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Synthesis of (±)-3-Methoxyestra-1,3,5(10)-trienes by the Repetitive Use of Negishi Reagent†

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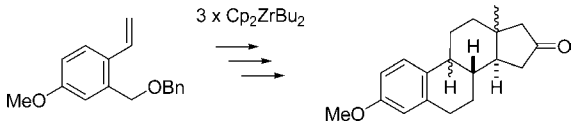
ABSTRACT



The repetitive use of Cp_2ZrBu_2 (Negishi reagent) was applied in the synthesis of three 3-methoxyestra-1,3,5(10)-trienone isomers within four steps from the advanced intermediate 11. The overall synthesis is based on three zirconium-mediated reactions: (a) oxidative addition of a benzyl ether, (b) cyclization of an allyl-ene compound, and (c) cyclocarbonylation of a diene. The presented synthesis demonstrates that complex organic compounds can be prepared by the repetitive use of one reagent.

The introduction of transition-metal compounds into organic synthesis has been responsible for an unprecedented explosion of new and efficient C−C bond formation reactions. Their use in syntheses of natural compounds has often been regarded as the touchstone of their synthetic utility.[1] In this regard, one of the favorite targets is steroids and their derivatives. There have been reported several syntheses of the steroid framework that relied in one of their key steps on a transition-metal-based reaction such as Co-catalyzed [2 + 2 + 2]-cyclotrimerization of alkynes,[2,3] Pd-catalyzed Heck reaction[4,5] and cascade cyclization of polyenes and polyynes,[6−8] Rh-catalyzed dimerization of diallenes,[9] zirconocene-mediated cyclization of dienes,[10] or oxidative addition to zirconocene.[11] Nonetheless, to the best of our knowledge, there has not been a report in which the synthesis of the whole steroid framework bearing the corresponding functional groups would be accomplished by the repetitive use of one transition-metal-based reagent. Herein, we would like to report on a new synthetic strategy for the synthesis

† Dedicated to Professor Ei-ichi Negishi on the occasion of his 70th birthday.

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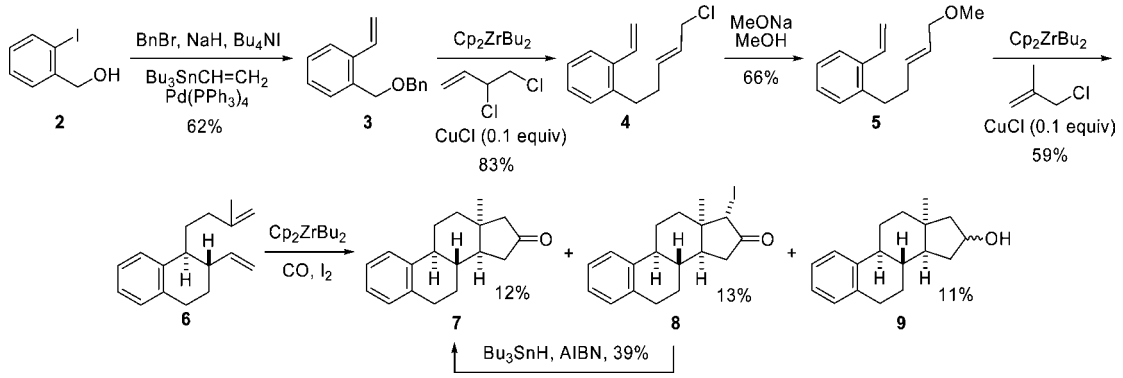
Scheme 1. Synthesis of Estratrienes **7**−**9**



of steroids based on the exclusive application of known zirconocene methodology. The construction of steroid framework including the required functional groups is demonstrated in the total synthesis of stereoisomers of (±)-3-methoxyestra-1,3,5(10)-trien-16-ones **1a**−**c** (Figure 1).

