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Synthesis of Novel Structurally Simplified Estrogen Analogues

Lutz F. Tietze,*[a] Carsten A. Vock,[a] Ilga K. Krimmelbein,[a] J. Matthias Wiegand,[a] Linda Nacke,[a] Tokala Ramachandar,[a] Kazi M. D. Islam,[b] and Christiane Gatz[b]

Abstract: A library of 17 novel estrogen analogues **3** and **4** containing different substituents at rings A and D (steroid nomenclature) was prepared in a five- to seven-step synthesis. The key transformation is a Sonogashira-coupling of cyclic vinyl iodides of type **7** or **8** with phenylacetylenes of type **9**. Reduction of the keto function in **3** led to the estradiol analogue **5**.

Keywords: alkynes · estrogens · palladium · Sonogashira reaction · steroids · vinyl halides

Introduction

Steroids play very important roles in medicinal therapy of different diseases. Among them, estrogens—for example, naturally occurring estrone **1** and 17β-estradiol **2** (Scheme 1)—and their derivatives are of particular interest. While they were recognized as sexual hormones quite early, more recent investigations have shown a much broader spectrum of biological activity of estrogens, underlining the fundamental importance of these hormones in mammalian, especially human, organisms. Thus, they have been identified to display a beneficial effect on blood vessels and the coronary heart system, being responsible for a significantly lower risk of arteriosclerotic diseases and therefore on average increased life expectancies in women.[1,2] In addition, long-term application of estrogens has been shown to induce coronary vessel relaxation in mammalian studies[3] and in women during postmenopausal hormone displacement therapy.[4] However, the discovery of severe long-term side effects[5]—the induction of estrogen-dependent cancers such as mamma carcinoma, for example—has led to a reduction in their application.

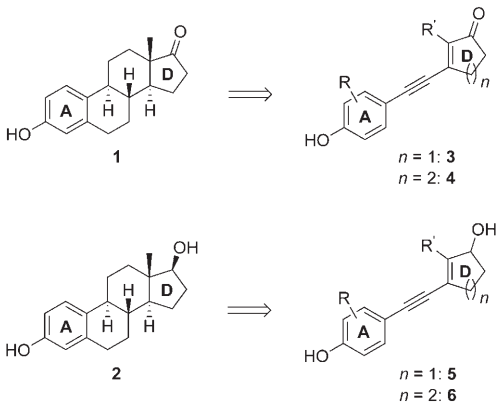
[a] Prof. Dr. L. F. Tietze, Dr. C. A. Vock, Dr. I. K. Krimmelbein, Dr. J. M. Wiegand, Dipl.-Chem. L. Nacke, T. Ramachandar
Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399476
E-mail: ltietze@gwdg.de

[b] Dr. K. M. D. Islam, Prof. Dr. C. Gatz
Albrecht-von-Haller-Institut für Pflanzenwissenschaften der Georg-August-Universität Göttingen
Untere Karspüle 2, 37073 Göttingen (Germany)

Several mechanisms for the estrogen-induced vessel relaxation have been discussed. A genomic long-term effect might be the increased expression of important vasodilatory enzymes such as prostacyclin- or NO-synthase. Nongenomic effects might include the direct stimulation of NO-synthase by estrogen binding to membrane-bound known[6] or unknown[6,7] estrogen receptors or the interaction of estrogen with ion channels located in endothelial smooth muscle cells.[8] In this context, the findings of Valverde et al.[9] that 17β-estradiol (**2**) influences the opening of the $BK_{Ca^{2+}}$ channels by binding to their extracellularly located β-subunits have attracted much attention. The design of new estrogen analogues that selectively interact with the β-subunits of the $BK_{Ca^{2+}}$ channels—four β-subunits (β1–β4) expressed in different tissues are known[10,11]—is therefore of great importance.

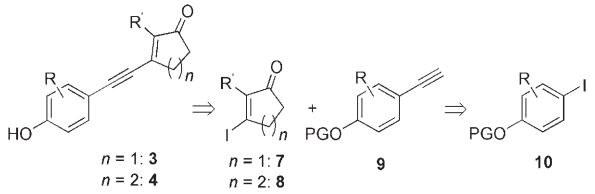
Many elegant syntheses of the characteristic steroidal framework and of steroid analogues have been published in the last decades.[12] A highly efficient synthesis of enantiopure estradiol by means of a double Heck reaction has been developed in our group and has also recently been applied to the synthesis of desogestrel.[13] Moreover, we have prepared estradiol derivatives of modified B-ring size, in line with the assumption that the interaction of estrone (**1**) and estradiol (**2**) with the corresponding receptors mainly occurs with participation of the oxygen functionalities at C-3 and C-17 and that the steroidal activity might be adjustable through changing the intramolecular O–O distance.[13] However, the enantioselective synthesis of estradiol derivatives is still a challenging task, and for practical reasons research is focusing more and more on easily accessible nonsteroidal SERMs (selective estrogen receptor modulators) with as few stereogenic centers as possible.[14,15]

Here we present a new class of structurally simplified nonsteroidal estrone and estradiol analogues **3**–**6** based on the assumption that the B- and C-ring system of the steroidal framework can be completely removed if the steric rigidity is conserved by a suitable spacer: in our case an alkyne moiety (Scheme 1). It was further anticipated that



Scheme 1. Novel estrogen analogues **3**–**6** based on estrone (**1**) and 17β-estradiol (**2**).

the lack of steric demand due to the loss of the bulky ring systems B and C might be partly compensated by introduction of suitable substituents R at the rings A and D (steroid nomenclature).[16] For the synthesis of **3** and **4**, retrosynthetic analysis prompted us to use Sonogashira reactions between the cyclic vinyl iodides **7** or **8** and the phenylacetylenes **9** (Scheme 2). Compounds **7** and **8** were synthesized from the

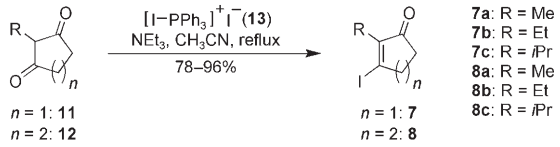


Scheme 2. Retrosynthetic analysis of **3** and **4**.

corresponding substituted 1,3-cycloalkanediones by known literature methods,[16] and phenylacetylenes **9** were prepared from halogenated benzene derivatives **10**, again by use of Sonogashira reactions.

