JOC Article

Formal Total Synthesis of (±)-Estrone and Zirconocene-Promoted Cyclization of 2-Fluoro-1,7-octadienes and Ru-Catalyzed Ring Closing Metathesis

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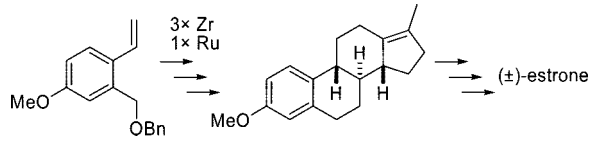

A new and diastereoselective method for the synthesis of the estrone skeleton from a substituted styrene based on sequential 3-fold use of Cp_2ZrBu_2 (oxidative addition−alkylation and two cyclization−alkylation sequences) and a ruthenium complex catalyzed RC-metathesis of a sterically hindered diene was developed. The prepared estratetraene was obtained in 7 steps from a commercially available starting material and thus the overall synthesis of estrone could be accomplished in 9 steps. Moreover, we have also found that the course of the reaction of substrates bearing the 2-halo-1,7-diene moiety with Cp_2ZrBu_2, i.e., cyclization or oxidative addition to the C−X bond, could be controlled by the nature of the halogen leaving group.

Introduction

Steroids have been in the center of synthetic interest for many decades. Among them a prominent role is reserved for estrone that since its first synthesis[1] has been an object of unabating synthetic interest due to its high molecular complexity and biological properties. In this regard a special place is occupied by methodologies exploiting transition metal based reactions.[2] Co-catalyzed cyclotrimerization,[2a,b] Pd-catalyzed coupling reactions,[2c,d] Ru-catalyzed metathesis,[2e] and others[3] can be considered as typical examples. In this regard, also the early examples of the application of Zr-mediated reactions such as cyclocarbonylation of a diene[4] or oxidative addition of benzyl ethers[5] should not be omitted. From the synthetic point of view the Zr-based methodology for oxidative dimerization of dienes to cyclic compounds is especially attractive because the formed intermediate organozirconium compounds can be used in further C−C bond-formation reactions. Thus Zr-mediated cyclizations of dienes and their derivatives were used in the synthesis of various natural compounds, such as the dolabellane skeleton,[6] dendrobine,[7] kainic acid,[8] haliclonadiamine,[9] elemol,[10] pisiferanol,[11] phorbole,[12] and a decahydroquinoline (+)-*trans*-195A.[13]

Since the zirconocene-based chemistry with respect to transformations of various functional groups is very rich,[14] we have become interested in its repetitive application in the synthesis of complex organic compounds. In this regard, we have recently reported a short pathway to 16-ketoestratrienes from an advanced styrene derivative that was based on three consecutive dibutylzirconocene (Cp_2ZrBu_2, a.k.a Negishi re-

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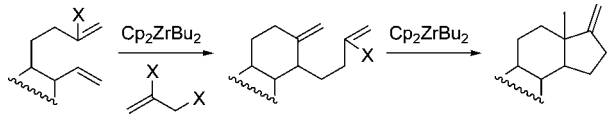
SCHEME 1. A Plan for the Construction of C and D Steroid Rings



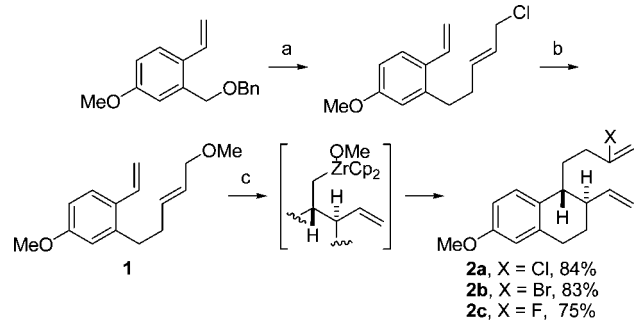
agent[15])-mediated reactions.[16a] These comprised (i) oxidative addition of dibenzyl ether followed by alkylation, (ii) metallo-ene reaction followed by alkylation, and finally (iii) cyclocarbonylation. One of the important results obtained in this study was the finding that zirconocene-mediated cyclization aiming at B-ring closure proceeded with trans stereochemistry that is common in natural steroids.[16,17] Moreover, this relative configuration controls the relative configuration of other stereogenic centers in further steroid framework build-up. Our next goal was the expansion of this methodology for estrone synthesis. Herein we would like to report a successful accomplishment of this task, which is based on a combination of Zr and Ru chemistry for the construction of the steroid C and D rings.