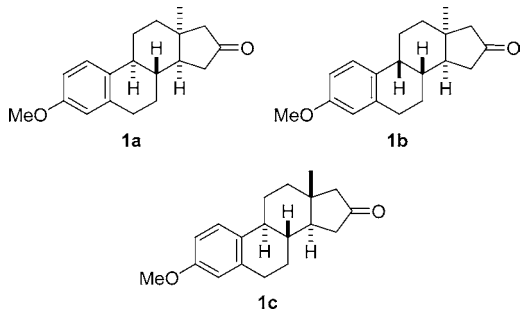


Figure 1. Three stereoisomers of (±)-3-methoxyestra-1,3,5(10)-triene-16-one.

The initial impetus for this venture was our interest in synthesis of complex organic compounds (e.g., natural compounds) by the repetitive use of one reagent that would act as a molecular "monkey-wrench" and would introduce various structural features of the target compound in each step. In this regard, we focused on the use of zirconocene-based methodology because of its well-known ability to form various types of organozirconium species that participate in a plethora of C−C bond formation reactions. The main advantage of the zirconocene methodology is that organozirconium species are usually easily prepared by a simple reaction of Cp_2ZrBu_2 (Negishi reagent) with various substrates.[12]

Initially, we decided to apply the above-mentioned methodology in the synthesis of the estra-1,3,5(10)-triene skeleton (Scheme 1) to verify its feasibility. The starting compound, styrene **3**, was prepared in two steps (62% yield) by benzylation of the commercially available iodobenzyl alcohol **2** followed by Stille coupling under standard conditions.[13] The oxidative addition of the ether C−O bond[14,15] of **3** to Cp_2ZrBu_2 (easily prepared from Cp_2ZrCl_2 and *n*-BuLi) followed by CuCl-catalyzed reaction with 3,4-dichlorobutene[16] yielded the unstable chloroallyl-ene **4** (83%), which was immediately converted into the methoxyallyl-ene **5** by the reaction with MeONa (66%). The cyclization of **5** with Cp_2ZrBu_2 gave a monorganozirconium species[17,18] that reacted with methallyl chloride in the presence of a catalytic amount of CuCl to furnish the *trans*-diene **6**.

Treatment of diene **6** with Cp_2ZrBu_2 and CO afforded after quenching with molecular iodine a complex reaction mixture. Out of it was isolated the ketone **7** (12%), the iodoketone **8** (13%), a mixture of compounds that, according to NMR analysis, seemed to be a mixture alcohols **9** (11%), and a fraction that was a mixture of the alcohols **9** and the ketone **7** (10%). Thus, the total amount of isolated tetracyclic compounds was 46%. The ketone **7** was desired target compound (12%), however, with an unnatural cis configuration on the fusion of the ring C and D. The formation of the iodoketone **8** was rather surprising because, to the best

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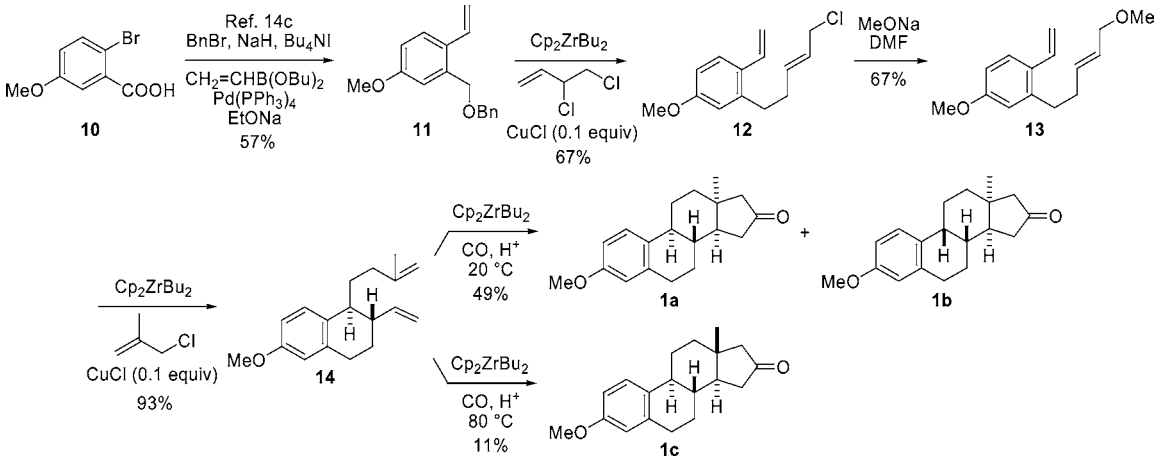
Scheme 2. Synthesis of 3-Methoxyestratrienes **1a**−**c**