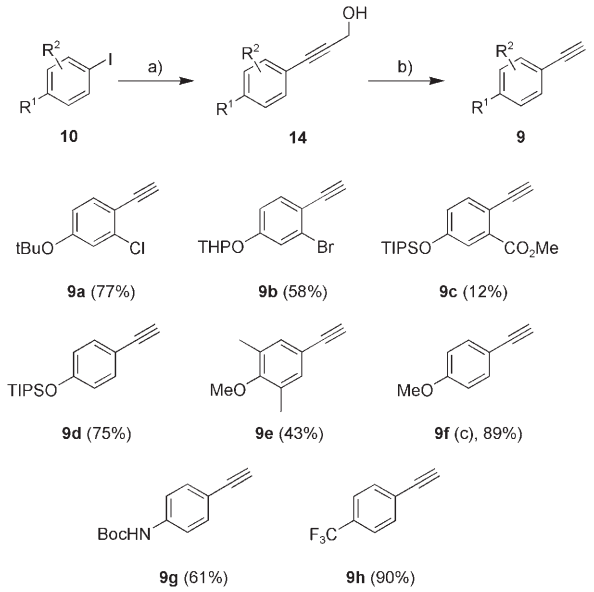
Results and Discussion

The synthesis of the required cyclic vinyl iodides **7** and **8** was carried out according to a procedure published by Piers et al.[16] by treatment with **13**, which was prepared in situ from PPh_3 and I_2. Heating of **13** with the alkylated 1,3-cycloalkanediones **11a**–**c** and **12a**–**c**, which were either commercially available or synthesized by known literature procedures,[17] in CH_3CN in the presence of NEt_3 at reflux gave the desired compounds **7a**–**c** and **8a**–**c** in very good yields (Scheme 3).



Scheme 3. Synthesis of **7a**–**c** and **8a**–**c**.

For the synthesis of phenylacetylenes **9** the iodobenzene derivatives **10** were transformed into the corresponding phenylpropargyl alcohol derivatives **14** by means of Sonogashira reactions with propargyl alcohol followed by oxidative elimination of the CH_2OH groups under basic conditions (Scheme 4). For the Sonogashira reactions we used [Pd-$(PPh_3)_2Cl_2$] and CuI in iPr_2NH or DMF, while the oxidative cleavage of compounds **14** was performed with an excess of activated MnO_2 and KOH powder in Et_2O or Et_2O/CH_2Cl_2 in 12–90% yields.



Scheme 4. Synthesis of phenylacetylenes **9**: a) propargyl alcohol, [Pd-$(PPh_3)_2Cl_2$], CuI, iPr_2NH, RT; b) MnO_2, KOH powder, Et_2O, RT; c) Pd-$(OAc)_2$ as catalyst.

As protecting groups for the phenolic compounds **9a**–**f** we used *tert*-butyl and methyl ethers, as well as the THP and the TIPS groups. In addition to compounds **9a**–**f**, possessing OR substituents, we also prepared the compounds **9g** and **9h**, containing a NHBoc and a CF_3 group, respectively. The necessary iodophenols **10** used as starting material for the synthesis of **9a**–**f** were either commercially available or were prepared from the corresponding anilines through Sandmeyer reactions. The protection of the phenolic hydroxy groups was carried out by standard methods; commer-

cially available 4-bromo-2,5-dimethylanisole and 4-iodoanisole were used for the synthesis of phenylacetylenes **9e** and **9f**. The phenylacetylenes **9g** and **9h** were synthesized from the corresponding commercially available iodo derivatives.

The synthesis of the target compounds **3** and **4** was accomplished through Sonogashira reactions between the cyclic vinyl iodides **7** or **8** and the phenylacetylenes **9** to give the protected estrone analogues **3** and **4** (Table 1). Since the vinyl iodide functionalities in **7** and **8** are rather sensitive to reactions with nucleophiles, the coupling was carried out under very mild conditions, by a procedure by Tamura et al.[18] with an excess of the tertiary amine NEt_3 as base in DMF as solvent and $[Pd(PPh_3)_2Cl_2]$ (1.0–2.5 mol%) and CuI (2.5–5.0 mol%) as catalyst system.

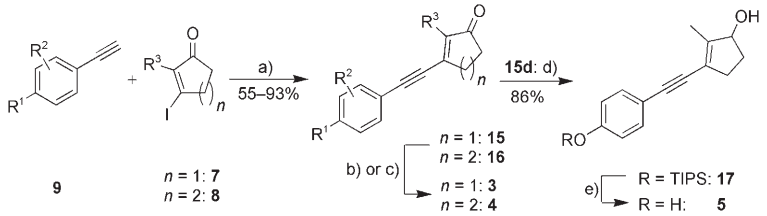
In most cases the reaction was exothermic; however, to start the transformation, the mixture was heated slightly to 50–60°C. The subsequent deprotection of the phenolic hydroxy group was performed under standard conditions. The THP acetals and the *tert*-butyl ethers, as well as compounds **15e** and **16g**, each containing a *N*-Boc-protected amino group, were stirred at room temperature in a solution of CH_2Cl_2 containing 10–30% of CF_3COOH, while the TIPS protecting group was removed with nBu$_4$NF·3H$_2$O in THF to give the estrone analogues **3d**, **4d** and **4e** (Table 1). However, the cleavage of the methoxy group was less successful. Here we variously used BBr_3 in CH_2Cl_2 (alone or with addition of K_2CO_3 as acid scavenger), $[NMe_4]^+[Al_2Cl_7]^-$ in CH_2Cl_2 under microwave irradiation conditions,[19] and BF_3·Et_2O in Me_2S. In all cases addition reactions at the triple bond were observed, and the obtained complex mixtures could not usually be separated. Compound **3f** was obtained from **15f** in 33% yield by treatment with BBr_3 in CH_2Cl_2 with subsequent purification by preparative reversed-phase HPLC.

A comparison of the different protecting groups at the phenolic hydroxy group showed that the THP group has by far the best properties wit regard to introduction, stability, and removal. The other tested protecting groups each had at least one disadvantage. The methyl protecting group was easy to introduce and showed perfect stability, but its cleavage was problematic. The *t*Bu group was nearly as stable as a methyl group under reaction conditions while being easily removable, but its introduction turned out to be quite difficult.

The *t*Boc group was used for the protection of the NH_2 group as a carbamate in **9g** and the following Sonogashira reaction coupling could be performed without any difficulties.

Finally, we also reduced the keto groups in the estrone analogues to give estradiol analogues **5** and **6**. As an example we performed a selective reduction of the TIPS-protected **15d** under Luche conditions[20] with $NaBH_4$ and $CeCl_3$ in MeOH at room temperature to give the allylic alcohol **17** in 86% yield. Subsequent removal of the TIPS group was carried out under mild conditions with CsF in CH_3CN,[21] and the desired estradiol analogue **5** was obtained in 57% yield after chromatography on silica gel with small amounts of NEt_3 to remove traces of acid. Compound **5**, containing an allylic alcohol moiety, turned out to be rather unstable in pure form, however, decomposing quite rapidly at room temperature and only being stable for a longer time when stored at −28°C. The allylic alcohols **5** and **6** are thus not suitable as estradiol analogues due to their instability and no further investigations were performed with these compounds.

