DOI: 10.1002/ejoc.200900937

Synthesis of an (±)-Estrone Precursor: The Scope of Zr- and Co-Mediated Cycloannulations

Robert Betík,[a] Pavel Herrmann,[a,b] and Martin Kotora*[a,b]

Dedicated to John M. Birmingham on the occasion of his 80th birthday

Keywords: Zirconium / Cobalt / Cyclization / Carbonylation / Steroids

The synthesis of an estrone intermediate based on a new approach was studied. The construction of the basic framework was carried out in three steps from a simple styrene derivative. The crucial reaction sequence for the steroid skeleton construction relied on a Zr-mediated cyclization (Zr-ene reaction)/propargylation followed by a Co-mediated diastereoselective Pauson–Khand reaction that afforded various D-ring-substituted tetracyclic ketones **11** with natural *trans-anti* stereochemistry. The conjugated addition reaction of Me_2Cu-Li to tetracyclic ketone **11a** aiming at the installation of the angular methyl group in the 13-position gave rise exclusively to product **12** with unnatural *trans-anti-cis* stereochemistry The successful synthesis of known estrone intermediate **4** with natural *trans-anti-trans* stereochemistry was accomplished by chemoselective reduction of the carbonyl group of ketone **11b**. Attempts to use other metallo-ene reactions to affect the synthesis of steroid B-ring are also described.

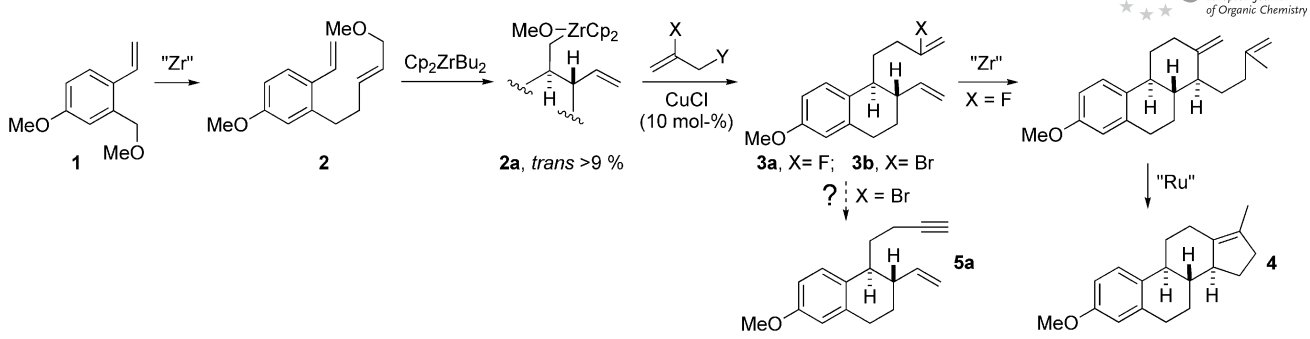
Introduction

The discovery of estrone (oestrone) almost 80 years ago was a milestone in the chemistry of steroids.[1] Soon thereafter, an era of its total syntheses started and it continues to span to the present day. The first synthesis of estrone was based on the hydrogenation of equilenine,[2] also a natural hormone, and was soon followed by a total synthesis.[3] Starting with pioneering synthetic work in the 1940s,[4] a number of other syntheses based on condensation reactions,[5] the Diels–Alder reaction,[6] cleavage of the cyclobutane ring,[7] a radical cascade reaction,[8] Friedel–Crafts alkylation,[9] and photochemically induced cycloaddition,[10] to name a few, appeared. Some of the early syntheses still serve even today as an inspiration for more sophisticated approaches, Torgov's intermediate being a typical example.[11] However, since the advent of organometallic chemistry the scope of possible synthetic strategies has greatly expanded. One of such early examples was the utilization of the Cu-catalyzed conjugate addition of Grignard reagents.[12] Soon it was followed by other transition-metal-mediated or -catalyzed reactions. Typical examples include Co-catalyzed intermolecular co-cyclotrimerization of a diyne with an alkyne,[13] Rh-catalyzed intramolecular C–H activation in diazoketo esters,[14] Tl-mediated fragmentation of an androstane precursor,[15] Pd-catalyzed inter- and intramolecular double Heck reaction of a halovinylaryl halide,[16] Cu-catalyzed intermolecular allylic substitution,[17] and Ru-catalyzed diene metathesis.[18] Despite these achievements there has been an ever-continuing interest in the development of new synthetic strategies as well as application of various synthetic methods for estrone preparation.

In our last report,[19] we demonstrated that a consecutive sequence of several zirconium-mediated reactions (oxidative addition/allylation and two cyclization/allylation sequences) followed by ring-closing metathesis could be used for the synthesis of estratetraene **4**, an intermediate in the synthesis of estrone,[20] from simple starting styrene **1** (Scheme 1). Especially, the first cyclization/allylation sequence of suitably substituted allylene **2** with a stoichiometric amount of dibutyl zirconocene (also known as the Negishi reagent) proceeded with high *trans* selectivity (>98%), giving alkylzirconium compound **2a**, which was easily alkylated with a number of allyl or acyl halides to give bicyclic compounds **3** (Scheme 1).[19b] Out of these compounds only fluorodiene **3a**, so far, was utilized in further transformations to estratetraene **4**, the direct precursor of estrone (in total, seven steps from a commercially available starting material).

Since the above-mentioned procedures represented comparatively easy synthetic operations, we wanted to explore whether also other alkylation products, such as bromodiene **3b**, could be used for the alternative preparation of estrone

[a] Department of Organic and Nuclear Chemistry, Faculty of Science, Charles University in Prague,
Hlavova 8, 12843 Praha 2, Czech Republic
Fax: +420-221-951-326
E-mail: kotora@natur.cuni.cz
[b] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic,
Flemingovo n. 2, 16610 Praha 6, Czech Republic
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900937.



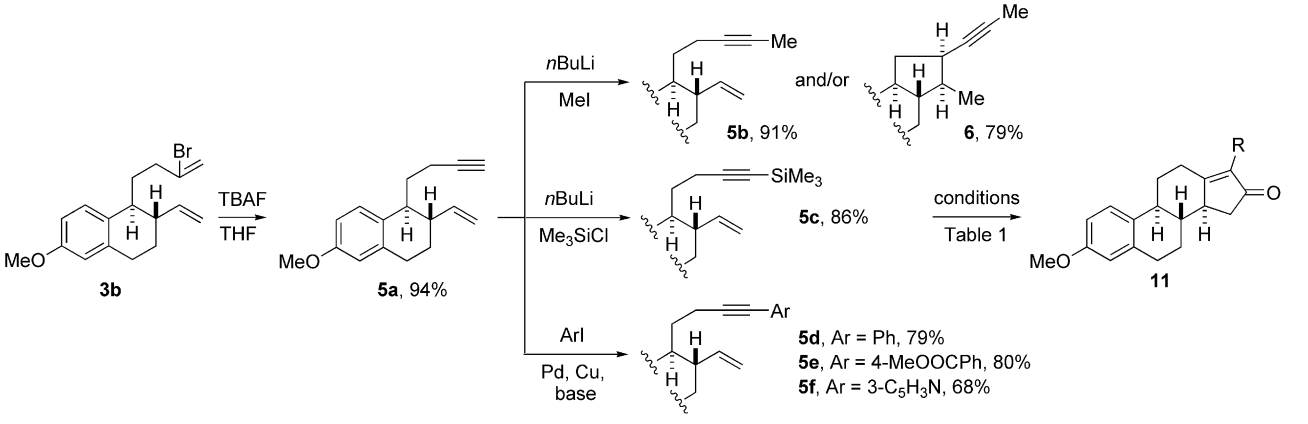
Scheme 1. Synthesis of estratetraene **4** from styrene **1**.

derivatives that would enable greater synthetic flexibility. In this regard, it was conceived that its dehydrobromination could yield enyne **5a**, a potential candidate for Pauson–Khand reaction, a procedure by which the steroid C and D rings could be easily assembled in one step. Moreover, the presence of the carbonyl group and the conjugated double bond would ensure their further transformation into estrone or its derivatives.

Results and Discussion

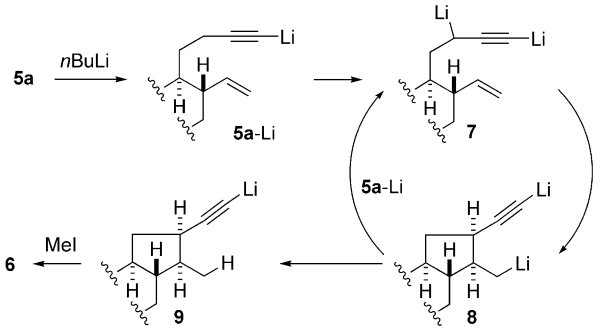
In the first step, dehydrohalogenation of **3b** was attempted. Since we observed problems accompanying dehydrohalogenation of **3b** and its chloride derivative in the presence of strong bases,[19b] the elimination was carried out under mild conditions by using tetra-*n*-butylammonium fluoride (TBAF) in DMF[21] to avoid any potential undesirable side reactions. The reaction proceeded smoothly and uneventfully, yielding enyne **5a** in high 94% isolated yield (Scheme 2). Having **5a** in hand, further functionalization of the terminal alkynyl group was done to extend the series of compounds for the Pauson–Khand reaction to assess its scope with respect to the substitution pattern.

