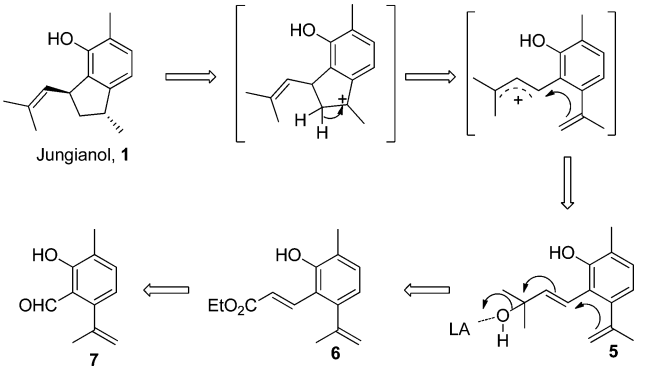


Figure 1. Selected examples of natural products that contains the indane framework.

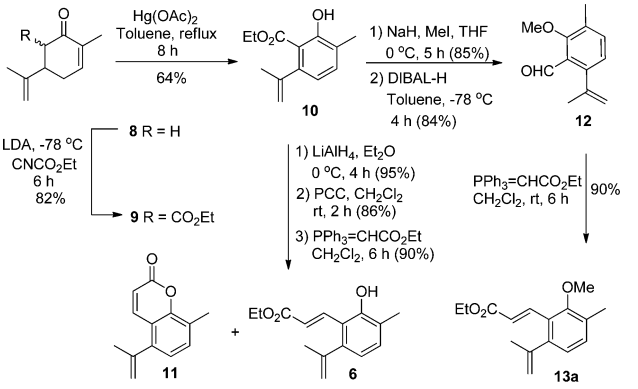
In this context, herein we report inexpensive and environmentally benign[6] $FeCl_3$ catalyzed Prins-type cyclization for the synthesis of various 1,3-disubstituted indenes and transformation of suitably substituted indene derivatives into natural product jungianol **1**. Jungianol **1** was isolated in 1977 from a South American plant, *Jungia malvaefolia*, by Bolhmann et al.[7] Structurally it is composed of an indane moiety containing a trisubstituted phenol substructure having methyl and isobutene side chains on the 1 and 3 position of the indane five-member ring respectively. Initial stereochemical assignments of side chains by isolation group was later revised by Hashmi et al. unambiguously by first total synthesis of jungianol and its epimer;[8] prior to their work Ho et al. reported the total synthesis and revision of another isomeric natural product mutisianthol in 1997[1b] that differs only in the position of the phenolic hydroxyl group. Although the biological activity of jungianol is not known, its isomer mutisianthol **2** exhibits moderate antitumor activity.[1e]

Retrosynthetically jungianol **1** could be obtained from allylic alcohol **5** by Lewis acid catalyzed Prins-type cyclization followed by regio- and stereoselective hydrogenation of an endocyclic double bond thus formed. Compound **5** could be prepared from ester **6** by a Grignard reaction. Ester **6** in turn could be synthesized from aldehyde **7** using a Wittig reaction (Scheme 1). Regioselective synthesis of highly substituted aromatic rings is a challenging task in organic synthesis. Altough cyclotrimerization of alkynes is a well-known method for preparation of aromatic compounds,[9] regio- and chemoselectivity still remain a problem.

Scheme 1. Retrosynthetic Analysis of Jungianol, **1**



Scheme 2. Synthesis of Diene Ester **13a**



In this regard we have exploited the previously reported aromatization of carvone **8**. In 1953 Treibs et al. reported the aromatization of carvone **8** at 140 °C using stoichiometric $Hg(OAc)_2$ and acetic acid.[10] We modified and optimized this reaction for the preparation of highly substituted aromatic diene ester **6** as shown in Scheme 2. Thus treatment of (±)-carvone **8** with LDA at −78 °C followed by quenching of the kinetic enolate thus generated by ethyl cyanoformate produced the diastereomeric mixture of β-ketoesters **9**.[11] Having the ketoester **9** in hand, the stage was set for the aromatization reaction; after several different conditions were tried, ketoesters **9** using stoichiometric $Hg(OAc)_2$ in toluene under reflux conditions gave a 64% yield of the desired phenol **10**. Our efforts to replace the toxic mercury reagent with DDQ (3 equiv) for the aromatization reaction also resulted in the formation of phenol **10**, but in only 30% yield. Reduction of ester

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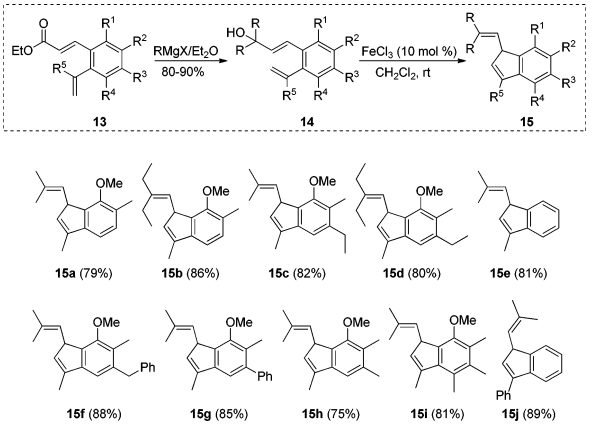
using LAH followed by PCC oxidation and Wittig olefination of the resultant aldehyde using $Ph_3P{=}CHCO_2Et$ generated the key intermediate diene ester **6** in 60% yield, along with a substantial amount of lactone **11** (20%). To avoid the formation of lactone byproduct, phenol **10** was protected as its methyl ether. Reduction of ester using DIBAL-H produced aldehyde **12** in 82% yield, which upon Wittig olefination produced the diene ester **13a** in very good yield.