Table 1. Synthesis of steroid analogues **3**, **4** and **5** from **7** or **8** and **9**, via **15** and **16**. Reagents and conditions: a) $[Pd(PPh_3)_2Cl_2]$, CuI, NEt_3, DMF, RT; b) CF_3COOH, CH_2Cl_2, RT; c) nBu$_4$NF·3H$_2$O, THF, 0°C to RT; d) $NaBH_4$, $CeCl_3$·7H$_2$O, MeOH/Et_2O, RT, 4 h, 86%; e) CsF, CH_3CN, 0°C to RT, 18.5 h, 57%.



Entry	n	Starting material	Substituents on ring A	Substituents on ring D		Products	Yield [%] (*: over two steps)
1	1	**7a**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=Me	**15a/3a**	76*
2	1	**7b**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=Et	**15b/3b**	70*
3	1	**7c**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=*i*Pr	**15c/3c**	75*
4	1	**7a**, **9d**	R^1=OTIPS$\xrightarrow{c)}$$R^1$=OH		R^5=Me	**15d/3d**	85*
5	1	**7a**, **9g**	R^1=NHBoc$\xrightarrow{b)}$$R^1$=$NH_2$		R^5=Me	**15e/3e**	87*
6	1	**7a**, **9f**	R^1=OMe		R^5=Me	**15f**	93
7	1	**7a**, **9e**	R^1=OMe	R^2=3-Me, 5-Me	R^5=Me	**15g**	86
8	1	**7a**, **9h**	R^1=CF_3		R^5=Me	**15h**	85
9	2	**8a**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=Me	**16a/4a**	76*
10	2	**8b**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=Et	**16b/4b**	55*
11	2	**8c**, **9a**	R^1=O*t*Bu$\xrightarrow{b)}$$R^1$=OH	R^2=2-Cl	R^5=*i*Pr	**16c/4c**	60*
12	2	**8a**, **9d**	R^1=OTIPS$\xrightarrow{c)}$$R^1$=OH		R^5=Me	**16d**[a]/**4d**	84*
13	2	**8a**, **9c**	R^1=OTIPS$\xrightarrow{c)}$$R^1$=OH	R^2=2-CO_2Me	R^5=Me	**16e/4e**	47*
14	2	**8a**, **9b**	R^1=OTHF$\xrightarrow{b)}$$R^1$=OH	R^2=Br	R^5=Me	**16f**[a]/**4f**	57*
15	2	**8a**, **9g**	R^1=NHBoc$\xrightarrow{b)}$$R^1$=$NH_2$		R^5=Me	**16g/4g**	41*
16	2	**8a**, **9f**	R^1=OMe		R^5=Me	**16h**	74
17	2	**8a**, **9e**	R^1=OMe	R^2=3-Me, 5-Me	R^5=Me	**16i**	82

[a] Compounds **16d** and **16f** were not isolated, but were directly subjected to deprotection.

Conclusion

A library of 17 novel estrone analogues **3** and **4** was synthesized from phenylacetylenes **9** and cyclic vinyl iodides **7** or **8** through palladium-catalyzed Sonogashira reactions in five to seven synthetic steps starting from commercially available materials. The compounds are

highly stable solids and a large variety of substitution patterns has been produced. Selective reduction of the keto functionality of TIPS-protected **15d** and subsequent deprotection gave the estradiol analogue **5**, but this lacks sufficient stability. The evaluation of the biological properties of the new compounds with regard to their steroidal activities is currently underway.

Experimental Section

General methods: All reactions were performed under argon in flame-dried flasks. THF and Et_2O were dried and distilled prior to use by usual laboratory methods, while all other solvents were used from commercial sources and stored over molecular sieves; Petrol ether (PE) b.p. range 35–75 °C. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SILG/UV254 plates (Macherey–Nagel), and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Vanillin in methanolic sulfuric acid was used as a staining reagent for TLC. UV spectra were taken in CH_3CN or MeOH with a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films between NaCl plates with a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Mercury 200, VXR 200, Unity 300, Inova 500, Unity Inova 600 (Varian), or AMX 300 (Bruker) spectrometers. Chemical shifts are reported in ppm with tetramethylsilane (TMS) or the solvent as internal standard. Multiplicities of ^{13}C NMR peaks were determined by use of the APT pulse sequence. Mass spectra were measured with Finnigan MAT 95, TSQ 7000, or LCQ instruments. Elemental analysis: Mikroanalytisches Labor, Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), sept. (septet), m (multiplet), br (broad), and combinations thereof.

General Procedure A—Synthesis of vinyl iodides 7 and 8: I_2 was added at room temperature to a stirred solution of PPh_3 in CH_3CN, and stirring was continued for 15 min, after which NEt_3 (15.0 mL, 11.0 g, 108 mmol) was added. After another 5 min of stirring the 1,3-dione **11** or **12** was added and the solution was heated to reflux. After completion of the reaction the solvent was evaporated in vacuo, the residue was dissolved in Et_2O (10 mL mmol^{-1}), the mixture was stirred, and the solvent was decanted. This procedure was repeated three times. The combined organic layers were filtered over SiO_2 with the aid of Et_2O and the solvent was then evaporated in vacuo to give the vinyl iodides **7a–c** and **8a–c**.

3-Iodo-2-methylcyclopent-2-en-1-one (7a): The title compound was synthesized according to General Procedure A by use of PPh_3 (11.5 g, 44.0 mmol) in CH_3CN (400 mL), I_2 (11.7 g, 46.0 mmol), NEt_3 (6.50 mL, 4.75 g, 46.9 mmol), and 2-methylcyclopentane-1,3-dione (4.48 g, 40.0 mmol). The mixture was heated for 6 h at 80–90 °C. Workup and filtration gave **7a** as a yellowish white solid (8.50 g, 38.3 mmol, 96 %). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.80$ (t, $J = 2.2$ Hz, 3H; 2-CH_3), 2.48–2.55 (m, 2H; 5-H_2), 2.99 ppm (tq, $J = 4.7$, 2.3 Hz, 2H; 4-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 12.91$ (2-CH_3), 36.45 (C-5), 39.02 (C-4), 133.8 (C-3), 147.8 (C-2), 202.6 ppm (C-1); HRMS (EI$^+$): m/z: calcd for C_6H_7IO: 221.9542 $[M]^+$; found: 221.9542.