Further functionalization of enyne **5a** into **5b**–**f** was carried out by using several commonly used procedures (Scheme 2). When the standard procedure for methylation of the terminal triple bond was applied, that is, lithiation with *n*BuLi followed by the addition of MeI, strong dependence of the course of the reaction on the conditions used was observed. Except for desired enyne **5b**, variable amounts of compound **6** were also found. When the solution of lithiated enyne **5a**-Li (the metalation was done with 1.1 equiv. of *n*BuLi to ensure quantitative metalation of the terminal triple bond) was warmed to 20 °C, the formation of **6** in 79% yield along with **5b** in 20% yield was observed after the addition of MeI. The formation of the five-membered ring can be explained by lithiation of the propargylic position, followed by intramolecular carbolithiation of the double bond. The lithiation of the propargylic position of terminal alkynes is known to proceed in the presence of an excess amount of alkyllithiums.[22] Also, intramolecular cyclization of unsaturated organolithium compounds is not surprising and was observed previously.[23] However, the *catalytic* nature of the observed cyclization is rather unique and could be rationalized in the following terms (Scheme 3): After initial lithiation of terminal alkyne **5a** to **5a**-Li, the unreacted *n*BuLi lithiated the propargylic position, giving **7**; then ensued intramolecular carbolithiation, yielding cycloalkyllithium **8**. Since iso-organolithiums are strong bases,[24] the newly formed cycloalkyllithium **8** acted as a strong base and intermolecularly lithiated the propargylic position in **5a**-Li through Li–H exchange to form **9**, which after addition of MeI afforded **6** (its configuration was determined by analogy with related compounds[19]). To



Scheme 2. Dehydrobromination of bromodiene **3b** to enyne **5a** and its conversion into enynes **5b**–**f**, followed by cyclocarbonylation to **11**.

avoid the above-mentioned cyclization, a modified approach was used. It relied on the lithiation of **5a** below 0 °C, followed by the addition of MeI, yielding enyne **5b** in 91% isolated yield (it is important to emphasize that both reactants should be meticulously dried prior to the reaction).

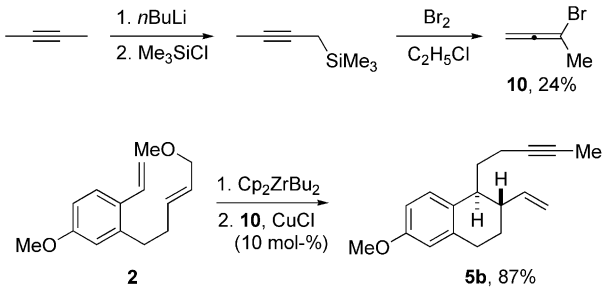


Scheme 3. Organolithium-catalyzed cyclization of **5a**-Li and formation of **6**.

The same method was also applied for the preparation of trimethylsilyl derivative **5c**. Lithiation of **5a** followed by the addition of trimethylsilyl chloride produced, after isolation, **5c** in 86% yield. The attachment of various aryl groups was done through Sonogashira coupling under standard conditions;[25] the corresponding aryl enynes **5d**–**f** were obtained in good isolated yields (68–80%; Scheme 2).

Obviously, construction of enyne **5b** in a one-step (or one-pot) procedure from advanced intermediate **2** would constitute a synthetic shortcut in terms of yield and efficiency in comparison with the above-mentioned three-step procedure. In this regard, the S_N2' alkylation of bromoallene with an organotitanium compound in the presence of a catalytic amount of CuCl provided us a necessary hint.[26] Thus, it was envisioned that the reaction of intermediate **2a** with 3-bromo-1,2-butadiene (**10**) could yield desired enyne **5b** in a one-pot procedure. Since the only procedure for its preparation was based on the use of organomercury compounds,[27] we opted for a two-step sequence, avoiding manipulation with hazardous organomercury compounds (Scheme 4). In the first step, 1-trimethylsilylbut-2-yne was prepared by lithiation of 2-butyne with the subsequent addition of Me_3SiCl in 89% yield,[28] then reaction with elemental bromine afforded 3-bromo-1,2-butadiene.[29] The reaction was carried out in chloroethane instead of dichloromethane to partially circumvent problems associated with the separation of the product from the solvent. Nonetheless, **10**, of suitable purity for further synthetic use, was obtained in overall 24% isolated yield (low thermal stability of the product can also account for the low isolated yield). Thus, carrying out the one-pot cyclization of **2** with dibutyl zirconocene followed by the reaction with freshly prepared bromoallene **10** afforded **5b** in 87% isolated yield.

Since its discovery in the early 1970s,[30] the Pauson–Khand reaction, that is, the three-component coupling of an alkyne, an alkene, and CO, has become an indispensable synthetic tool for the construction of the cyclopentenone



Scheme 4. Preparation of bromoallene **10** and one-pot synthesis of **5b**.

moiety.[31] Interestingly, despite its synthetic scope it has found just one application in the synthesis of steroids:[32] cyclocarbonylation of steroidal enynes having different spatial arrangement of the double and triple bonds in comparison with **5b**.[33] The Pauson–Khand reaction of prepared enynes **5** was studied under various reaction conditions (Table 1). The best results were obtained with the classical procedure (method A), relying on the use of a stoichiometric amount of $Co_2(CO)_8$, followed by decomplexation of the formed complex with DMSO instead of *N*-methylmorpholine *N*-oxide (NMO).[33] Under these conditions, the corresponding estratetraenes **11a**, **11b**, **11d**–**f** were isolated in high yields (84–95%; Table 1, Entries 1, 2, 4–6). Only in the case of enyne **5c** did cyclocarbonylation afford the corresponding product **11c** in mediocre 41% isolated yield. An attempt to carry out the cyclocarbonylation of enyne **5a** by using $Mo(CO)_6$ (method B)[34] was not met with success, as not even a trace amount of the expected product was detected. To exploit the catalytic cyclocarbonylation reaction by avoiding the use of gaseous CO,[35] the carbonylation of enyne **5e** with 2-naphthaldehyde in the presence of $Rh(BF_4)(cod)_2$/dppp[36] [method C; cod = *cis,cis*-1,5-cyclooctadiene, dppp = 1,3-bis(diphenylphosphanyl)propane] was attempted. Disappointingly, the reaction did not proceed and the starting material was recovered. Similar results were obtained also with 4-trifluoromethylbenzaldehyde (method D). The last tested method was Negishi's protocol for cyclocarbonylation (method E),[37] which is based on the reaction of "in situ" formed zirconacyclopentenes with CO. This method proved to be superior in the case of trimethylsilyl-substituted enyne **6c**: the corresponding estratetraene **11c** was obtained in 58% isolated yield (Table 1, Entry 8). It is worth mentioning that the cyclocarbonylations afforded only products with the required natural *trans-anti* stereochemistry on ring junctions in all cases.

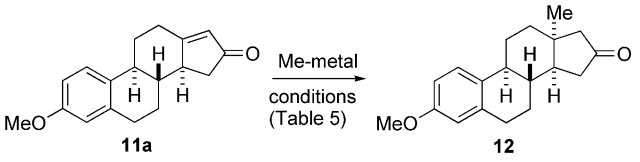
Conjugated enone **11a** (Scheme 5) seemed to be an ideal intermediate for the installation of the angular methyl group of the estrone skeleton. The conjugate addition was carried out under various conditions (Table 2). Initially it was attempted to carry out the catalytic conjugate addition with Me_3Al/Ni-cat.,[38] Me_3Al/Cu-cat.,[39] or Me_2Zn/Cu-cat.[40] systems. In no case was any conjugate addition product obtained, and the starting material remained intact. The low reactivity could be probably attributed to the β,β-disubstituted enone arrangement and steric hindrance caused by

Table 1. Cyclocarbonylation of **5** to **11** under various conditions.

Entry	Enyne **5**	Method[a]	Enone **12**	Yield [%][b]
1	**5a**, R = H	A	**11a**	95
2	**5b**, R = Me	A	**11b**	88
3	**5c**, R = TMS	A	**11c**	41
4	**5d**, R = Ph	A	**11d**	92
5	**5e**, R = 4-MeOOCPh	A	**11e**	84
6	**5f**, R = 3-C_5H_3N	A	**11f**	88
7	**5b**, R = Me	E	**11b**	31
8	**5c**, R = TMS	E	**11c**	58

[a] Method A: 1. $Co_2(CO)_8$ (1.3 equiv.), toluene, 20 °C, 4 h; 2. DMSO (5 equiv.), 80 °C, overnight. Method E: 1. Cp_2ZrBu_2 (1.05 equiv.), THF; 2. CO. [b] Isolated yield.

the rigid tetracyclic framework. A partial success was observed in the conjugate addition of MeMgBr catalyzed by CuI (10 mol-%) in the presence of the activating Lewis acid $BF_3{\cdot}Et_2O$, where product **12** (with unnatural *cis*-stereochemistry on the junction of the C and D rings) was obtained in 5–30% yields (Table 2, Entries 1–3). Interestingly, the reaction in the presence of a stoichiometric amount of CuI did not lead to an improved yield (Table 2, Entry 4). The most successful reaction was the conjugate addition of cuprate Me_2CuLi, which yielded diastereoselectively **12** in 80% yield (Table 2, Entry 5). The origin of the observed stereoselectivity can be easily explained by attack of the double bond at C13 from the less-hindered (bottom) side of **11a** (Figure 1). Additional unfavorable steric hindrance preventing the attack from the top side could also be exercised by the hydrogen atoms on C8 and C11.