Results and Discussion

At the outset, we envisioned that the application of rarely used zirconcocene-mediated cyclization of 2-halo-α,ω-dienes[18] could provide a useful tool for the formation of steroid C and D rings (Scheme 1). Thus it was expected that the cyclization of an intermediate bearing the 2-halo-α,ω-diene moiety with dibutylzirconocene followed by alkylation with an 1,2-dihalopropene would yield 1-(2-halobut-1-en-4-yl)-2-methylidenecycloalkane. Then again its reaction with dibutylzirconocene should yield a product having a methylidenecyclopentane ring (a direct precursor of estrone).

The starting allylically substituted diene compound **1** was prepared according to the previously reported reaction sequence[16a] (oxidative addition of dibenzyl ether to dibutyl zirconocene,[5,19] allylation of the formed organozirconium intermediate with 3,4-dichlorobutene,[20] and methoxylation of the formed allyl chloride). Its further cyclization in the presence of dibutylzirconocene followed by CuCl-catalyzed alkylation with 2,3-dichloro- or 2,3-dibromoropene afforded the required 2-chloro- and 2-bromo-1,7-dienes **2a** and **2b** in 84% and 83% isolated yields, respectively (Scheme 2).[16c]

SCHEME 2. Formation of 2[a]



[a] Reagents and conditions: (a) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) 3,4-dichlorobutene, CuCl (10 mol %), 20 °C, 2 h, (3) 3 M HCl; (b) MeONa, DMF, 20 °C, 2h; (c) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) 2,3-dihalopropene, CuCl (10 mol %), 20 °C, 2 h, (3) 3 M HCl.

Next, the cyclization−alkylation sequence was attempted. However, the reaction of **2a** with dibutylzirconocene followed by the CuCl-catalyzed reaction with 2,3-dichloropropene resulted in the formation of several products. Unfortunately, the expected product, i.e., halodiene **3**, was formed only in about 10% yield. The major reaction path proceeded via oxidative addition of dibutylzirconocene into the C−Cl bond to give a vinyl zirconium compound[21] that upon the reaction with 2,3-dichloropropene gave rise to dimer **4**[22] and the allylation product **5** in 20% and 45% yields, respectively (Scheme 3). A change of the substrate to bromodiene **2b** (more reactive C−Br bond) did not improve the situation and after workup of the reaction mixture halodiene **3** was not detected at all. The cyclization was also attempted with the Ti(O-*i*-Pr)$_4$/*i*-PrMgX system,[23] but the reaction did not proceed and the starting compound **2a** was recovered.

Because the zirconocene methodology failed, the intramolecular carbolithiation was attempted in the next step (Scheme 4).[24] Thus treatment of the chloroderivative **2a** with *t*-BuLi