2-Ethyl-3-iodocyclopent-2-en-1-one (7b): The title compound was synthesized according to General Procedure A by use of PPh_3 (11.4 g, 43.4 mmol), I_2 (11.6 g, 45.6 mmol), NEt_3 (6.50 mL, 4.75 g, 46.9 mmol), and 2-ethylcyclopentane-1,3-dione (5.00 g, 39.6 mmol) in CH_3CN (400 mL). The mixture was heated for 8 h at reflux. Workup and filtration gave **7b** as a yellow oil (8.66 g, 36.7 mmol, 93 %). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.5$ Hz, 3H; 2-CH_2CH_3), 2.27 (tq, $J = 7.5$ Hz, 1.0 Hz, 2H; 2-CH_2CH_3), 2.51 (m, 2H; 5-H_2), 2.96–3.02 ppm (m, 2H; 4-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 11.74$ (2-CH_2CH_3), 20.91 (2-CH_2CH_3), 36.77 (C-5), 39.08 (C-4), 133.1 (C-3), 152.4 (C-2), 202.3 ppm (C-1); HRMS (EI$^+$): m/z: calcd for C_7H_9IO: 235.9698 $[M]^+$; found: 235.9696.

3-Iodo-2-isopropylcyclopent-2-en-1-one (7c): The title compound was synthesized according to General Procedure A by use of PPh_3 (10.3 g, 39.2 mmol), I_2 (10.5 g, 41.3 mmol), NEt_3 (5.90 mL, 4.31 g, 42.6 mmol), and 2-isopropylcyclopentane-1,3-dione (5.00 g, 35.7 mmol) in CH_3CN (400 mL). The mixture was heated for 15 h at reflux. Workup and filtration gave **7c** as light yellow crystals (6.96 g, 27.8 mmol, 78 %). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 7.0$ Hz, 6H; 2-CH(CH_3)$_2$), 2.47 (m, 2H; 5-H_2), 2.82 (sept., $J = 7.0$ Hz, 1H; 2-CH(CH_3)$_2$), 2.97 ppm (m, 2H; 4-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 19.15$ (2-CH(CH_3)$_2$), 30.19 (2-CH-(CH_3)$_2$), 37.52 (C-4), 39.56 (C-5), 132.5 (C-3), 154.0 (C-2), 201.9 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_8H_{11}IO$: 249.9855 $[M]^+$; found: 289.9850.

3-Iodo-2-methylcyclohex-2-en-1-one (8a): The title compound was synthesized according to General Procedure A by use of PPh_3 (27.04 g, 103 mmol) in CH_3CN (750 mL), I_2 (27.17 g, 107 mmol), NEt_3 (15.0 mL, 11.0 g, 108 mmol), and 2-methylcyclohexane-1,3-dione (10.0 g, 79.3 mmol) in CH_3CN (50 mL). The mixture was heated for 10 h at reflux. Workup and filtration gave **8a** as a yellow solid (16.06 g, 68.0 mmol, 86 %). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$–2.02 (m, 2H; 5-H_2), 2.03 (t, $J = 2.0$ Hz, 3H; 2-CH_3), 2.46–2.53 (m, 2H; 6-H_2), 3.04 ppm (tq, $J = 6.0$, 2.0 Hz, 2H; 4-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 21.71$ (2-CH_3), 24.52 (C-5), 37.81 (C-6), 42.71 (C-4), 128.0 (C-3), 142.0 (C-2), 193.2 ppm (C-l).

2-Ethyl-3-iodocyclohex-2-en-1-one (8b): The title compound was synthesized according to General Procedure A by use of PPh_3 (9.72 g, 37.0 mmol), I_2 (9.76 g, 38.4 mmol), NEt_3 (13.1 mL, 3.94 g, 39.0 mmol), and 2-ethylcyclohexane-1,3-dione (4.05 g, 28.9 mmol) in CH_3CN (270 mL). The mixture was heated for 17 h at reflux. Workup and filtration gave **8b** as a light yellow solid (6.54 g, 26.2 mmol, 90 %). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H; 2-CH_2CH_3), 1.90–2.00 (m, 2H; 5-H_2), 2.43–2.53 (m, 4H; 4-H_2, 2-CH_2CH_3), 3.03 ppm (t, $J = 6.1$ Hz, 2H; 6-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.29$ (2-CH_2CH_3), 24.53 (C-5), 28.94 (2-CH_2CH_3), 38.12 (C-6), 42.90 (C-4), 127.2 (C-3), 147.0 (C-2), 192.8 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_8H_{11}IO$: 249.9855 $[M]^+$; found: 289.9854.

3-Iodo-2-isopropylcyclohex-2-en-1-one (8c): The title compound was synthesized according to General Procedure A by use of PPh_3 (8.83 g, 33.6 mmol), I_2 (8.87 g, 34.9 mmol), NEt_3 (4.90 mL, 3.58 g, 35.3 mmol), and 2-isopropylcyclohexane-1,3-dione (4.00 g, 25.9 mmol) in CH_3CN (250 mL). The mixture was heated for 23 h at reflux. Workup and filtration gave **8c** as a light yellow solid (6.02 g, 22.8 mmol, 88 %). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, $J = 7.0$ Hz, 6H; 2-CH(CH_3)$_2$), 1.84–1.95 (m, 2H; 5-H_2), 2.41–2.48 (m, 2H; 4-H_2), 2.94 (sept., $J = 7.0$ Hz, 1H; 2-CH(CH_3)$_2$), 3.04 ppm (t, $J = 6.1$ Hz, 2H; 6-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 19.84$ (2-CH(CH_3)$_2$), 24.32 (C-5), 39.78 (C-6), 40.32 (2-CH-(CH_3)$_2$), 43.72 (C-4), 127.3 (C-3), 148.8 (C-2), 192.7 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_9H_{13}IO$: 265.0011 $[M]^+$; found: 265.0011.

General Procedure B—Synthesis of phenylacetylenes 9: Propargyl alcohol and, after degassing, .[$Pd(PPh_3)_2Cl_2$] and CuI were added at room temperature to a stirred solution of the iodobenzene derivative **10** either in iPr_2NH or in DMF and NEt_3 or in CH_3CN, H_2O, and NEt_3. The mixture was normally briefly heated to 50–60 °C and then stirred at room temperature for the given time. The mixture was diluted with Et_2O (150 mL) and filtered over silica gel (20 g) with the aid of Et_2O (4× 100 mL), and the filtrate was evaporated in vacuo. Activated MnO_2 and KOH powder were added at room temperature to a stirred solution of the residue in Et_2O (50–250 mL), and stirring was continued for the given time. In some cases the treatment with MnO_2 was repeated. The mixture was filtered over a pad of silica gel with the aid of Et_2O (4× 100 mL), and evaporation of the solvent in vacuo gave the title compound **9**.