Scheme 5. Conjugate additions to **11a**.

Table 2. Conjugate additions to **11a**.

Entry	Me-metal	Catalyst[a]	Additive	Solvent	Yield [%][b]
1	MeMgBr	CuOTf	$BF_3{\cdot}Et_2O$	THF	≈5
2	MeMgBr	CuI	$BF_3{\cdot}Et_2O$	THF	≈30
3	MeMgBr	CuI	$BF_3{\cdot}Et_2O$	Et_2O	≈30
4	MeMgBr	CuI[c]	$BF_3{\cdot}Et_2O$	Et_2O	≈25
5	Me_2CuLi	–		Et_2O	80

[a] 10 mol-% unless otherwise noted. [b] Isolated yield. [c] 100 mol-%.

Since the conjugate addition failed to give the product with desired natural stereochemistry, we had to look for an alternative method. As the next candidate for the synthesis of estrone, conjugated enone **11b** was chosen. We conceived that the reduction of the carbonyl group would afford estratetraene **4**, which is a known intermediate of estrone.[20] The reduction of the carbonyl group to the methylene group was attempted by using known methods based on metal hydride

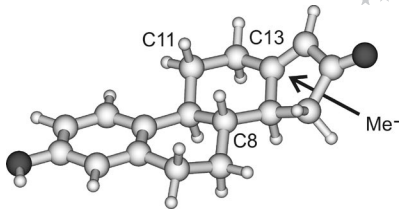
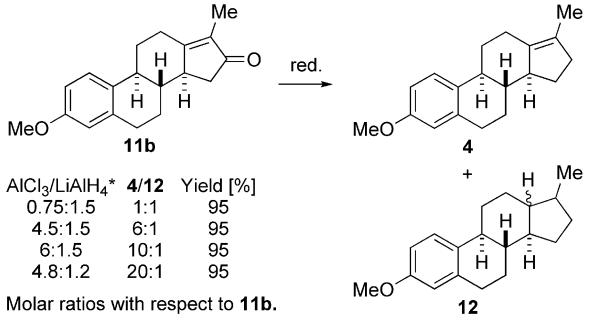


Figure 1. Approach of Me^- to the conjugated double bond in **11a** from the least-hindered side [the structure of **11a** was calculated by using B3LYP/6-311G(2d,p)].

reductions.[41] The first method relied on the known combination of $Et_3SiH/BF_3{\cdot}Et_2O$.[42] Although the reduction proceeded reasonably well in terms of the reduction of the carbonyl group, the C–C double bond was reduced as well, giving rise to an inseparable mixture of estratetraene **4**, estratriene **13**, and other unidentified products. Varying the molar ratios of the reactants with respect to enone **11b** did not have any dramatic effect on the ratio of obtained products **4** and **13** or on the chemoselectivity of the reaction. It should be added that the use of classic reduction methods such as the Wollf–Kishner reaction or its modifications resulted in the formation of intractable reaction mixtures.[43]

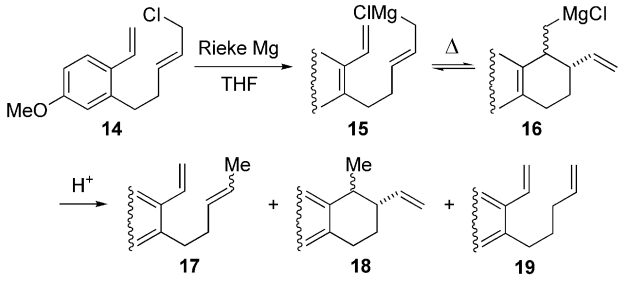
Next we switched to aluminum hydride based procedures. The aluminum hydrides of general formula AlH_xCl_y, generated from $AlCl_3$ and $LiAlH_4$ depending on the molar ratios ($0.33 \approx 4:1$), are capable of reducing the carbonyl group[44] to the methylene group, including the one in the enone system.[45] Similarly to the above-mentioned silane-induced reductions, the reaction proceeded well with high yields but was plagued by the formation of a mixture of **4/13** in various ratios. Gratifyingly, changing the $AlCl_3/LiAlH_4$ ratio to 4.8:1.2 with respect to **11b** resulted in the selective reduction of the carbonyl group with only minimal reduction of the double bond (combined yield of 95%). Thus, desired estratetraene **4** (Scheme 6) was obtained in 90% isolated yield containing only <5% of estratriene **13**.



Scheme 6. Reduction of the carbonyl group in enone **11b** to estratetraene **4**.

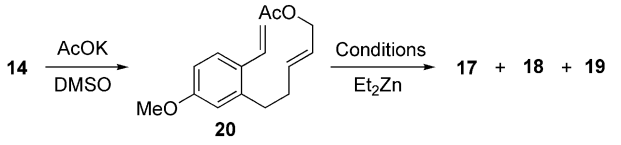
Although the dibutyl zirconocene mediated cyclization of **1** proved to be highly efficient and stereoselective, we wanted to look for an alternative methodology that would enable cyclization under simpler or catalytic conditions. In this regard, Oppolzer's metallo-ene reaction of Grignard

reagents seemed to be a method worthy to try.[46] Compound **14** was chosen as the Grignard reagent precursor, and it was prepared by the previously reported method from **1**.[19] After considerable experimentation, required Grignard reagent **15** (Scheme 7) was generated from **14** and Rieke magnesium in high yield. Initially, the metallo-ene reaction was run at 60 °C for 24 h. After hydrolysis an inseparable mixture of uncyclized and cyclized products was obtained in 88% isolated yield. It was composed of a mixture of *cis*- and *trans*-**17** (31%), **19** (31%), and a mixture of *cis*- and *trans*-**18** (15 and 11%). Carrying out the reaction at 100 °C for 24 h gave the identical substances in 70% isolated yield; however, their distribution was shifted in favor of the cyclized products: *cis*- and *trans*-**18** (45 and 21%), a mixture *cis*- and *trans*-**17** (<2%), and **19** (<2%). Heating of the reaction mixture to 140 °C for 24 h did not change the *cis*/*trans* ratio of **18**.



Scheme 7. Oppolzer's magnesio-ene reaction of **15**.

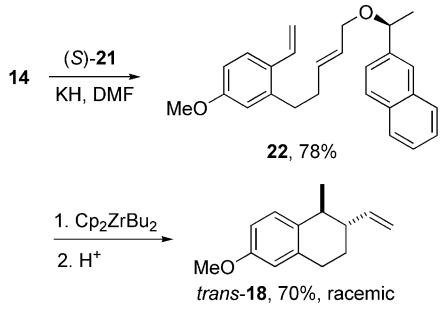
Next, a Pd-catalyzed[47] variant of Oppolzer's metallo-ene reaction with diethylzinc was tested. Starting acetate **20** (Scheme 8) was prepared by the reaction of **14** with potassium acetate in DMSO (100 °C, 10 min) in 82% isolated yield. The cyclization was run under two different conditions, A and B. Under conditions A, only a minor amount of the starting material was converted almost exclusively into *cis*-**18** (14%) (the amount of *trans*-**18** was <1%); the major products were uncyclized compounds **17** and **19**. Under conditions B, no cyclization was observed at all.



A: $Pd(OAc)_2$ (10 mol-%), PBu_3 (10 mol-%) Et_2Zn (10 equiv.), Et_2O	39%	14%	39%
B: $Pd(PPh_3)_4$ (10 mol-%), Et_2Zn (10 equiv.), toluene	50%	0%	41%

Scheme 8. Palladium-catalyzed metallo-ene reaction of **20**.

Since the zirconocene-mediated cyclization of **2** is a convenient method for the synthesis of bicyclic intermediates **3**, we wanted to explore a possible enantioselective variant of this method. In our previous reports we showed that the catalytic cyclization of **2** by using chiral zirconocene [(*R*,*R*)-(ebthi)$ZrCl_2$][19d] [ebthi = ethylenebis(4,5,6,7-tetrahydro-1-indenyl)] in the presence of a Grignard reagent did not furnish the expected organomagnesium intermediates and, in addition, the diastereo- and enantioselectivity was not good enough.[19d] Thus, we decided to use a different approach. It was shown that titanium-mediated cyclization of enynes carrying a chiral acetal moiety yielded chiral cycloalkanes with reasonable selectivity; we assumed that the zirconocene-mediated reaction of a diene carrying a chiral ether moiety could bring about asymmetric cyclization. The reaction of **14** with the potassium salt of (*S*)-(2-naphthyl)-ethanol **21** gave rise to the diene-carrying chiral ether moiety **22** (Scheme 9). Although the ensuing zirconocene-mediated cyclization afforded expected product **18** with the usual *trans*-selectivity in 70% isolated yield, no asymmetric induction was observed.