of our knowledge, the formation of an iodoketone in this reaction has not been reported before. (On the other hand, the formation of α-iodoketones in steroids was reported under similar conditions.)[19] The structure and stereochemistry of **8** was derived from NMR spectra and confirmed by a single-crystal X-ray diffraction analysis (see the Supporting Information). The iodoketone **8** was transformed into the ketone **7** by reductive dehalogenation with tributyltin hydride in 39% yield, confirming that the both compounds have the same stereochemistry.

Although the final cyclization proceeded with *cis*-stereoselectivity[20] and the final target compounds had unnatural *trans-anti-cis* relative stereochemistry, this result proved that our strategy was correct, and we decided not to optimize the synthetic steps, but instead to embark directly on the synthesis of (±)-3-methoxyestra-1,3,5(10)-trien-16-ones **1**.

The starting point of our synthesis of 3-methoxyestra-1,3,5(10)-trien-16-ones **1** (Scheme 2) was styrene **11**, which was prepared from the commercially available benzoic acid **10** by reduction with BH_3·THF, alkylation with BnBr,[14c] and vinylation under Suzuki conditions (57% for three steps).[21] (It is necessary to note that Suzuki coupling was unexpectedly accompanied by reductive dehalogenation of the starting material to 3-methoxybenzyl ether (30%), which was inseparable from **11**. Thus, it was necessary to use the mixture of both compounds in the next step.)

The oxidative addition of the styrene **11** to Cp_2ZrBu_2 followed by CuCl-catalyzed reaction with 3,4-dichlorobutene yielded the desired chloroallyl-ene **12** in 67% isolated yield. Methoxylation of **12** with MeONa proved to be rather troublesome; nonetheless, a reasonable yield of the methoxy derivative **13** (67%) was achieved in DMF (carrying out the reaction in MeOH as in the previous case furnished **13** in 13% yield only). The stereoselective cyclization of **13** with Cp_2ZrBu_2 and CuCl-catalyzed alkylation of the formed organozirconium intermediate with methallyl chloride afforded the *trans*-diene **14** in good 93% yield. Carbonylation of the zirconacyclopentane formed by treatment of **14** with Cp_2ZrBu_2 afforded, after workup and column chromatography, a mixture of *trans-anti-cis* **1a**[22] and *cis-anti-cis* **1b** in combined yield of 49% in 3:1 ratio. In contrast to the previous method, the reaction mixture was quenched with 3 M HCl to avoid the formation of iodoketone. Since it has been shown that intramolecular reaction of dienes with Cp_2ZrBu_2 can be carried out under conditions of either kinetic or thermodynamic control,[19,23] the zirconacycle formed by the reaction of the diene **14** with Cp_2ZrBu_2 was equilibrated at 80 °C for 4 h before carbonylation. Although considerable thermal degradation was observed under these conditions, the product **1c** with the natural *trans-anti-trans* relative stereochemistry[24] was isolated in 11% yield along with a number of other unidentified products.

The structure of **1a** was confirmed by a single-crystal X-ray analysis (see Figure 2). The relative configurations at carbon atoms 8, 9, 13, and 14 in compounds **7**−**9** and **1a**−**c** were also established from detailed analysis of NMR spectra. The observed characteristic vicinal *J*(H,H) and NOE contacts in stereoisomers **1a**−**c** are shown in Figure 3.