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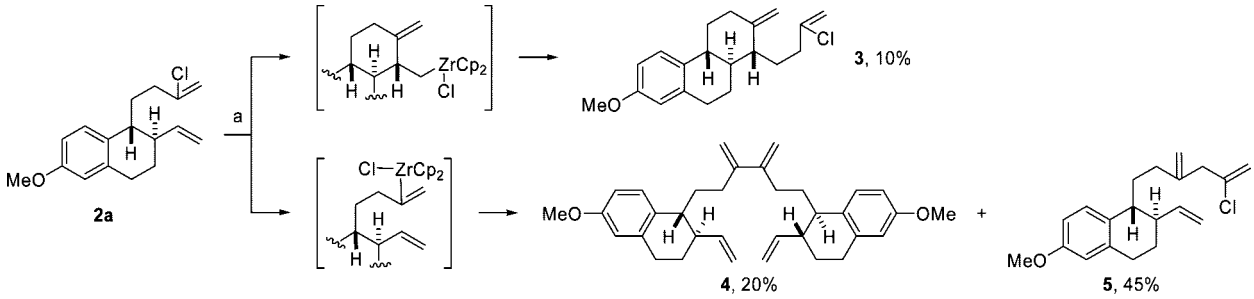
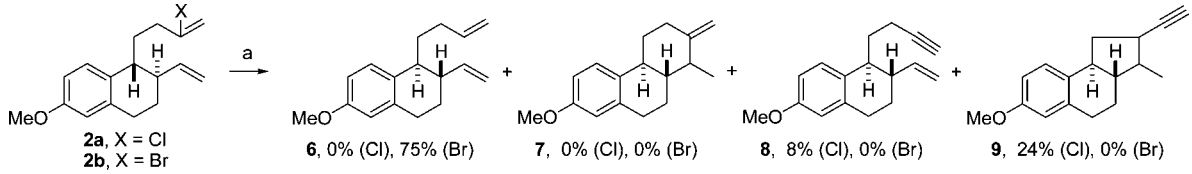
SCHEME 3. Attempts of the Cp_2ZrBu_2-Mediated C-Ring Closure[a]



[a] Reagents and conditions: (a) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) 2,3-dichloropropene, CuCl (10 mol %), 20 °C, 2 h, (3) 3 M HCl.

SCHEME 4. Attempts of the C-Ring Closure through Carbolithiation[a]



[a] Reagents and conditions: (a) (1) *t*-BuLi (2 equiv), TMEDA (2.2 equiv), (2) H^+.

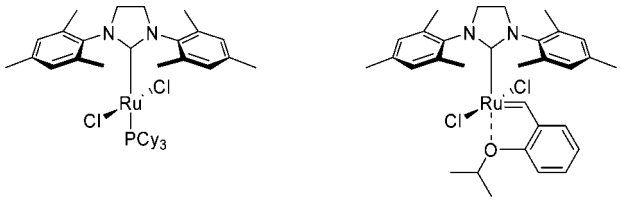
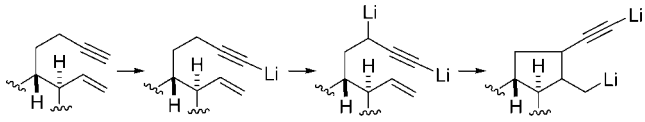


FIGURE 1. Grubbs 2nd generation and Hoveyda−Grubbs 2nd generation catalysts.

SCHEME 5. Probable Intermediates During Formation of 9



afforded a complex mixture, from which we isolated alkyne **8**, the product of the dehydrochlorination reaction, and (cycloalkyl)-alkyne **9** in 8% and 24% yields, respectively. The formation of the latter could be explained by the following reaction sequence: lithiation of alkyne **8** then a second lithiation of one of the propargylic hydrogens followed by intramolecular carbolithiation (Scheme 5). The products of simple dehalogenation of **6** or carbolithiation of **7** were not detected. Similarly, the reaction of the bromoderivative **2b** under identical conditions yielded only **6** in 75% isolated yield.