Scheme 9. Cyclization of chiral ether **22** with Cp_2ZrBu_2.

Conclusions

In summary, we have demonstrated that the sequential application of Zr- and Co-mediated cyclizations is a suitable synthetic pathway to compounds with the steroidal skeleton. The former process, Cp_2ZrBu_2-mediated cyclization/allylation (propargylation), selectively furnished compounds with a *trans*-substituted steroidal B ring, and the latter process, $Co_2(CO)_8$-mediated cyclocarbonylation, gave rise diastereoselectively to unsaturated tetracyclic ketones with natural *trans-anti* stereochemistry. It could be also substituted by the Cp_2ZrBu_2-mediated cyclocarbonylation reaction (Negishi protocol). Further elaboration of the selected ketones either by diastereoselective conjugate addition or by chemoselective reduction of the carbonyl group yielded steroidal compounds with the unnatural *trans-anti-cis* stereochemistry or compounds with natural *trans-anti-trans* stereochemistry, respectively. In this regard, estratetraene **4**, the known intermediate in estrone synthesis, could be prepared in just seven steps from commercially available 2-bromo-5-methoxybenzoic acid in 51% yield overall. Thus, the above-described strategy provides a simple and reliable synthesis of the steroid framework. Attempts to substitute the Zr-mediated cyclization (Zr-ene reaction) by a Mg-mediated or Pd-catalyzed process did not meet expectations with respect to synthetic generality, clearly demonstrating the synthetic power of zirconium-based chemistry.

Experimental Section

General Methods: All solvents unless otherwise stated were used as obtained. THF and Et_2O were distilled from $LiAlH_4$, DCM and Et_3N from CaH_2, toluene from sodium benzophenone ketyl. All other reagents were obtained from commercial sources. ^1H and ^{13}C NMR spectra were recorded with a Varian UNITY 400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) and Varian UNITY 300 (^1H at 300 MHz, ^{13}C at 75 MHz) spectrometers as solutions in $CDCl_3$ or C_6D_6 at 25 C sharply. Melting points (uncorrected) were determined by using a Kofler apparatus. Mass spectra were recorded with a ZAB-SEQ (VG-Analytical) instrument. Infrared spectra were recorded with a Bruker IFS 55 spectrometer as THF solutions. Fluka 60 silica gel was used for flash chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets (Merck). All reactions were carried out under an argon atmosphere with the use of flasks. Compound **3b** was prepared by a previously reported procedure.[19a,19c]

(±)-*anti*-1-But-3-ynyl-6-methoxy-2-vinyl-1,2,3,4-tetrahydronaphthalene (5a): Tetrabutylammonium fluoride (15.5 mmol, 4.9 g) was added to a solution of **3b**[19c] (3.1 mmol, 1 g) in DMF (20 mL), and the reaction mixture was stirred at 60 °C for 2 h. Then, DMF was removed under reduced pressure and water (150 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were dried with anhydrous $MgSO_4$. Volatiles were removed under reduced pressure, and column chromatography of the residue on silica gel (hexane/CH_2Cl_2, 1:1) yielded the title compound as a colorless viscous liquid (0.7 g, 94%). ^1H and ^{13}C NMR spectra were in agreement with the previously reported data.[19c]

(±)-*anti*-6-Methoxy-1-pent-3-ynyl-2-vinyl-1,2,3,4-tetrahydronaphthalene (5b)

Alkylation of 5a with MeI: *n*BuLi (1.13 mmol, 0.7 mL, 1.6 M in hexanes) was added to a stirred solution of **5a** (1 mmol, 240 mg) in THF (5 mL) at –78 °C. The reaction mixture was warmed gradually to –30 °C and stirred for 1 h at this temperature; then it was cooled again to –78 °C followed by the addition of MeI (dried with anhydrous $MgSO_4$ prior to use; 1.5 mmol, 213 mg). The mixture was warmed to 20 °C and stirred for 5 h. Then, water (100 mL) and HCl (10%, 5 mL) were added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were dried with anhydrous $MgSO_4$. Volatiles were removed under reduced pressure, the residue was dissolved in toluene (5 mL), and the solvent was evaporated under reduced pressure (repeated 2×) to remove residual MeI. Column chromatography of the residue on silica gel (hexane/CH_2Cl_2, 1:1) yielded of title compound as a colorless viscous liquid (230 mg, 91%).

Alkylation of 2 with 3-Bromobuta-1,2-diene (10): *n*BuLi (3.4 mmol, 2.13 mL, 1.6 M in hexanes) was added to a stirred solution of Cp_2ZrCl_2 (1.7 mmol, 498 mg) in THF (15 mL) at –78 °C. After 1 h, methoxydiene **2** (1.63 mmol, 377 mg) in THF (1 mL) was added, and the reaction mixture was warmed gradually to 20 °C over 2 h. Then, 3-bromobuta-1,2-diene (2.44 mmol, 325 mg) and CuCl (0.16 mmol, 16 mg) were added, and the reaction mixture was stirred for 2 h. Solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 mL) and hexane (20 mL) and filtered through Celite. Volatiles were removed under reduced pressure, and column chromatography of the residue on silica gel (hexane/CH_2Cl_2, 1:1) furnished the title compound as a colorless viscous liquid (358 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.7 (p, J = 6 Hz, 1 H, CH*H*), 1.79 (t, J = 2.4 Hz, 3 H, C≡C-CH_3), 1.8–1.9 (m, 2 H, CH_2), 1.91–2.00 (m, 1 H, C*H*), 2.08–2.16 (m, 2 H, CH_2), 2.38–2.46 (m, 1 H, C*H*), 2.66–2.80 (m, 3 H, CH*H*, CH_2), 3.77 (s, 3 H, OCH_3), 4.96–5.02 (m, 1 H, CH=CH*H*), 5.04–5.10 (m, 1 H, CH=CH*H*), 5.82 (ddd, J = 17.4, 10.4, 7.6 Hz, 1 H, C*H*=CH_2), 5.98–6.02 (m, 1 H, Ar-*H*), 6.10–6.14 (m, 1 H, Ar-*H*), 7.08–7.12 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.49 (CH_3), 16.03 (CH_2), 25.67 (CH_2), 27.08 (CH_2), 35.38 (CH_2), 40.88 (CH), 41.20 (CH), 55.11 (OCH_3), 75.78 (C≡C), 79.17 (C≡C), 112.07 (CH, Ar), 113.26 (CH, Ar), 114.21 (C=C), 130.01 (CH, Ar), 130.99 (C, Ar), 137.89 (C, Ar), 142.15 (C=*C*), 157.39 (COMe, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 2953, 2885, 1721, 1442, 1183, 1062, 1035, 988, 923 cm^{-1}. MS (EI): *m*/*z* (%) = 254.2 (35) [M^+], 225 (40), 200 (50), 187.1 (100), 185.1 (55), 159.1 (25), 115 (25). HRMS (EI+): calcd. for $C_{18}H_{22}O$ 254.1671; found 254.1677. R_f (hexane/CH_2Cl_2, 1:1) = 0.65.

(±)-*anti*-6-Methoxy-1-(4-trimethylsilylbut-3-ynyl)-2-vinyl-1,2,3,4-tetrahydronaphthalene (5c): *n*BuLi (1.65 mmol, 1.03 mL, 1.6 M in hexanes) was added to a stirred solution of **5a** (1.5 mmol, 359 mg) in Et_2O (10 mL) at –78 °C. After 1 h, TMSCl (3 mmol, 327 mg) was added, and the reaction mixture was warmed gradually to 20 °C and kept for 3 h at this temperature. Then, the volatiles were removed under reduced pressure, and column chromatography of the residue on silica gel (hexane/CH_2Cl_2, 1:1) yielded the title compound as a colorless viscous liquid (401 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.14 [s, 9 H, -Si(CH_3)$_3$], 1.60–1.70 (m, 1 H, CH*H*), 1.84–2.00 (m, 3 H, CH_2, C*H*), 2.18–2.26 (m, 2 H, CH_2), 2.4–2.5 (m, 1 H, C*H*), 2.68–2.82 (m, 3 H, CH*H*, CH_2), 3.76 (s, 3 H, OCH_3), 4.96–5.01 (m, 1 H, CH=CH*H*), 5.03–5.10 (m, 1 H, CH=C*H*H), 5.81 (ddd, J = 17.4, 10.2, 7.6 Hz, 1 H, C*H*=CH_2), 6.57–6.6 (m, 1 H. Ar-*H*), 6.68–6.74 (m, 1 H, Ar-*H*), 7.06–7.10 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.14 [Si(CH3)3], 17.35 (CH_2), 25.55 (CH_2), 27.02 (CH_2), 35.09 (CH_2), 40.92 (CH), 40.96 (CH), 55.12 (OCH3), 84.84 (C≡C), 107.51 (C≡C), 112.12 (CH, Ar), 113.30 (CH, Ar), 114.27 (C=C), 130.021 (CH, Ar), 130.92 (C, Ar), 137.91 (C, Ar), 142.02 (C=C), 157.43 (C, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 2954, 2886, 1720, 1439, 1275, 1180, 1061, 1035, 988, 857 cm^{-1}. MS (EI): *m*/*z* (%) =312 (50) [M^+], 297 (30), 200 (65), 187 (100), 73 (55). HRMS (EI+): calcd. for $C_{20}H_{28}OSi$ 312.1909; found 312.1917. R_f (hexane/CH_2Cl_2, 1:1) = 0.7.

