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# New synthesis of a selective estrogen receptor modulator using an enatioselective phosphine-mediated 2+3 cycloaddition

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ABSTRACT

A new synthetic approach to the selective estrogen agonist **1** is described. The key steps in the route are a phosphine catalyzed 2+3 cycloaddition between an indanone enone and allenyl methyl ketone, and an unusual Robinson annulation to afford a bicylco[3.2.1]octane. The potential benefits of the new route are discussed along with efforts to render the approach asymmetric.

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## Introduction

As part of a past project at Merck and Co. for the treatment of menopausal vasomotor instability[1] we described the asymmetric synthesis of a selective estrogen receptor beta (ER-β) agonist **1**.[2] The synthesis started with the chlorination of a commercially available 5-methoxyindanone **2** to give **3** in 85:15 selectivity in favor of the desired 4-isomer. A three step sequence involving alkylation of the corresponding *N*,*N*-dimethylhydrazone was used to introduce the 2 carbon side chain bearing a masked leaving group in **4**. Phase transfer catalyzed conjugate addition of **4** to methyl vinyl ketone proceeded in 52% ee and Robinson annulation afforded the tricyclic **5**, at which stage the enantiomeric excess could be upgraded. The phenoxy group was converted into a bromide by reaction with boron tribromide (along with de-methylation) and cyclization to **6** was achieved by heating in IPA. A final chlorination then afforded the desired compound (Scheme 1).

While this synthesis was suitable for generation of multi-kilogram quantities of the target compound some shortcomings could be identified. Firstly the use of a number of potentially hazardous, toxic or difficult to source reagents was required, including *N*,*N*-dimethylhydrazine,[3] and methyl vinyl ketone.[4] Secondly, the enantiomeric excess obtained in the phase transfer catalyzed addition to methyl vinyl ketone was modest, requiring a yield depleting upgrade after the subsequent step. Finally, two separate chlorination reactions were used to introduce the chlorine atoms, the first of which led to a mixture of aromatic regioisomers. As such we required a route to eliminate the hazardous reagents, increase the regio- and enantioselectivity and reduce the overall number of steps. In this Letter we describe an alternate synthesis of **1** which addresses a number of these objectives and discuss the benefits and limitations of the new approach.

## Results and discussion

An alternate disconnection for compound **1**, would be to reverse the order of formation of the bridged rings such that the Robinson annulation would be preceded by formation of the five membered ring. The desired spirocycle **7a** for this transformation could potentially be accessed using a phosphine promoted 2+3 cycloaddition between an indanone enone **8** and allenyl methyl ketone, taking advantage of recently published methodology from our laboratories (Scheme 2).[5–7] This approach would eliminate some of the undesirable reagents used previously and potentially be rendered asymmetric by use of a chiral phosphine catalyst. Further streamlining appeared possible by carrying out a late stage double chlorination reaction.

The desired enone **8** for the key 2+3 cycloaddition was prepared by the reaction of 5-methoxyindanone with formaldehyde and *N*-methylanilinium trifluoroacetate using the method of Gras.[8] Complete conversion was seen within four hours and a pure sample of enone could be obtained by column chromatography following an aqueous work-up. However the enone proved to be quite unstable and prone to rapid dimerization even under low temperature storage. Interestingly, better stability was obtained when purification was not carried out and typically crude enone (100% mass recovery) was used in the subsequent cycloaddition.

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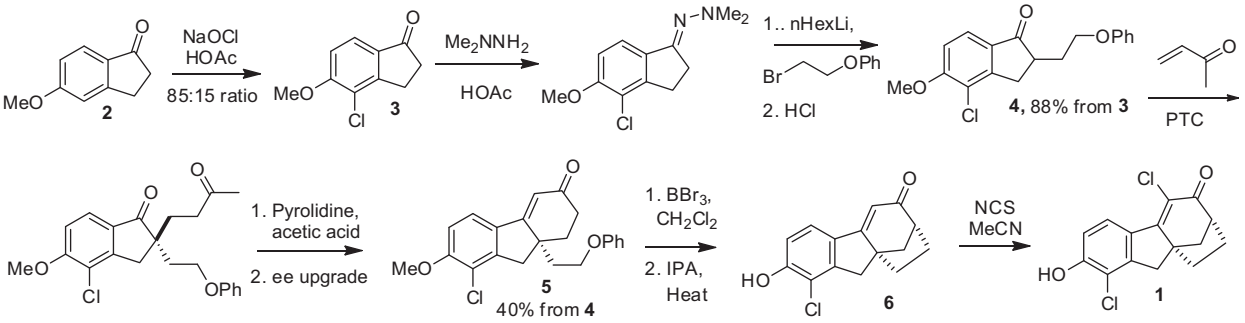
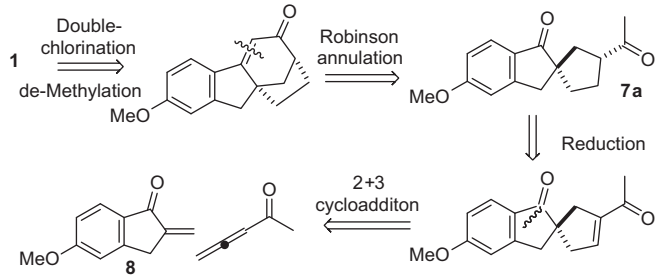
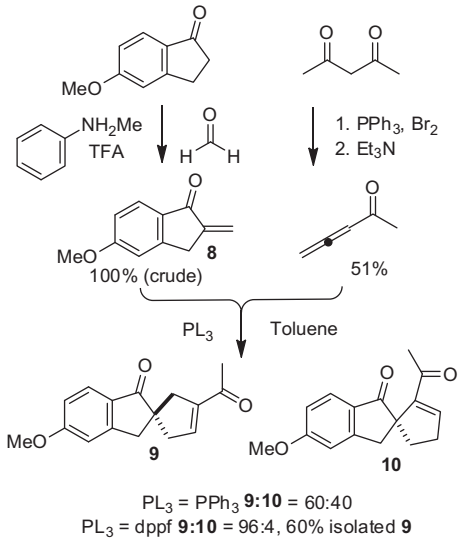