Since the carbolithiation also failed, we decided to resort back to zirconocene methodology and to try to solve the crucial problem of the cyclization step, i.e., the competition between oxidative addition to the C−X bond and cyclization of the alkene moieties. We assumed that using a substrate with a shorter (stronger) C−X bond and hence less reactive could favor the cyclization of the double bonds on the zirconium atom over the oxidative addition. The obvious choice was to use a substrate with the C−F bond. In this regard, 2-fluoro-1,7-diene **2c** was prepared in 75% yield similarly to the synthesis of **2a** and **2b** (Scheme 2).[16c] Fortunately, in this case the reaction of **2c** with Cp_2ZrBu_2 proceeded via cyclization of the alkene moieties to furnish an organozirconium intermediate that upon CuCl-catalyzed allylation with 3-chloro-2-fluoropropene yielded new fluorodiene **10** in 62% isolated yield (Scheme 6). The oxidative addition to the C−F bond proceeded only to the extent of 10%. In this way the construction of the steroid C ring by zirconocene methodology was successfully accomplished.

Then we embarked on the synthesis of the steroid D ring. Once again it was presumed that dibutylzirconocene mediated cyclization of **10** would help us reach the goal. Although the reaction proceeded well, the oxidative addition of the C−F bond to the zirconium atom was prefered over the cyclization. Diene **11**, formally originating in the reductive defluorination, was obtained as the major product (33% after isolation) (Scheme 6). The desired exocyclic alkene **12** was formed only in a negligible amount (>5%). Its formation was confirmed by characteristic ^{1}H NMR signals of the exo methylene double bond (δ 4.72−4.74, m, 2H) and the angular methyl group (δ 1.02, s, 3H). Since the known methylidene derivative prepared from natural estrone had signals of the exo methylene double bond and the angular methyl group at 4.67 and 0.81 ppm,[25] respectively, it was concluded that compound **12** had an unnatural cis configuration on the fusion of rings C and D. The change of solvent from THF to toluene did not have any effect on the product yields and distribution. Despite the low yield, the obtained mixture of compounds (**11** and **12**) was oxidized by the $OsO_4/NaIO_4$ system and GC/MS analysis confirmed the presence of methoxyestrone (for details see the Supporting Information). To shift the course of the reaction to cyclization, the reaction was carried out under various conditions. An attempt to carry out the cyclization in the presence PMe_3 as a stabilizing agent for the intermediate zirconocene−olefin complex[26] did not have the desired effect on the product distribution (23% of a mixture of **11** and **12**). The use of zirconacyclopentane[27] instead of Cp_2ZrBu_2 led only to a selective substitution of one ethylene ligand on the zirconium atom by the vinyl fluoride moiety giving rise to a product with the ethylated double bond **13** in 34% isolated yield. Also an attempt to promote the cyclization of the oxidative addition intermediate by converting it to a cationic zirconium species by the addition of MAO[18c] failed. An inseparable complex reaction mixture was formed,

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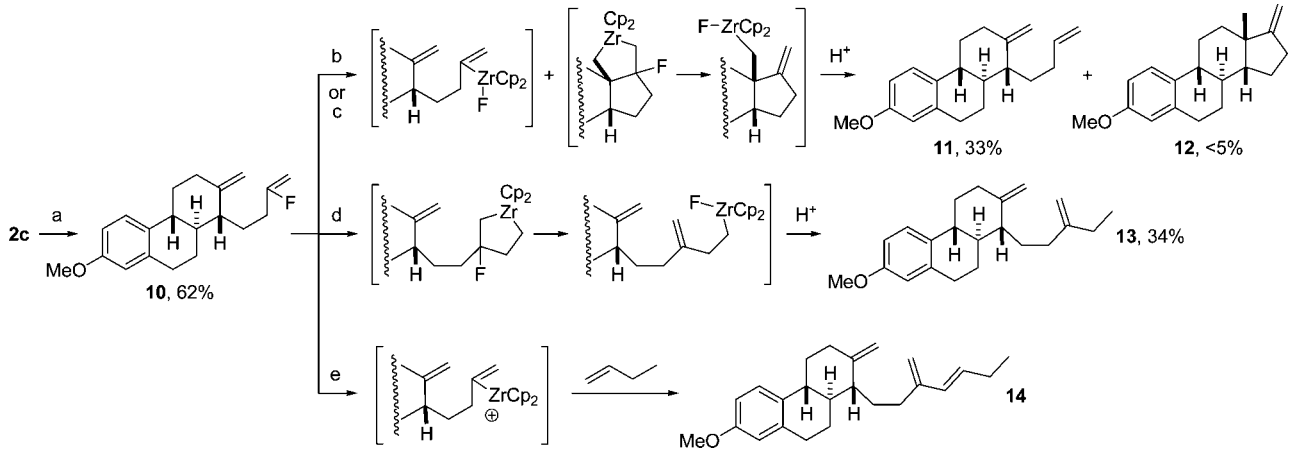
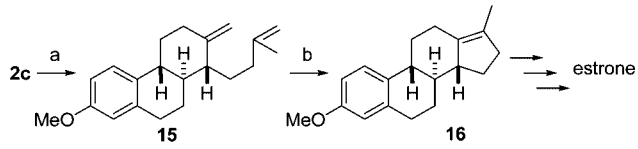
SCHEME 6. Reactions of 2c with Negishi Reagent (Cp_2ZrBu_2) under Various Conditions[a]