General Method for the Sonogashira Coupling of 5a with Aryl Halides: To a stirred solution of **5a** (1 mmol, 239 mg), $Pd(PPh_3)_4$ (0.01 mmol, 11 mg), and CuI (0.02 mmol, 5 mg) in a mixture of THF (6 mL) and Et_3N (2 mL) was added the corresponding substituted phenyl iodide (1.1 mmol). The reaction was stirred for 10 h and then filtered through a short pad of Celite, and the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel furnished the desired products.

(±)-*anti*-6-Methoxy-1-(4-phenylbut-3-ynyl)-2-vinyl-1,2,3,4-tetrahydronaphthalene (5d): Iodobenzene (1.1 mmol, 224 mg) was used. Column chromatography of the residue on silica gel (hexane/CH_2Cl_2, 1:1) yielded the title compound as a colorless viscous liquid (249 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.7 (m, 1 H, CH*H*), 1.94–2.04 (m, 3 H, CH_2, C*H*), 2.38–2.52 (m, 3 H, CH_2, C*H*), 2.70–2.78 (m, 2 H, CH_2), 2.82–2.90 (m, 1 H, CH*H*), 3.77 (s, 3 H, OCH_3), 4.98–5.02 (m, 1 H, CH=CH*H*), 5.06–5.14 (m, 1 H, CH=C*H*H), 5.83 (ddd, J = 17.6, 10.4, 7.4 Hz, 1 H, C*H*=CH_2), 6.58–6.62 (m, 1 H, Ar-*H*), 6.70–6.75 (m, 1 H, Ar-*H*), 7.10–7.16 (m, 1 H, Ar-*H*), 7.23–7.29 (m, 3 H, 3 × Ar-*H*), 7.36–7.40 (m, 2 H, 2 × Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.80 (CH_2), 25.72 (CH_2), 27.13 (CH_2), 35.03 (CH_2), 40.99 (CH), 41.22 (CH), 55.14 (OCH_3), 80.99 (C≡C), 90.23 (C≡C), 112.15 (CH, Ar), 113.35

(CH, Ar), 114.36 (C=C), 123.99 (C, Ar), 127.51 (CH, Ar), 128.18 (2×CH, Ar), 130.04 (CH, Ar), 130.88 (C, Ar), 131.53 (2×CH, Ar), 137.98 (C, Ar), 142.09 (C=C), 157.45 (COMe, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2886, 1720, 1442, 1342, 1183, 1060, 1036, 987, 923, 857 cm^{-1}. MS (EI): *m*/*z* =316 (85) [M^+], 262 (40), 187 (100), 171 (20), 158 (25), 146 (30), 128 (25), 115 (65), 83 (45). HRMS (EI+): calcd. for $C_{20}H_{28}OSi$ 316.1827; found 316.1832. R_f (hexane/CH_2Cl_2, 1:1) = 0.6.

(±)-*anti*-6-Methoxy-1-[4-(4-methoxycarbonylphenyl)but-3-ynyl]-2-vinyl-1,2,3,4-tetrahydronaphthalene (5e): Methyl 4-iodobenzoate (1.1 mmol, 288 mg) was used. Column chromatography on silica gel (CH_2Cl_2) yielded the title compound as a colorless viscous liquid (298 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.72 (m, 1 H, C*H*H), 1.96–2.08 (m, 3 H, C*H*, CH_2), 2.34–2.54 (m, 3 H, C*H*, CH_2), 2.70–2.78 (m, 2 H, CH_2), 2.82–2.88 (m, 1 H, CH*H*), 3.77 (s, 3 H, OCH_3), 3.91 (s, 3 H, COOCH_3), 4.98–5.04 (m, 1 H, CH=CH*H*), 5.06–5.14 (m, 1 H, CH=C*H*H), 5.83 (ddd, *J* = 17.5, 10, 7.3 Hz, 1 H, C*H*=CH$_2$), 6.58–6.62 (m, 1 H, Ar-*H*), 6.70–6.76 (m, 1 H, Ar-*H*), 7.10–7.16 (m, 1 H, Ar-*H*), 7.40–7.46 (m, 2 H, 2×Ar-*H*), 7.92–7.98 (m, 2 H, 2×Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.80 (CH_2), 25.85 (CH_2), 27.21 (CH_2), 34.68 (CH_2), 41.01 (CH), 41.31 (CH), 52.12 (COO*C*H$_3$), 55.13 (OCH$_3$), 80.50 (C≡C), 93.76 (C≡C), 112.17 (CH, Ar), 113.38 (CH, Ar), 114.41 (C=C), 128.80 (C, Ar), 128.86 (C, Ar), 129.38 (2×CH, Ar), 129.92 (CH, Ar), 130.64 (C, Ar), 131.44 (2×CH, Ar), 138.03 (C, Ar), 142.03 (C=C), 157.49 (COMe, Ar), 166.63 (COOMe) ppm. IR (KBr): $\tilde{\nu}$ = 2956, 2887, 2170, 1757, 1720, 1441, 1247, 1182, 1061, 1035, 987, 923, 844 cm^{-1}. MS (EI): *m*/*z* (%)= 374.2 (100) [M^+], 345 (40), 320 (85), 261 (50), 187 (100), 158 (50), 146 (30), 128 (20), 115 (25), 91 (15). HRMS (EI+): calcd. for $C_{25}H_{26}O_3$ 374.1882; found 374.1878. R_f (hexane/CH_2Cl_2, 1:1) = 0.65.

(±)-*anti*-6-Methoxy-1-[4-(3-pyridyl)but-3-ynyl]-2-vinyl-1,2,3,4-tetrahydronaphthalene (5f): 3-Iodopyridine (1.1 mmol, 225 mg) was used. Column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1) yielded the title compound as a colorless viscous liquid (215 mg, 68%). ^1H NMR (400 MHz, C_6D_6): δ = 1.40–1.52 (m, 1 H, CH*H*), 1.70–1.80 (m, 1 H, C*H*), 1.85–1.93 (m, 2 H, CH_2), 2.21–2.32 (m, 3 H, C*H*, CH_2), 2.46–2.64 (m, 2 H, CH_2), 2.72–2.79 (m, 1 H, CH*H*), 3.38 (s, 3 H, OCH_3), 4.92–4.98 (m, 1 H, CH=CH*H*), 5.00–5.06 (m, 1 H, CH=C*H*H), 5.72 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1 H, C*H*=CH$_2$), 6.52–6.58 (m, 1 H, pyr-*H*), 6.60–6.62 (m, 1 H, Ar-*H*), 6.70–6.75 (m, 1 H, Ar-*H*), 7.00–7.04 (m, 1 H, Ar-*H*), 7.35–7.40 (m, 1 H, pyr-*H*), 8.32–8.38 (m, 1 H, pyr-*H*), 8.95 (br. s, 1 H, pyr-*H*) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 17.84 (CH_2), 27.19 (CH_2), 28.42 (CH_2), 35.90 (CH_2), 42.32 (CH), 42.71 (CH), 55.66 (OCH$_3$), 79.5 (C≡C), 94.97 (C≡C), 113.63 (CH, Ar), 114.89 (CH, Ar), 115.37 (C=C), 123.81 (CH, pyr), 122.21 (C, pyr), 131.12 (CH, Ar), 131.56 (C, Ar), 138.89 (C, Ar), 139.02 (CH, pyr), 143.27 (C=C), 149.41 (CH, pyr), 153.85 (CH, pyr), 159.25 (C, Ar) ppm. IR (KBr): $\tilde{\nu}$ = 3352, 2951, 2886, 2224, 1769, 1721, 1607, 1440, 1343, 1183, 1061, 1035, 989, 924, 858, 706 cm^{-1}. MS (EI): *m*/*z* (%) = 317.1 (100) [M^+], 263.1 (45), 187.1 (90), 158 (30), 146 (40), 128 (25), 115 (45), 103 (25), 91 (30), 77 (25). HRMS (EI+): calcd. for $C_{22}H_{23}NO$ 317.1780; found 317.1783. R_f (CH_2Cl_2/Et_2O, 20:1) = 0.25.