**Scheme 1.** Original synthesis of compound **1**.




**Scheme 2.** Alternate route to compound **1**.




**Scheme 3.** 2+3 Cycloaddition.

Allenyl methyl ketone was prepared from acetylacetone using the two step procedure of Constantieux.[9] Significant yield loss occurred during the final vacuum distillation and hence this compound was also used crude as a 40 wt % solution in methyl *tert*-butyl ether.

The 2+3 cycloaddition was initially evaluated using achiral phosphines. The use of triphenylphosphine led to a ca 60:40 mixture of the desired **9** and isomeric **10**, which provided genuine samples of both isomers. Tributylphosphine, which had been favored in our previous work,[5] gave variable results, possibly due to reagent quality. After further screening 1′1′-Bis(diphenyl-phosphino)ferrocene (dppf) was found to give complete reaction and a 96:4 regioselectivity in favor of **9**. After purification by column chromatography a 60% yield of **9**[10] from 5-methoxyindanone (two steps) was obtained (Scheme 3).

The next synthetic operation required was the reduction of the enone double bond in the 5-membered ring. Reaction using Pearlman's catalyst in ethanol led to rapid reduction of the double bond to give a mixture of isomers **7a** and **7b**, however the indanone carbonyl proved very susceptible to reduction leading to about 20% of alcohol **11** as by-product. Attenuation of reaction rate by switching the solvent to ethyl acetate gave better control, but still led to around 5% of **11**. The best procedure was found to be use of Pd/C in isopropanol at room temperature which gave complete reduction of the enone double bond (90:10 isomer ratio) after 24 h with <1% of carbonyl reduction seen. Based on NOE studies the major isomer from the reduction step was confirmed to be **7a** (Scheme 4). After removal of catalyst by filtration the mixture of **7a** and **7b** was used in the subsequent Robinson annulation without further purification.

The Robinson annulation of **7a** to **12** proved to be more challenging than anticipated. Although a commonly used procedure for the synthesis of cyclohexenones, a literature survey indicated only two examples of Robinson annulations to afford a bicylco[3.2.1] octane system[11] and in the current case the fused indanone system adds additional complexity. Based on stereochemical constraints only one of the methyl ketone isomers would be able to cyclize (**7a**) and hence a procedure to equilibrate **7b** to **7a** (via enolization of the tertiary center), promote cyclization onto the indanone ketone (via enolization of the methyl group), and dehydrate the resulting alcohols was required. Use of pyrolidine/acetic acid gave no reaction, and other acid catalyzed procedures were also unsuccessful. Use of KOtBu in THF led to equilibration of the ketone isomers (now favoring the undesired isomer **7b**) but no cyclization products were seen. KOtBu in isopropyl alcohol gave some evidence of cyclization to a mixture of alcohols **13** but no dehydrated product. Substituting toluene as solvent led to a number of decomposition products at room temperature; however, when the reaction started at −78 °C reasonably clean conversion into a 1:1 mixture of the desired product **12** and oxygenated by-product **14** was obtained (Scheme 5). Use of a new bottle of anhydrous toluene and rigorous de-gassing of the reaction mixture prior to addition of base was found to be sufficient to reduce the side product to about 5% in most cases. Using this optimized procedure a 60% yield of **12** from **9** (two steps) was obtained.

To convert **12** into the target molecule now required conversion of the aromatic methoxy group into a phenol and introduction of the two chlorine atoms. Chlorination of both **12** and phenol **15**[12] was initially evaluated using NCS in MeCN, the same conditions used for chlorination of enone **6** in the original route (Scheme 6). On heating to 60 °C clean introduction of the α-chlorine atom was seen for both substrates, however, on further heating to achieve the aromatic chlorination an increasingly complex mixture was formed. Mass spectral analysis indicated the presence of several di-chlorinated species, a number of tri-chlorinated compounds

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