4-*tert*-Butoxy-2-chloro-1-ethynylbenzene (9a): The title compound was synthesized according to General Procedure B with 4-*tert*-butoxy-2-chloro-1-iodobenzene (4.05 g, 13.0 mmol) in iPr_2NH (31.5 mL) and propargyl alcohol (2.30 mL, 2.18 g, 38.9 mmol), [$Pd(PPh_3)_2Cl_2$] (137 mg, 195 μmol, 1.50 mol %), and CuI (74.8 mg, 393 μmol, 3.02 mol %) for

15.5 h, followed by MnO_2 (16.95 g, 195 mmol) and KOH powder (5.47 g, 97.5 mmol) in Et_2O (150 mL) for 1.5 h. This was followed by repeated treatment with MnO_2 (16.95 g, 195 mmol) and KOH powder (5.47 g, 97.5 mmol) for 30 min. Product: reddish oil (2.10 g, 10.1 mmol, 77% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 9H; 4-OC(CH_3)$_3$), 3.31 (s, 1H; 2′-H), 6.85 (dd, $J = 8.6$, 2.4 Hz, 1H; 5-H), 7.05 (d, $J = 2.4$ Hz, 1H; 3-H), 7.42 ppm (d, $J = 8.6$ Hz, 1H; 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 28.77$ (4-OC(CH_3)$_3$), 80.00, 80.16 (4-OC(CH$_3$)$_3$, C-1′), 81.37 (C-2′), 116.4 (C-1), 121.8 (C-5), 124.2 (C-3), 134.1 (C-6), 136.3 (C-2), 156.7 ppm (C-4); HRMS (EI$^+$): m/z: calcd for $C_{12}H_{13}ClO$: 208.0655 $[M]^+$; found: 208.0655.

2-(3-Bromo-4-ethynylphenoxy)tetrahydropyran (9b): The title compound was synthesized according to General Procedure B with 2-(3-bromo-4-iodophenoxy)tetrahydropyran (990 mg, 2.58 mmol) in iPr$_2$NH (5.2 mL) and propargyl alcohol (0.460 mL, 437 mg, 7.79 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (45.3 mg, 64.5 μmol, 2.50 mol%), and CuI (24.6 mg, 129 μmol, 5.01 mol%) for 4 h at room temperature and 4 h at 50–60 °C, followed by MnO_2 (8.97 g, 100 mmol) and KOH powder (2.90 g, 51.7 mmol) in Et_2O (50 mL) for 45 min. Product: reddish brown oil (420 mg, 1.49 mmol, 58% crude yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$–2.10 (m, 6H; 3-H$_2$, 4-H$_2$, 5-H$_2$), 3.28 (s, 1H; 2″-H), 3.61 (dtd, $J = 11.3$, 3.9, 1.5 Hz, 1H; 6-H$_A$), 3.82 (ddd, $J = 11.3$, 10.0, 3.1 Hz, 1H; 6-H$_B$), 5.42 (t, $J = 2.9$ Hz, 1H; 2-H), 6.95 (dd, $J = 8.6$, 2.5 Hz, 1H; 6′-H), 7.30 (d, $J = 2.5$ Hz, 1H; 2′-H), 7.43 ppm (d, $J = 8.6$ Hz, 1H; 5′-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 18.32$ (C-4), 24.97 (C-5), 29.99 (C-3), 61.90 (C-6), 80.16 (C-2″), 81.92 (C-1″), 96.30 (C-2), 115.4 (C-6′), 117.1 (C-4′), 120.3 (C-2′), 126.0 (C-3′), 133.4 (C-4′), 157.7 ppm (C-1′).

2-Ethynyl-5-(triisopropylsilanyloxy)benzoic acid methyl ester (9c): The title compound was synthesized according to General Procedure B with 2-iodo-5-(triisopropylsilanyloxy)benzoic acid methyl ester (11.00 g, 25.3 mmol) in DMF (45 mL) and NEt_3 (10.9 mL, 7.96 g, 78.6 mmol) and propargyl alcohol (4.50 mL, 4.27 g, 76.2 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (444 mg, 633 μmol, 2.50 mol%), and CuI (241 mg, 1.27 mmol, 5.00 mol%) in DMF (15 mL) (inverse addition) for 41 h. The reaction mixture was poured into H_2O (250 mL), and the aqueous phase was saturated with NaCl and extracted with Et_2O (4×100 mL). The combined organic layers were washed with brine (3×50 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo after addition of silica gel (20 g). The crude product was purified by column chromatography (silica gel; Et_2O/CH_2Cl_2 3:1 → Et_2O/CH_2Cl_2 5:1) to give 2-(3-hydroxyprop-1-ynyl)-5-(triisopropylsilanyloxy)benzoic acid methyl ester (4.23 g, 11.7 mmol, 46%) as a red oil.

Activated MnO_2 (10.10 g, 116 mmol) and KOH powder (3.25 g, 57.9 mmol) were added to a solution of this compound (4.21 g, 11.6 mmol) in Et_2O (120 mL). The reaction mixture was stirred at room temperature for 30 min and filtered over silica gel with the aid of Et_2O (6×50 mL), the resulting solution was filtered, and the solvent was evaporated. The crude product was purified by column chromatography (silica gel; PE/EE 20:1 → PE/EE 15:1 → PE/EE 10:1) to give the title compound with some TIPSOH contamination (1.20 g; product/TIPSOH ratio 2.75:1, calculated from ^{13}C NMR signals; 3.03 mmol, 12% over two steps) as a light red oil, which partly recrystallized to afford a red solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (d, $J = 7.1$ Hz, 18H; 3×SiCH(CH_3)$_2$), 1.19–1.36 (m, 3H; 3×SiCH(CH$_3$)$_2$), 3.29 (s, 1H; 2′-H), 3.92 (s, 3H; 1-COOCH_3), 6.97 (dd, $J = 8.5$, 2.6 Hz, 1H; 4-H), 7.42 (d, $J = 2.6$ Hz, 1H; 6-H), 7.49 ppm (d, $J = 8.5$ Hz, 1H; 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.57$ (3×SiCH(CH$_3$)$_2$), 17.82 (3×SiCH(CH$_3$)$_2$), 52.22 (1-COOCH$_3$), 80.46 (C-2′), 82.04 (C-1′), 114.9 (C-2), 121.6 (C-6), 123.4 (C-4), 133.8 (C-l), 136.3 (C-3), 156.3 (C-5), 166.2 ppm (1-COOCH$_3$); HRMS (EI$^+$): m/z: calcd for $C_{19}H_{28}O_3Si$: 332.1808 $[M]^+$; found: 332.1808.