[a] Reagents and conditions: (a) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) 3-chloro-2-fluoropropene, CuCl (10 mol %), 20 °C, 2 h; (b) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h; (c) Cp_2ZrBu_2/PMe_3, −78 to 20 °C, 1.5 h; (d) $Cp_2Zr(CH_2)_4$, −78 to 20 °C, 1.5 h; (e) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) MAO, 20 °C, 2 h.

SCHEME 7. D-Ring Closure of the Estrone Framework via Metathesis[a]



[a] Reagents and conditions: (a) (1) Cp_2ZrBu_2, −78 to 20 °C, 1.5 h, (2) methallyl chloride, CuCl (10 mol %), 20 °C, 2 h, 80%; (b) Grubbs 2nd generation catalyst, toluene, 90 °C, 16 h, 82%.

out of which was identified by ^{1}H NMR and GC-MS only the polyene **14** in 43% GC yield (δ 4.64−4.96, m, 4H, $=CH_2$; 5.78, dt, J = 15.6, 6.6 Hz, 1H, −CH=; 6.05, d, J = 15.6 Hz, 1H, −CH=; m/z 336.3, M^+), presumably a product of the reaction of the cationic zirconium species with 1-butene (the product of Cp_2ZrBu_2 decomposition). The reluctance of **10** to cyclize probably could be attributed to steric hindrance in the vicinity of the exocyclic double bond resulting in a preferential attack of the C−F bond by Cp_2ZrBu_2.

At that moment we decided to switch the synthetic strategy because the limits of zirconocene-based methodology were evidently achieved. Nevertheless, Zr-mediated cyclization of **2c** was used once again for the closure of the steroid C ring and was followed by allylation with methallyl chloride affording diene **15** in 80% isolated yield.

It was presumed that the ring closing metathesis[28] of **15** could bring about the closure of the steroid D ring. Gratifyingly, inspite of the fact that tetrasubstituted alkenes are difficult to form,[29,30] heating of a 0.0033 M toluene solution of **15** with Grubbs second generation catalyst[31] (20 mol %) (Figure 1) at 90 °C resulted in the quantitative formation of the tetracyclic compound **16**, which was isolated in 82% yield (Scheme 7). The same reaction carried out with Hoveyda−Grubbs second generation catalyst[32] (Figure 1) at 25 °C overnight did not proceed to completion (**15**/**16** = 25/75). Since cycloalkene **16** is a known intermediate[33] and was previously converted to 3-methoxyestrone in two steps,[34] the successful formal total synthesis of estrone was accomplished.