Finally treatment of diene ester **13a** with excess MeMgI generated the key intermediate allylic *tert*-alcohol **14a** in 89% yield. With **14a** in hand, the stage was set for the key cyclization reaction. Several different conditions were tried such as TFA (40 mol %), $Sc(OTf)_3$ (10 mol %), $Yb(OTf)_3$ (10 mol %), $Cu(OTf)_2$ (10 mol %), and $BF_3{\cdot}OEt_2$ (20 mol %) using CH_2Cl_2 as solvent which resulted in the formation of **15a** in poor to moderate yield via Prins-type cyclization. TFA and $BF_3{\cdot}OEt_2$ afforded **15a** in 30% and 44% yield, while $Sc(OTf)_3$, $Yb(OTF)_3$, and $Cu(OTf)_2$ resulted in 41%, 45%, and 39% yield respectively. Interestingly tertiary alcohol **14a** on treatment with 10 mol % anhydrous $FeCl_3$ using CH_2Cl_2 as solvent underwent smooth cyclization to afford **15a** in 79% yield. Under the optimized conditions (10 mol % $FeCl_3$, CH_2Cl_2, rt), we explored the substrate scope of the reaction. Compound **14b** was synthesized by treatment of **13a** with an excess of EtMgBr. Compounds **14c**–**d** and **14f**–**i** were prepared from corresponding carvone derivatives in a similar manner as shown in Scheme 2 (see Supporting Information). Scheme 3 shows the results

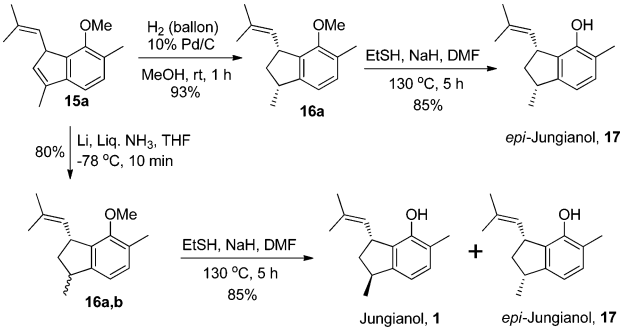
Scheme 3. Intramolecular Prins-Type Cyclization for Synthesis of Indenes



of the conversions of allylic tertiary alcohols **14a**–**j** to corresponding indene derivatives **15a**–**j**. Several substitution patterns on the aromatic ring were tolerated and provided good yields of the desired indene derivatives **15a**–**i**. To check the effect of the *ortho*-methoxy group on this cyclization we prepared compound **14e** (see Supporting Information) which also underwent smooth cyclization to generate the desired product **15e** in 81% yield using 10 mol % $FeCl_3$, showing that the reaction is quite general and has a larger substrate scope.

It was envisioned that jungianol could be generated by stereoselective hydrogenation of indene derivative **15a**, obtained earlier by Prins-type cyclization of tertiary alcohol **14a**. Hoping that hydrogenation would be regioselective, indene derivative **15a** was hydrogenated using 10% Pd/C. Interestingly the hydrogenation reaction turned out to be highly regio- and stereoselective to give the indane **16a** in very good yield (Scheme 4). *Cis* stereochemistry was assigned based on the assumption that the approach of hydrogen would be opposite to that of the isobutenyl group generating 1,3 *cis* substituted indane, which was confirmed by deprotection of indane **15a** using thioethanol in the presence of sodium hydride and matching the spectral data with those of *epi*-jungianol **17**. Finally after trying several different reduction conditions, chemoselective reduction of the benzylic double bond of **15a** using Li/liq NH_3 resulted in a 1:1 inseparable mixture of *cis* and *trans* isomers **16a,b**. Deprotection of phenol followed by careful column chromatography of the mixture of isomers furnished jungianol **1** and *epi*-jungianol **17** whose spectral data (IR, ^1H, ^{13}C, and HRMS) were in complete agreement with those reported in literature.[7,8]

Scheme 4. Total Synthesis of Jungianol (**1**) and *epi*-Jungianol (**17**)



In conclusion, syntheses of various highly substituted indenes were achieved using $FeCl_3$ catalyzed Prins-type cyclization, which was further applied in the total synthesis of natural product jungianol, **1** (8.15% overall yield), and its epimer, **17** (18.75% overall yield); in the process, known $Hg(OAc)_2$ mediated aromatization of carvone was exploited for the development of regioselective synthesis of highly substituted aromatic rings.

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Supporting Information Available. Synthetic procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.