(4-Ethynylphenoxy)triisopropylsilane (9d): The title compound was synthesized according to General Procedure B with (4-iodophenoxy)triisopropylsilane (1.89 g, 5.02 mmol) in iPr$_2$NH (10 mL), propargyl alcohol (0.890 mL, 845 mg, 15.1 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (35.4 mg, 50.4 μmol, 1.00 mol%), and CuI (20.1 mg, 106 μmol, 2.11 mol%) for 15 h, followed by MnO_2 (4.37 g, 50.3 mmol) and KOH powder (1.41 g, 25.1 mmol) in Et_2O (50 mL) for 45 min. Product: colorless oil (1.04 g, 3.79 mmol, 75% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.09$ (d, $J = 7.0$ Hz, 18H; 3×SiCH(CH_3)$_2$), 1.18–1.34 (m, 3H; 3×SiCH(CH$_3$)$_2$), 2.99 (s, 1H; 2′-H), 6.78–6.85 (m, 2H; 2-H, 6-H), 7.33–7.40 ppm (m, 2H; 3-H, 5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 12.63$ (3×SiCH(CH$_3$)$_2$), 17.85 (3×SiCH(CH_3)$_2$), 75.78 (C-2′), 83.77 (C-1′), 114.4 (C-4), 119.9 (C-2, C-6), 133.6 (C-3, C-5), 156.7 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{17}H_{26}OSi$: 274.1753 $[M]^+$; found: 274.1753.

5-Ethynyl-2-methoxy-1,3-dimethylbenzene (9e): The title compound was synthesized according to General Procedure B with 4-bromo-2,6-dimethylanisol (4.30 g, 20.0 mmol) in iPr$_2$NH (40 mL) and propargyl alcohol (3.55 mL, 3.37 g, 60.1 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (351 mg, 500 μmol, 2.50 mol%), and CuI (191 mg, 1.00 mmol, 5.01 mol%) at 75–85 °C for 6 h, followed by activated MnO_2 (17.39 g, 200 mmol) and KOH powder (5.61 g, 100 mmol) in Et_2O (200 mL) for 1 h. Product: yellow liquid (1.38 g, 8.61 mmol, 43% over two steps). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.25$ (s, 6H; 1-CH$_3$, 3-CH$_3$), 2.98 (s, 1H; 2′-H), 3.72 (s, 3H; 2-OCH$_3$), 7.17 ppm (s, 2H; 4-H, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 15.89$ (1-CH$_3$, 3-CH$_3$), 59.72 (2-OCH$_3$), 75.94 (C-2′), 83.61 (C-1′), 117.2 (C-5), 131.1 (C-1, C-3), 132.6 (C-4, C-6), 157.7 ppm (C-2); HRMS (EI$^+$): m/z: calcd for $C_{11}H_{12}O$: 160.0888 $[M]^+$; found: 160.0888.

1-Ethynyl-4-methoxybenzene (9f): The title compound was synthesized according to General Procedure B with 1-iodo-4-methoxybenzene (20.0 g, 85.5 mmol) in a mixture of CH_3CN (210 mL) and H_2O (40 mL) together with propargyl alcohol (14.9 mL, 14.1 g, 252 mmol), NEt_3 (35.7 mL, 26.1 g, 258 mmol), PPh_3 (1.12 g, 4.27 mmol, 4.99 mol%), Pd(OAc)$_2$ (479 mg, 2.13 mmol, 2.50 mol%), and CuI (814 mg, 4.27 mmol, 4.99 mol%) at room temperature without heating for 42 h. The CH_3CN was mostly removed in vacuo, and the residue was diluted with H_2O (100 mL) and extracted with Et_2O (200 mL, 3×100 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$, and the solvent was evaporated down to give a volume of 50–75 mL. This was filtered over silica gel (150 g), the residue was washed with Et_2O, and the solvent was evaporated. The resulting alcohol (2.43 g, 15.0 mmol) in Et_2O (150 mL) was treated with MnO_2 (13.0 g, 150 mmol) and KOH powder (4.21 g, 75.0 mmol) at room temperature for 45 min. Product: yellow, low-melting solid (1.76 g, 13.3 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.00$ (s, 1H; 2′-H), 3.81 (s, 3H; 4-OCH$_3$), 6.81–6.87 (m, 2H; 3-H, 5-H), 7.40–7.46 ppm (m, 2H; 2-H, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 55.24$ (4-OCH$_3$), 75.75 (C-2′), 83.62 (C-1′), 113.9 (C-3, C-5), 114.1 (C-1), 133.5 (C-2, C-6), 159.9 ppm (C-4); HRMS (EI$^+$): m/z: calcd for C_9H_8O: 132.0575 $[M]^+$; found: 132.0575.

(4-Ethynylphenyl)carbamic acid *tert*-butyl ester (9g): The title compound was synthesized according to General Procedure B with (4-iodophenyl)-carbamic acid *tert*-butyl ester (1.60 g, 5.01 mmol) in DMF (10 mL), propargyl alcohol (0.890 mL, 845 mg, 15.1 mmol), and NEt_3 (2.15 mL, 1.57 g, 15.5 mmol), together with [Pd(PPh$_3$)$_2$Cl$_2$] (35.2 mg, 50.1 μmol, 1.00 mol%) and CuI (19.1 mg, 100 μmol, 2.00 mol%) in DMF (2.5 mL) (inverse addition) for 20 h. The reaction mixture was poured into ice-cold H_2O (45 mL) and extracted with Et_2O (4×20 mL). The combined organic layers were washed with brine (3×15 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was dissolved in Et_2O, and column filtration over silica gel (30 g) gave the slightly impure alcohol as a light brown oil (1.13 g, 4.57 mmol, 91%).

Activated MnO_2 (3.90 g, 44.9 mmol) and KOH powder (1.26 g, 22.5 mmol) were added to a solution of the alcohol (1.11 g, 4.49 mmol) in Et_2O (45 mL), and the reaction mixture was stirred at room temperature for 45 min. Product: colorless solid (653 mg, 3.01 mmol, 61% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (s, 9H; C(CH$_3$)$_3$), 3.02 (s, 1H; 2′-H), 6.55 (brs, 1H; NH), 7.30–7.35 (m, 2H; 3-H, 5-H), 7.39–7.44 ppm (m, 2H; 2-H, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 28.27$ (C(CH$_3$)$_3$), 77.20 (C-2′), 80.93 (C(CH$_3$)$_3$), 83.52 (C-1′), 116.2 (C-4), 117.9 (C-2, C-6), 133.0 (C-3, C-5), 138.9 (C-1), 152.3 ppm (COOtBu); HRMS (EI$^+$): m/z: calcd for $C_{13}H_{15}NO_2$: 217.1103 $[M]^+$; found: 217.1103.