Conclusion

In conclusion, a short formal total synthesis of estrone by means of two zirconocene and one RC-metathesis step from advanced intermediate **1** was accomplished (totally 9 steps from the commercially available starting material). As far as the zirconocene-based methodology is concerned, varying the halogen leaving group in 2-halodienes can have a profound effect on the course of the reaction, especially when cyclization and oxidative addition compete owing to structural features of the substrate (e.g., steric hindrance). This finding could have a positive effect on further developments in organozirconium chemistry and its application in organic synthesis. In addition, the facile ring closing metathesis of a diene to sterically hindered tetrasubstituted cycloalkene is also noteworthy and could provide a useful example for application of this methodology in the synthesis of compounds with highly substituted double bonds.

Experimental Section

***anti*-1-[(3-Fluorobut-3-en-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (2c).** *n*-BuLi (1.6 M solution in hexanes, 26 mmol) was added to a stirred solution of Cp_2ZrCl_2 (3.68 g, 12.6 mmol) in THF (70 mL) at −78 °C. After 1 h methoxydiene **1** (2.79 g, 12 mmol) in THF (10 mL) was added then the reaction mixture was warmed gradually to 20 °C and stirred for 1.5 h. To this solution was added 3-chloro-2-fluoropropene (1.7 g, 18 mmol) and CuCl (120 mg, 1.2 mmol), and the reaction mixture was stirred for 2 h. Then, 3 M HCl (aq) was added, the mixture was stirred for 0.5 h, extracted with hexanes, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 2.35 g (75%) of **2c** as a colorless oil. ^{1}H

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NMR (600.1 MHz, $CDCl_3$) δ 1.62−1.69 (m, 1H), 1.85−1.98 (m, 3H), 2.10−2.20 (m, 2H), 2.38−2.42 (m, 1H), 2.70−2.76 (m, 3H), 3.77 (s, 3H), 4.20 (ddt, J = 50.3, 2.8, 0.9, 0.9 Hz, 1H), 4.49 (dd, J = 17.6, 2.8 Hz, 1H), 5.00 (ddd, J = 10.4, 1.8, 0.9 Hz, 1H), 5.06 (ddd, J = 17.3, 1.8, 1.1 Hz, 1H), 5.79 (ddd, J = 17.3, 10.4, 7.8 Hz, 1H), 6.60 (dt, J = 2.8, 0.5 Hz, 1H), 6.72 (ddt, J = 8.4, 2.8, 0.8 Hz, 1H), 7.07 (dd, J = 8.4, 0.5 Hz, 1H); ^{13}C NMR (125.7 MHz $CDCl_3$) δ 26.1, 27.4, 28.6 (d, J(C,F) = 27.3 Hz), 31.5 (d, J(C,F) = 1.7 Hz), 41.0, 41.4, 55.1, 89.4 (d, J(C,F) = 20.5 Hz), 112.2, 113.3, 114.4, 129.7, 130.7, 138.1, 142.1, 157.4, 167.0 (d, J(C,F) = 256.8 Hz); IR (CCl_4) 3079, 3000, 2935, 2836, 1671, 1610, 1578, 1501, 1465, 1257, 1160, 1042, 995, 916, 846; MS-EI (m/z) 259.9 (M^+); HR-EI for $C_{17}H_{21}FO$ calcd 260.1576, found 260.1580. R_f (96/4 hexanes/Et_2O) 0.7.