3-Bromobuta-1,2-diene (10): A solution of Br_2 (15.5 mmol, 2.5 g) in chloroethane (10 mL) was added dropwise to a stirred solution of 1-trimethylsilylbut-2-yne (16.2 mmol, 2 g)[2] in chloroethane (30 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. Then, silica gel (2 g) was added at –78 °C, and the suspension was filtered through silica gel (5 g). Chloroethane was allowed to evaporate at room temperature, and the residue was further purified by distillation under reduced pressure to yield the product as a colorless liquid (0.5 g, 24%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (t, *J* = 3.3 Hz, 3 H, CH_3), 4.79 (q, *J* = 3.3 Hz, 2 H, C=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.94 (CH_3), 80.54 (=CH_2), 87.42 (=CBrMe), 204.53 (=C=) ppm.

General Method for the Pauson–Khand Reaction: To a solution of enyne **5a**–**f** (1 mmol) in toluene (5 mL) was added $Co_2(CO)_8$ (1.3 mmol, 445 mg), and the reaction mixture was stirred at 20 °C for 4 h. Then, DMSO (5 mmol, 354 μL, 390 mg) was added, and the reaction mixture was stirred at 80 °C for 5 h. It was quenched with HCl (1%, 100 mL) and extracted with CH_2Cl_2 (3×15 mL); the combined organic fractions were dried with anhydrous $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel yielded the desired products.

(±)-3-Methoxy-16-ketoestra-1,3,5(10),13(17)-tetraene (11a): Enyne **5a** (1 mmol, 239 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 50:1) followed by recrystallization (MeOH) yielded the title compound as a colorless solid (254 mg, 95%). M.p. 114–115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.30 (m, 1 H, C*H*), 1.36–1.48 (m, 1 H, CH*H*), 1.52–1.66 (m, 1 H, CH*H*), 1.96–2.04 (m, 1 H, CH*H*), 2.12–2.22 (m, 1 H, CH*H*), 2.44–2.74 (m, 5 H, 2×C*H*, CH_2, CH*H*), 2.82–2.90 (m, 2 H, CH_2), 2.98–3.04 (m, 1 H, CH*H*), 3.78 (s, 3 H, OCH_3), 5.89 (s, 1 H, C=C*H*), 6.61–6.65 (m, 1 H, Ar-*H*), 6.71–6.77 (m, 1 H, Ar-*H*), 7.19–7.25 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.47 (CH_2), 30.11 (CH_2), 30.63 (CH_2), 31.58 (CH_2), 40.65 (CH_2), 41.75 (CH), 47.16 (CH), 48.06 (CH), 55.19 (OCH$_3$), 112.04 (CH, Ar), 113.72 (CH, Ar), 126.91 (CH, Ar), 127.04 (C=C), 130.50 (C, Ar), 137.86 (C, Ar), 157.72 (C, Ar), 183.15 (C=C), 208.81 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3014, 2952, 2933, 2865, 2854, 2836, 1699, 1674, 1616, 1498, 1449, 1434, 1278, 1256, 1198, 1145, 1045, 1027, 863, 845 cm^{-1}. MS (EI): *m*/*z* (%) = 268 (100) [M^+], 239 (10), 211 (10), 173 (35), 159 (15), 147 (30), 115 (20), 91 (15). HRMS (EI+): calcd. for $C_{18}H_{20}O_2$ 268.1463; found 268.1459. R_f (CH_2Cl_2/MeOH, 50:1) = 0.3.

(±)-3-Methoxy-17-methyl-16-ketoestra-1,3,5(10),13(17)-tetraene (11b): Enyne **5b** (1 mmol, 253 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 100:1) followed by recrystallization (MeOH) yielded the title compound as a colorless solid (247 mg, 88%). M.p. >220 °C (decomp.). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.20 (m, 1 H, C*H*), 1.30–1.42 (m, 1 H, CH*H*), 1.50–1.64 (m, 1 H, CH*H*), 1.72 (s, 3 H, CH_3), 1.96–2.04 (m, 1 H, CH*H*), 2.08–2.18 (m, 1 H, CH*H*), 2.32–2.44 (m, 1 H, C*H*), 2.44–2.52 (m, 1 H, CH*H*), 2.58–2.74 (m, 3 H, C*H*, 2×CH*H*), 2.82–2.88 (m, 2 H, CH_2), 2.98–3.08 (m, 1 H, CH*H*), 3.78 (s, 3 H, OCH_3), 6.62–6.64 (m, 1 H, Ar-*H*), 6.72–6.76 (m, 1 H, Ar-*H*), 7.21–2.25 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.68 (CH_3), 28.25 (CH_2), 28.52 (CH_2), 30.13 (CH_2), 31.22 (CH_2), 39.48 (CH_2), 42.10 (CH), 45.67 (CH), 47.92 (CH), 55.19 (OCH$_3$), 111.99 (CH, Ar), 113.70 (CH, Ar), 126.88 (CH, Ar), 130.79 (C, Ar), 133.15 (C=C), 137.98 (C, Ar), 157.67 (C, Ar), 174.17 (C=C), 208.87 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3013, 2936, 2858, 1690, 1694, 1607, 1498, 1447, 1264, 1148, 1042, 866, 819, 789 cm^{-1}. MS (EI): *m*/*z* (%) = 282.2 (100) [M^+], 253.1 (25), 219 (20), 173.1 (75), 159.1 (35), 147.1 (90), 115.1 (25). $C_{19}H_{22}O_2$ (282.38): calcd. C 80.82, H 7.85; found 81.05, H 8.13. HRMS (EI+): calcd. for $C_{19}H_{22}O_2$ 282.1620; found 282.1617. R_f (CH_2Cl_2/MeOH, 50:1) = 0.4.

(±)-3-Methoxy-17-trimethylsilyl-16-ketoestra-1,3,5(10),13(17)-tetraene (11c): Enyne **5c** (1 mmol, 312 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2) yielded the

title compound as a colorless viscous liquid (139 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 [s, 9 H, Si(CH_3)$_3$], 1.20–1.27 (m, 1 H, CH), 1.35–1.46 (m, 1 H, CH*H*), 1.53–1.64 (m, 1 H, CH*H*), 1.95–2.00 (m, 1 H, CH*H*), 2.07–2.15 (m, 1 H, CH*H*), 2.40–2.75 (m, 5 H, 2×C*H*, CH_2, CH*H*), 2.82–2.87 (m, 2 H, CH_2), 3.15–3.23 (m, 1 H, CH*H*), 3.78 (s, 3 H, OCH_3), 6.62–6.64 (m, 1 H, Ar-H), 6.70–6.76 (m, 1 H, Ar-H), 7.20–7.24 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = C), 137.88 (C, Ar), 157.69 (C, Ar), 189.96 (C=C), 212.12 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 2948, 2912, 2858, 2833, 1686, 1591, 1499, 1449, 1279, 1246, 1198, 1140, 1044, 841 cm^{-1}. MS (EI): *m*/*z* (%) = 340.2 (100) [M$^+$], 325.2 (90), 174.1 (45), 147.1 (35), 115 (20), 73 (70). HRMS (EI+): calcd. for $C_{21}H_{28}O_2Si$ 340.1859; found 340.1859. R_f (CH_2Cl_2) = 0.2.

(±)-3-Methoxy-17-phenyl-16-ketoestra-1,3,5(10),13(17)-tetraene (11d): Enyne **5d** (1 mmol, 315 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 100:1) followed by recrystallization (MeOH) yielded the title compound as a colorless solid (315 mg, 92%). M.p. 178–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.50 (m, 2 H, C*H*, CH*H*), 1.55–1.72 (m, 1 H, CH*H*), 2.01–2.10 (m, 1 H, CH*H*), 2.25–2.35 (m, 1 H, C*H*H), 2.46–2.57 (m, 1 H, C*H*), 2.62–2.95 (m, 6 H, 2×CH_2, C*H*, CH*H*), 3.18–3.27 (m, 1 H, CH*H*), 3.79 (s, 3 H, OCH_3), 6.63–6.67 (m, 1 H, Ar-*H*), 6.71–6.77 (m, 1 H, Ar-*H*), 7.19–7.24 (m, 1 H, Ar-*H*), 7.27–7.37 (m, 3 H, 3×Ph-*H*), 7.38–7.46 (m, 2 H, 2×Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.55 (CH_2), 28.94 (CH_2), 30.09 (CH_2), 31.50 (CH_2), 40.14 (CH_2), 41.95 (CH), 45.60 (CH), 48.08 (CH), 55.16 (OCH_3), 112.00 (CH, Ar), 113.70 (CH, Ar), 126.84 (CH, Ar), 127.67 (CH, Ph), 128.28 (2×CH, Ph), 129.23 (2×CH, Ph), 130.61 (C, Ar), 131.32 (C=C), 137.87 (C, Ar), 157.70 (C, Ar), 176.03 (C=C), 206.42 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3054, 2925, 2856, 2836, 1696, 1608, 1499, 1443, 1366, 1234, 1137, 1043, 698 cm^{-1}. MS (EI): *m*/*z* (%) = 344.1 (100) [M$^+$], 173 (60), 147 (80), 128 (30), 115 (50), 91 (25), 69 (40), 57 (50), 43 (55). HRMS (EI+): calcd. for $C_{24}H_{24}O_2$ 344.1776; found 344.1780. R_f (CH_2Cl_2/MeOH,100:1) = 0.5.