1-Ethynyl-4-(trifluoromethyl)benzene (9h): The title compound was synthesized according to General Procedure B with 1-iodo-4-(trifluoromethyl)benzene (5.44 g, 20.0 mmol) in CH_3CN (49 mL) and H_2O (10 mL), propargyl alcohol (3.55 mL, 3.37 g, 60.1 mmol), NEt_3 (8.30 mL, 6.06 g, 59.9 mmol), PPh_3 (263 mg, 1.00 mmol, 5.01 mol%), Pd(OAc)$_2$ (112 mg,

499 μmol, 2.49 mol%), and CuI (191 mg, 1.00 mmol, 5.01 mol%) for 16 h at room temperature without heating. The CH_3CN was mostly removed under reduced pressure, and the residue was diluted with H_2O (25 mL) and brine (25 mL) and extracted with Et_2O (4×25 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$, and the solvent was evaporated. The crude product was dissolved in Et_2O and filtered over silica gel (75 g), which was then washed with Et_2O. Evaporation of the solvent gave the alcohol as a brown solid, which was dissolved in Et_2O (160 mL). Subsequent treatment with MnO_2 (13.91 g, 160 mmol) and KOH powder (4.49 g, 80.0 mmol) at room temperature for 2 h gave a light yellow solid (1.49 g, 8.76 mmol, 90% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.20 (s, 1H; 2′-H), 7.59 ppm (s, 4H; 2-H, 3-H, 5-H, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=79.61 (C-2′), 82.19 (q, J=0.7 Hz, C-1′), 123.8 (q, J=273 Hz, 4-CF_3), 125.3 (q, J=3.8 Hz, C-3, C-5), 125.9 (q, J=1.8 Hz, C-1), 130.6 (q, J=32.8 Hz, C-4), 132.4 ppm (C-2, C-6).

General Procedure C—Synthesis of protected estrogen analogues 15 and 16: NEt_3 was added to a solution of the vinyl iodide **7** or **8** and the phenylacetylene **9** in DMF and the reaction mixture was degassed. After addition of $[Pd(PPh_3)_2Cl_2]$ and CuI the solution was briefly heated to 50–60°C and was then stirred at room temperature for the given time. Afterwards the mixture was poured into H_2O and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ or Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by column chromatography.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-methylcyclopent-2-enone (15a): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (501 mg, 2.40 mmol), vinyl iodide **7a** (559 mg, 2.52 mmol), $[Pd(PPh_3)_2Cl_2]$ (25.5 mg, 36.4 μmol, 1.52 mol%), CuI (14.9 mg, 78.3 μmol, 3.26 mol%), and NEt_3 (0.400 mL, 292 mg, 2.88 mmol) in DMF (6.0 mL). After 16 h at room temperature and workup, **15a** was isolated by column chromatography (silica gel, pentane/ethyl acetate 90:10) as a yellow solid (588 mg, 1.94 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (s, 9H; 4″-OC(CH_3)$_3$), 1.95 (t, J=2.0 Hz, 3H; 2-CH_3), 2.45–2.51 (m, 2H; 5-H_2), 2.71–2.78 (m, 2H; 4-H_2), 6.90 (dd, J=8.5, 2.3 Hz, 1H; 5″-H), 7.10 (d, J=2.3 Hz, 1H; 3″-H), 7.45 ppm (d, J=8.5 Hz, 1H; 6″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=9.78 (2-CH_3), 28.80 (4″-OC(CH)$_3$), 29.85 (C-4), 34.01 (C-5), 80.31 (4″-OC(CH_3)$_3$), 89.18 (C-1′), 102.0 (C-2′), 116.3 (C-1″), 121.7 (C-5″), 124.0 (C-3″), 133.8 (C-6″), 136.5 (C-2″), 144.9, 149.8 (C-2, C-3), 157.6 (C-4″), 209.0 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{18}H_{19}ClO_2$: 302.1074 [M]$^+$; found: 302.1068.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-ethylcyclopent-2-enone (15b): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (399 mg, 1.91 mmol), vinyl iodide **7b** (478 mg, 2.02 mmol), $[Pd(PPh_3)_2Cl_2]$ (20.6 mg, 29.4 μmol, 1.54 mol%), CuI (12.5 mg, 65.7 μmol, 3.44 mol%), and NEt_3 (0.320 mL, 234 mg, 2.30 mmol) in DMF (5.0 mL). After 22 h at room temperature and workup, **15b** was isolated by column chromatography (silica gel, pentane/CH_2Cl_2/Et_2O 70:20:10) as a light yellow solid (486 mg, 1.53 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (t, J=7.5 Hz, 3H; 2-CH_2CH_3), 1.38 (s, 9H; 4″-OC(CH_3)$_3$), 2.38–2.48 (m, 4H; 5-H_2, 2-CH_2CH$_3$), 2.69–2.75 (m, 2H; 4-H_2), 6.88 (dd, J=8.5, 2.3 Hz, 1H; 3″-H), 7.08 (d, J=2.3 Hz, 1H; 5″-H), 7.43 ppm (d, J=8.5 Hz, 1H; 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.48 (2-CH_2CH$_3$), 17.95 (2-CH$_2$CH$_3$), 28.76 (4″-OC(CH_3)$_3$), 29.85 (C-4), 34.22 (C-5), 80.27 (4″-OC(CH_3)$_3$), 89.04 (C-1′), 101.8 (C-2′), 116.3 (C-1″), 121.6 (C-5″), 124.0 (C-3″), 133.7 (C-6″), 136.5 (C-2″), 149.3, 150.1 (C-2, C-3), 157.5 (C-4″), 208.6 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{19}H_{21}ClO_2$: 317.13028 [M+H]$^+$; found: 317.13033.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-isopropylcyclopent-2-enone (15c): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (404 mg, 1.93 mmol), vinyl iodide **7c** (508 mg, 2.03 mmol), $[Pd(PPh_3)_2Cl_2]$ (20.8 mg, 29.7 μmol, 1.54 mol%), CuI (11.5 mg, 60.4 μmol, 3.13 mol%), and NEt_3 (0.320 mL, 234 mg, 2.30 mmol) in DMF (5.0 mL). After 16 h at room temperature and workup, **15c** was isolated by column chromatography (silica gel, pentane/CH_2Cl_2/Et_2O 75:20:5) as a light yellow solid (481 mg, 1.45 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (d, J=7.0 Hz, 6H; 2-CH(CH_3)$_2$), 1.38 (s, 9H; 4″-OC(CH_3)$_3$), 2.40–2.46 (m, 2H; 5-H_2), 2.68–2.74 (m, 2H; 4-H_2), 3.01 (sept., J=7.0 Hz, 1H; 2-CH(CH$_3$)$_2$), 6.89 (dd, J=8.5 Hz, 2.2 Hz, 1H; 5″-H), 7.08 (d, J=2.2 Hz, 1H; 3″-H), 7.43 ppm (d, J=8.5 Hz, 1H; 6″-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=20.13 (2-CH(CH_3)$_2$), 25.57 (2-CH(CH$_3$)$_2$), 28.77 (4″-OC(CH_3)$_3$), 30.35 (C-4), 34.43 (C-5), 80.27 (4″-OC(CH$_3$)$_3$), 89.35 (C-1′), 102.3 (C-2′), 116.5 (C-1″), 121.7 (C-5″), 124.1 (C-3″), 133.7 (C-6″), 136.5 (C-2″), 148.1 (C-3), 152.9 (C-2), 157.5 (C-4″), 208.4 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{20}H_{23}ClO_2$: 331.14593 [M+H]$^+$; found: 331.14596.