7-Methoxy-1-(3-methylbut-3-enyl)-2-methylene-1,2,3,4,4a,-9,10,10a-octahydrophenanthrene (15). *n*-BuLi (1.6 M solution in hexanes, 2.1 mmol) was added to a stirred solution of Cp_2ZrCl_2 (307 mg, 1.05 mmol) in THF (5 mL) at −78 °C. After 1 h diene **2c** (260 mg, 1 mmol) in THF (2 mL) was added and the reaction mixture was warmed gradually to 20 °C and stirred for 1.5 h. To this solution was added β-methallylchloride (136 mg, 1.5 mmol) and CuCl (10 mg, 0.1 mmol), and the reaction mixture was stirred for 2 h. Then, 3 M HCl (aq) was added, the mixture was stirred for 30 min, extracted with hexanes, and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 237 mg (80%) of diene **15** as a colorless oil. ^{1}H NMR (600.1 MHz, $CDCl_3$) δ 1.20−1.25 (m, 1H), 1.29−1.35 (m, 1H), 1.37−1.44 (m, 1H), 1.65−1.72 (m, 1H), 1.76 (t, J = 1.3 Hz, 3H), 1.85−1.92 (m, 2H), 1.99−2.05 (m, 1H), 2.12−2.25 (m, 3H), 2.47−2.54 (m, 3H), 2.81−2.84 (m, 2H), 3.77 (s, 3H), 4.67 (q, J = 1.6 Hz, 1H), 4.70−4.72 (m, 2H), 4.82 (qd, J = 1.6, 0.6 Hz, 1H), 6.62 (dt, J = 2.8, 1.0 Hz, 1H), 6.71 (ddt, J = 8.6, 2.8, 0.8 Hz, 1H), 7.19 (dd, J = 8.6, 1.0 Hz, 1H); ^{13}C NMR (150.9 MHz $CDCl_3$) δ 22.7, 26.1, 27.3, 30.4, 32.8, 34.7, 36.1, 42.6, 45.4, 46.9, 55.2, 106.1, 109.4, 111.6, 113.2, 126.6, 132.8, 138.0, 146.5, 150.6, 157.4; IR (CCl_4) 3083, 2994, 2936, 2836, 1645, 1611, 1502, 1465, 1443, 1435, 1278, 1257, 1238, 1044, 892; MS-EI (m/z) 296.1 (M^+); HR-EI for $C_{21}H_{28}O$ calcd 296.2140, found 296.2136. R_f (96/4 hexanes/Et_2O) 0.75.

(±)-3-Methoxy-17-methylestra-1,3,5(10),13(17)-tetraene (16). Diene **15** (30 mg, 0.1 mmol) was added into a stirred solution of Grubbs second generation catalyst (17 mg, 20 mol%) in toluene (30 mL) and the mixture was heated at 90 °C for 16 h. The mixture was cooled to 20 °C, solvent was removed under reduced pressure, and the residue was purified on PTLC plate to afford 22 mg (82%) of **16** as a colorless oil. ^{1}H NMR (600.1 MHz, $CDCl_3$) δ 0.97−1.04 (m, 1H), 1.11−1.18 (m, 1H), 1.35−1.43 (m, 2H), 1.63−1.64 (m, 3H), 1.93−2.00 (m, 2H), 2.10−2.15 (m, 1H), 2.21−2.32 (m, 3H), 2.40 (tm, J = 10.8 Hz, 1H), 2.44−2.48 (m, 1H), 2.66 (ddd, J = 14.2, 4.2, 2.3 Hz, 1H), 2.79−2.82 (m, 2H), 3.77 (s, 3H), 6.62 (dt, J = 2.8, 1.0 Hz, 1H), 6.71 (ddt, J = 8.8, 2.8, 0.7 Hz, 1H), 7.19 (dd, J = 8.8, 1.0 Hz, 1H); ^{13}C NMR (150.9 MHz $CDCl_3$) δ 13.5, 25.8, 27.6, 27.7, 30.4, 31.5, 37.2, 42.2, 49.0, 52.5, 55.2, 111.6, 113.6, 127.2, 128.6, 132.32, 135.9, 138.5, 157.2; IR (CCl_4) 3084, 2930, 2857, 2840, 1688, 1611, 1576, 1501, 1465, 1454, 1257, 1043; MS-EI (m/z) 268.1 (M^+); HR-EI for $C_{19}H_{24}O$ calcd 268.1827, found 268.1832. R_f (96/4 hexanes/Et_2O) 0.75.

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

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