(±)-3-Methoxy-17-(4-methoxycarbonylphenyl)-16-ketoestra-1,3,5(10),13(17)-tetraene (11e): Enyne **5e** (1 mmol, 373 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 100:1) followed by recrystallization (MeOH) yielded the title compound as a colorless solid (336 mg, 84%). M.p. 182–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.50 (m, 2 H, C*H*, CH*H*), 1.60–1.72 (m, 1 H, CH*H*), 2.02–2.10 (m, 1 H, CH*H*), 2.28–2.36 (m, 1 H, CH*H*), 2.48–2.61 (m, 1 H, C*H*), 2.64–2.84 (m, 4 H, C*H*, CH_2, CH*H*), 2.84–2.92 (m, 2 H, CH_2), 3.15–3.22 (m, 1 H, CH*H*), 3.78 (s, 3 H, OCH_3), 3.93 (s, 3 H, COOCH_3), 6.62–6.66 (m, 1 H, Ar-*H*), 6.71–6.77 (m, 1 H, Ar-*H*), 7.18–7.24 (m, 1 H, Ar-*H*), 7.36–7.42 (m, 2 H, 2×Ar-*H*), 8.04–8.12 (m, 2 H, 2×Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.58 (CH_2), 29.05 (CH_2), 30.08 (CH_2), 31.52 (CH_2), 40.15 (CH_2), 41.94 (CH), 45.81 (CH), 48.15 (CH), 52.12 (COO*C*H$_3$), 55.19 (OCH_3), 112.05 (CH, Ar), 113.74 (CH, Ar), 126.84 (CH, Ar), 129.27 (2×CH, Ar), 129.54 (2×CH, Ar), 130.42 (C, Ar), 136.11 (C, Ar), 136.63 (C=C), 137.82 (C, Ar), 157.76 (C, Ar), 166.86 (COO), 177.33 (C=C), 205.77 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3001, 2930, 2857, 1719, 1695, 1607, 1497, 1433, 1285, 1108, 1031, 927, 776, 706 cm^{-1}. MS (EI): *m*/*z* (%) = 402 (45) [M$^+$], 344 (5), 256 (5), 173 (30), 147 (35), 97 (40), 83 (45), 69 (65), 55 (90), 43 (100). HRMS (EI+): calcd. for $C_{26}H_{26}O_4$ 402.1831; found 402.1838. R_f (CH_2Cl_2/MeOH, 100:1) = 0.3.

(±)-3-Methoxy-17-(3-pyridyl)-16-ketoestra-1,3,5(10),13(17)-tetraene (11f): Enyne **5f** (1 mmol, 316 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 50:1) followed by recrystallization (MeOH/petroleum ether) yielded the title compound as a colorless solid (302 mg, 88%). M.p. 48–51 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.61–0.72 (m, 1 H, C*H*), 0.87–0.99 (m, 1 H, CH*H*), 1.05–1.17 (m, 1 H, CH*H*), 1.42–1.50 (m, 1 H, CH*H*), 1.77–1.90 (m, 3 H, 2×CH*H*, C*H*), 2.10–2.20 (m, 2 H, C*H*, CH*H*), 2.27–2.37 (m, 1 H, CH*H*), 2.52–2.59 (m, 2 H, CH_2), 2.75–2.84 (m, 1 H, CH*H*), 3.41 (s, 3 H, OCH_3), 6.64–6.68 (m, 1 H, Ar-*H*), 6.76–6.80 (m, 1 H, Ar-*H*), 6.88–6.98 (br. s, 1 H, pyr-*H*), 6.98–7.03 (m, 1 H, Ar-*H*), 7.72–7.79 (m, 1 H, pyr-*H*), 8.50–9.00 (br. d, 2 H, 2×pyr-*H*) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 29.29 (CH_2), 29.47 (CH_2), 30.87 (CH_2), 32.11 (CH_2), 40.62 (CH_2), 42.57 (CH), 46.18 (CH), 48.31 (CH), 55.46 (OCH_3), 113.00 (CH, Ar), 114.76 (CH, Ar), 127.75 (CH, Ar), 131.51 (C, Ar), 134.79 (C=C), 137.26 (CH, pyr), 138.56 (C, Ar), 159.15 (C, Ar), 176.39 (C=C), 204.81 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2951, 2921, 2858, 1702, 1692, 1608, 1501, 1414, 1252, 1237, 1141, 1043, 927, 808, 713 cm^{-1}. MS (EI): *m*/*z* (%) = 345 (100) [M$^+$], 316 (10), 175 (45), 159 (10), 147 (35), 115 (5). HRMS (EI+): calcd. for $C_{23}H_{23}O_2N$ 345.1729; found 345.1729. R_f (CH_2Cl_2/MeOH, 50:1) = 0.4.

General Method for Cyclocarbonylation with Cp_2ZrBu_2 (Negishi Protocol): *n*BuLi (2.1 mmol, 1.36 mL, 1.6 M in hexanes) was added to a stirred solution of Cp_2ZrCl_2 (1.05 mmol, 306 mg) in THF (10 mL) at –78 °C. After 1 h, enyne **5b**–**c** (1 mmol) in THF (1 mL) was added, and the reaction mixture was warmed gradually to 20 °C, after 2 h followed by CO bubbling through the reaction mixture for 20 min at 20 °C. Then, it was quenched with HCl (1%, 30 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried with anhydrous $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel yielded the desired products.

(±)-3-Methoxy-17-methyl-16-ketoestra-1,3,5(10),13(17)-tetraene (11b): Enyne **5b** (1 mmol, 253 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 100:1) yielded the title compound as a colorless solid (87 mg, 31%).

(±)-3-Methoxy-17-trimethylsilyl-16-ketoestra-1,3,5(10),13(17)-tetraene (11c): Enyne **5c** (1 mmol, 312 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2) yielded the title compound as a colorless viscous liquid (196 mg, 58%).

(±)-3-Methoxy-17-methylestra-1,3,5(10),13(17)-tetraene (4): To a solution of $LiAlH_4$ (0.6 mmol, 23 mg) in Et_2O (2 mL) was added $AlCl_3$ (2.4 mmol, 319 mg) at 20 °C. The resulting suspension was stirred for 15 min at 20 °C, and then it was left to stand for 10 min, allowing the insoluble materials to deposit. The solution was separated and added dropwise to a solution of **11b** (0.5 mmol, 140 mg) in Et_2O (8 mL) at –10 °C. The reaction mixture was then stirred at 20 °C for 30 min followed by quenching with HCl (5%, 3 mL). Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×15 mL) and dried with anhydrous $MgSO_4$, and the volatiles were removed under reduced pressure. Filtration over a short pad of silica gel (5 g) in CH_2Cl_2 yielded the title compound as a colorless solid (126 mg, 95%). Spectral characteristics were in agreement with the previously reported data.[20] R_f (CH_2Cl_2/hexane, 2:1) = 0.6.

Supporting Information (see footnote on the first page of this article): Synthetic procedures, experimental details, and copies of the ^{1}H and ^{13}C of spectra.

Acknowledgments

This work was supported by the Ministry of Education of the Czech Republic (grant project 1M0508 and MSM0021620857). The authors would like to thank to Dr. Jana Roithová for calculation of the structure presented in Figure 1.