In the synthesis of three estratrienes **1a**−**c** that is summarized in Scheme 2, the steroid framework was established in three zirconium-mediated steps: (a) oxidative addition of

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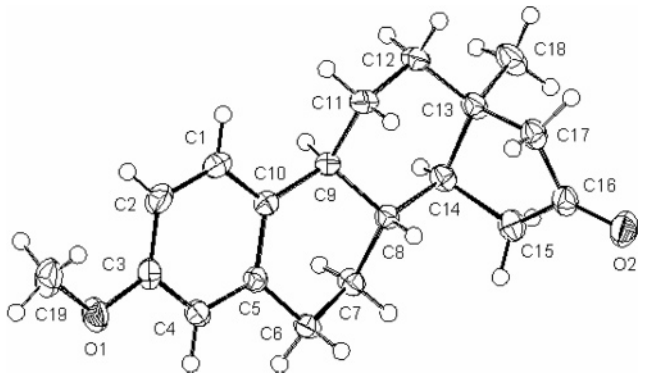

Figure 2. Overall view of **1a**. The displacement ellipsoids are drawn at the 50% probability level (PLATON).

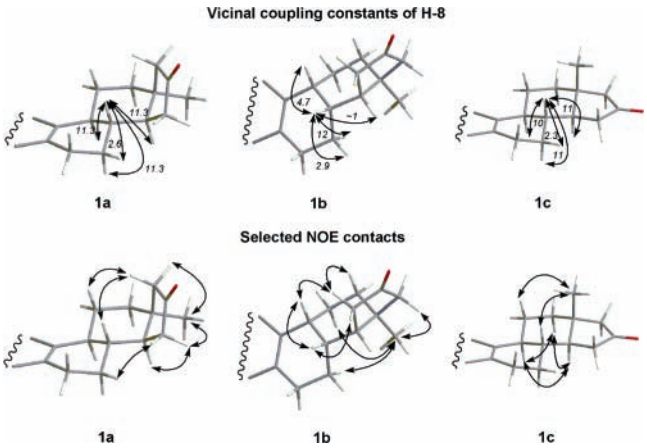

Figure 3. Characteristic vicinal coupling constants and NOE contacts in **1a**−**c**.

a benzyl ether, (b) cyclization of an allyl-ene, and (c) cyclocarbonylation of a diene. It is noteworthy that the cyclization of **5** to **6** and **13** to **14** proceeded with more than 98% stereoselectivity to give the desired *trans* isomers, despite the fact that zirconium-mediated cyclizations usually give preferentially *cis*-products when six-membered rings are formed.[12,21] Another interesting phenomenon is the formation of isomer **1b** during the final cyclocarbonylation. However, the origin of its formation is at the moment unclear. Attempts to isomerize **1a** into **1b** under the cyclocarbonylation or workup conditions were not met with success. One of the possible explanations may be based on the reversible 1,3-hydrogen shift caused by the abstraction of the allylic hydrogen on C-8 atom prior to the cyclization of the diene **14**.[25] Hopefully, future reactions with chiral intermediates will provide clear-cut clues at what carbon atom and in which stage of cyclocarbonylation actually a change of configuration takes place.

In conclusion, the presented results demonstrate a proof of the principle, i.e., synthesis of a complex organic compound can be achieved by the repetitive use of one reagent, which acts as a molecular "monkey-wrench". In this manner, stereoisomeric (±)-3-methoxyestra-1,3,5(10)-trienes **1a**−**c** were synthesized in four steps from the advanced intermediate styrene **11** or seven steps from the commercially available benzoic acid **10**. Optimization of individual steps, the scope of this methodology with respect to the synthesis of other steroid derivatives, and enantioselective synthesis are currently under investigation.

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Supporting Information Available: Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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