[1] For historical sketches, see: a) A. Butenandt, *Trends Biochem. Sci.* **1979**, *4*, 216–217; b) K. C. Nicolaou, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**; c) T. Hudlický, J. W. Reed in *The Way of Synthesis*, Wiley-VCH, Weinheim, **2007**.
[2] R. E. Marker, *J. Am. Chem. Soc.* **1938**, *60*, 1897–1980.
[3] W. E. Bachmann, S. Kushner, A. C. Stevenson, *J. Am. Chem. Soc.* **1942**, *64*, 974–981.
[4] a) G. Annu, K. Miescher, *Helv. Chim. Acta* **1948**, *31*, 2173–2183; b) W. S. Johnson, D. K. Banerje, W. P. Schneider, C. D. Gutsche, *J. Am. Chem. Soc.* **1950**, *72*, 1426–1427.
[5] a) T. B. Windholz, J. H. Fried, A. Patchett, *J. Org. Chem.* **1963**, *28*, 1092–1094; b) S. N. Ananchenko, I. V. Torgov, *Tetrahedron Lett.* **1963**, *4*, 1553–1558; c) C. H. Kuo, D. Taub, N. L. Wendler, *J. Org. Chem.* **1968**, *33*, 3126–3132; d) S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.
[6] T. Sugahara, K. Ogasawara, *Tetrahedron Lett.* **1996**, *37*, 7403–7407.
[7] a) H. Nemoto, M. Nagai, M. Mouzuji, K. Konzuli, K. Fukumoto, T. Kametani, *J. Am. Chem. Soc.* **1976**, *98*, 3378–3379; b) P. A. Grieco, T. Takigawa, W. J. Schillinger, *J. Org. Chem.* **1980**, *45*, 2247–2251.
[8] G. Pattenden, M. A. Gonzales, S. McCullogh, A. Walter, S. J. Woodhead, *Proc. Natl. Acad. Sci.* **2004**, *101*, 12024–12029.
[9] a) T. A. Brusin, C. J. Reichel, *Tetrahedron Lett.* **1980**, *21*, 2381–2384; b) A. R. Daniewski, T. Kowalczyk-Przewloka, *Tetrahedron Lett.* **1982**, *23*, 2411–2414; c) J. H. Hutchinson, T. Money, *Tetrahedron Lett.* **1985**, *26*, 1819–1822.
[10] G. Quinkert, W.-D. Weber, U. Schwarz, G. Dürner, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 1027–1029.
[11] a) Q.-Y. Hu, P. D. Rege, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 5984–5989; b) E. Cannales, E. J. Corey, *Org. Lett.* **2008**, *10*, 3271–3273.
[12] N. Cohen, B. L. Banner, W. F. Ráchel, D. R. Parrish, G. Saucy, J.-M. Casnal, W. Meier, A. Fürst, *J. Org. Chem.* **1975**, *40*, 681–685.
[13] a) R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 5253–5261; b) S. H. Lecker, N. H. Nguyen, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 856–858.
[14] D. F. Taber, K. Raman, M. D. Gaul, *J. Org. Chem.* **1987**, *52*, 28–34.
[15] P. Kočovský, R. S. Baines, *Tetrahedron Lett.* **1993**, *34*, 6139–6140.
[16] a) L. F. Tietze, T. Nöbel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977; b) L. F. Tietze, M. Wiegand, C. Vock, *J. Organomet. Chem.* **2003**, *687*, 346–352.
[17] D. Soorukam, P. Knochel, *Org. Lett.* **2007**, *9*, 1021–1023.
[18] K. Hanada, N. Miyazawa, K. Ogasawara, *Chem. Pharm. Bull.* **2003**, *51*, 104–106.
[19] a) P. Herrmann, M. Kotora, M. Buděšínský, D. Šaman, I. Císařová, *Org. Lett.* **2006**, *8*, 1315–1318; b) P. Herrmann, M. Buděšínský, M. Kotora, *Chem. Lett.* **2007**, *36*, 1268–1269; c) P. Herrmann, M. Buděšínský, M. Kotora, *J. Org. Chem.* **2008**, *73*, 6202–6206; d) P. Herrmann, M. Kotora, *Tetrahedron Lett.* **2007**, *48*, 3209–3212.
[20] P. A. Bartlett, W. S. Johnson, *J. Am. Chem. Soc.* **1973**, *95*, 7501–7502.
[21] M. Okutani, Y. Mori, *Tetrahedron Lett.* **2007**, *48*, 6856–6859.
[22] A. J. Quillinan, F. Scheinmann, *Org. Synth.* **1978**, *58*, 595–597 and references cited therein.
[23] For reviews, see: a) J. Claydon, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, **2002**, ch. 7, pp. 273–336; b) J. F. Normant, *Top. Organomet. Chem.* **2003**, *5*, 287–310; c) K. Tomooka, M. Ito in *Main Group Metals in Organic Synthesis* (Eds.: H. Yamamoto, K. Oshima), Wiley-VCH, Weinheim, **2004**, ch. 1, pp. 1–34.
[24] E. M. Arnett, K. D. Moe, *J. Am. Chem. Soc.* **1991**, *113*, 7068–7069.
[25] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630; c) S. Thorand, N. Krause, *J. Org. Chem.* **1998**, *63*, 8551–8553.
[26] F. Sato, H. Kodama, M. Sato, *Chem. Lett.* **1978**, 789–790.
[27] R. C. Larock, M.-S. Chow, *Organometallics* **1986**, *5*, 603–604.
[28] S. Iyer, L. S. Liebeskind, *J. Am. Chem. Soc.* **1987**, *109*, 2759–2770.
[29] a) T. Flood, P. E. Peterson, *J. Org. Chem.* **1980**, *45*, 5006–5007; b) E. J. Corey, J. Kang, *J. Am. Chem. Soc.* **1981**, *103*, 4618–4619; c) for an alternative procedure, see: E. J. Corey, B. De, *J. Am. Chem. Soc.* **1984**, *106*, 2735–2736.
[30] a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc. Perkin Trans. 1* **1973**, 975–977; b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Forman, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977–981.
[31] For reviews, see: a) K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263–3283; b) S. E. Gibson, A. Stevenazzi, *Angew. Chem.* **2003**, *116*, 1844–1854; *Angew. Chem. Int. Ed.* **2003**, *42*, 1800–1810; c) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2004**, 3377–3383; d) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. J. Perez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32–42; e) S. E. Gibson, N. Mainolfi, *Angew. Chem.* **2005**, *117*, 3082–3097; *Angew. Chem. Int. Ed.* **2005**, *44*, 3022–3037; f) S. Laschat, A. Becheanu, T. Bell, A. Baro, *Synlett* **2005**, 2547–2570; g) T. Shibata, *Adv. Synth. Catal.* **2006**, *348*, 2328–2336; h) T. Kondo, *Synlett* **2008**, 629–644.
[32] R. Skoda-Földes, L. Kollár, *Chem. Rev.* **2003**, *103*, 4095–4129.
[33] D. H. Kim, K. Kim, Y. K. Chung, *J. Org. Chem.* **2006**, *71*, 8264–8267.
[34] N. Jeong, S. J. Lee, B. Y. Lee, Y. C. Chung, *Tetrahedron Lett.* **1993**, *34*, 4027–4030.
[35] For reviews, see: a) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580–5588; b) T. Shibata, *Adv. Synth. Catal.* **2006**, *348*, 2328–2336.
[36] T. Morimoto, K. Fuji, K. Tsutsumi, K. Kakiuchi, *J. Am. Chem. Soc.* **2002**, *124*, 3806–3807.
[37] a) E. Negishi, F. E. Cederbaum, T. Takahashi, *Tetrahedron Lett.* **1986**, *27*, 2829–2832; b) E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. S. Swanson, T. Takahashi, *J. Org. Chem.* **1989**, *111*, 3336–3346. For reviews, see: c) E. Negishi in *Comprehensive Organic Synthesis* (Eds: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 5, pp. 1063–1084; d) I. Marek (Ed.), *Titanium and Zirconium in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; e) E. Negishi, *Dalton Trans.* **2005**, 827–848.
[38] P. Magnus, M. J. Waring, C. Ollivier, V. Lynch, *Tetrahedron Lett.* **2001**, *42*, 4947–4950.
[39] M. V. Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647–9662.
[40] W. Zhang, C. Wang, W. Gao, X. Zhang, *Tetrahedron Lett.* **2005**, *46*, 6087–6090.
[41] For a review, see: S. Yamamura, S. Nishiyama in *Comprehensive Organic Synthesis* (Eds: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 8, pp. 313–319.
[42] a) J. L. Fry, M. Orfanopoulos, M. G. Adlington, W. R. Dittman Jr., S. B. Silverman, *J. Org. Chem.* **1978**, *43*, 374–375; b) O. D. Dailey Jr., *J. Org. Chem.* **1987**, *52*, 1984–1989.
[43] L. Caglioti, *Org. Synth.* **1988**, *6*, 62–63 (collective volume).
[44] a) B. R. Brown, A. M. S. White, *J. Chem. Soc.* **1957**, 3755–3757; b) P. A. Jacobi, R. F. Frechette, *Tetrahedron Lett.* **1987**, *28*, 2937–2940.
[45] a) J. H. Brewster, H. O. Bayer, *J. Org. Chem.* **1964**, *29*, 116–121; b) J. H. Brewster, J. E. Privett, *J. Am. Chem. Soc.* **1966**, *88*, 1419–1424; c) M. P. Cava, K. Narasimhan, *J. Org. Chem.* **1969**, *34*, 3641–3642; d) L. A. Paquette, R. E. Maleczka Jr., *J. Org. Chem.* **1992**, *57*, 7118–7122.
[46] a) W. Oppolzer, R. Pitteloud, H. F. Strauss, *J. Am. Chem. Soc.* **1982**, *104*, 6476–6477; b) for a review, see: W. Oppolzer in *Comprehensive Organic Synthesis* (Eds: B. M. Trost, I. Flemming),

Pergamon Press, Oxford, **1991**, vol. 5, pp. 29–61 and references cited therein.
[47] a) W. Oppolzer, F. Schröder, *Tetrahedron Lett.* **1994**, *35*, 7939–7942; b) W. Oppolzer, B. Stammen, *Tetrahedron* **1997**, *53*, 3577–3586; c) W. Oppolzer, F. Flachsmann, *Tetrahedron Lett.* **1998**, *39*, 5019–5022; d) W. Oppolzer, F. Flachsmann, *Helv. Chim. Acta* **2001**, *84*, 416–430; e) J. M. Chalker, A. Yang, K. Deng, T. Cohen, *Org. Lett.* **2007**, *9*, 3825–3828.

Received: August 17, 2009
Published Online: December 18, 2009