2-Methyl-3-[4-(triisopropylsilanyloxy)phenylethynyl]cyclopent-2-enone (15d): The title compound was synthesized according to General Procedure C from phenylacetylene **9d** (3.00 g, 10.9 mmol), vinyl iodide **7a** (2.31 g, 10.4 mmol), $[Pd(PPh_3)_2Cl_2]$ (146 mg, 208 μmol, 2.00 mol%), CuI (80.0 mg, 420 μmol, 4.04 mol%) and NEt_3 (1.75 mL, 1.28 g, 12.6 mmol) in DMF (12.0 mL). After 40 h at room temperature and workup, **15d** was isolated by column chromatography (silica gel, pentane/ethyl acetate 7:1) as a yellow-brown solid (3.71 g, 10.1 mmol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$,): δ=1.10 (d, J=7.0 Hz, 18H; 3×SiCH(CH_3)$_2$), 1.19–1.35 (m, 3H; 3×SiCH(CH$_3$)$_2$), 1.91 (t, J=2.2 Hz, 3H; 2-CH_3), 2.43–2.49 (m, 2H; 5-H_2), 2.72 (tq, J=4.7, 2.2 Hz, 2H; 4-H_2), 6.84–6.90 (m, 2H; 3″-H, 5″-H), 7.37–7.44 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=9.70 (2-CH_3), 12.63 (3×SiCH(CH$_3$)$_2$), 17.84 (3×SiCH(CH$_3$)$_2$), 30.11 (C-4), 33.99 (C-5), 84.30 (C-1′), 106.2 (C-2′), 114.4 (C-1″), 120.2 (C-3″, C-5″), 133.6 (C-2″, C-6″), 143.7 (C-3), 150.5 (C-2), 157.6 (C-4″), 209.1 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{23}H_{32}O_2Si$: 368.2172 [M+H]$^+$; found: 368.2172.

[4-(2-Methyl-3-oxocyclopent-1-enylethynyl)phenyl]carbamic acid *tert*-butyl ester (15e): The title compound was synthesized according to General Procedure C from phenylacetylene **9g** (689 mg, 122 μmol) dissolved in DMF (0.50 mL), vinyl iodide **7a** (669 mg, 3.01 mmol) dissolved in DMF (3.0 mL), $[Pd(PPh_3)_2Cl_2]$ (42.0 mg, 59.8 μmol, 1.99 mol%), CuI (23.2 mg, 122 μmol, 4.05 mol%), and NEt_3 (0.650 mL, 475 mg, 4.69 mmol). After 18 h at room temperature and workup, **15e** was isolated by column chromatography (silica gel, pentane/ethyl acetate/NEt_3 60:20:1→45:30:1) as a yellow-brown solid (844 mg, 2.71 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.53 (s, 9H; C(CH_3)$_3$), 1.92 (t, J=2.2 Hz, 3H; 2″-CH_3), 2.43–2.50 (m, 2H; 4″-H_2), 2.72 (tq, J=4.7, 2.2 Hz, 2H; 5″-H_2), 6.68 (br s, 1H; NH), 7.37–7.50 ppm (m, 4H; 2-H, 3-H, 5-H, 6-H); ^{13}C NMR (75.5 MHz, $CDC1_3$): δ=9.67, 9.71 (2″-CH_3), 28.17, 28.24 (C-5″), 30.05 (C-4″), 33.94 (C(CH_3)$_3$), 80.97 (C(CH$_3$)$_3$), 84.49 (C-2′), 105.9 (C-1′), 115.9 (C-4), 118.0 (C-2, C-6), 132.9 (C-3, C-5), 139.8 (C-1), 143.9 (C-1″), 150.4 (C-2″), 152.3 (COOtBu), 209.2 ppm (C-3″); HRMS (EI$^+$): m/z: calcd for $C_{19}H_{21}NO_3$: 311.1521 [M]$^+$; found: 311.1521.

3-(4-Methoxyphenylethynyl)-2-methylcyclopent-2-enone (15f): The title compound was synthesized according to General Procedure C from phenylacetylene **9f** (1.77 g, 13.4 mmol) dissolved in DMF (10.5 mL), vinyl iodide **7a** (2.84 mg, 12.8 mmol) dissolved in DMF (12.0 mL), $[Pd(PPh_3)_2Cl_2]$ (180 mg, 256 μmol, 2.00 mol%), CuI (98.0 mg, 515 μmol, 4.02 mol%), and NEt_3 (2.20 mL, 1.61 g, 15.9 mmol). After 39 h at room temperature and workup, **15f** was isolated by column chromatography (silica gel, pentane/ethyl acetate 4:1 → 2.5:1) as a brown solid (2.68 g, 11.8 mmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.92 (t, J=2.2 Hz, 3H; 2-CH_3), 2.43–2.49 (m, 2H; 5-H_2), 2.72 (tq, J=4.5, 2.2 Hz, 2H; 4-H_2), 3.85 (s, 3H; 4″-OCH_3), 6.87–6.94 (m, 2H; 3″-H, 5″-H), 7.44–7.51 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (50.3 MHz, $CDC1_3$): δ=9.72 (2-CH_3), 30.10 (C-4), 33.99 (C-5), 55.35 (4″-OCH_3), 84.25 (C-1′), 106.0 (C-2′), 114.1 (C-l″), 114.2 (C-3″, C-5″), 133.6 (C-2″, C-6″), 143.7 (C-3), 150.5 (C-2), 160.6 (C-4″), 209.1 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{15}H_{14}O_2$: 226.0994 [M]$^+$; found: 226.1013.

3-(4-Methoxy-3,5-dimethylphenylethynyl)-2-methylcyclopent-2-enone (15g): The title compound was synthesized according to General Procedure C from phenylacetylene **9e** (678 mg, 4.23 mmol) dissolved in DMF (4.0 mL), vinyl iodide **7a** (892 mg, 4.02 mmol) dissolved in DMF (5.0 mL), $[Pd(PPh_3)_2Cl_2]$ (56.2 mg, 80.1 μmol, 1.99 mol%), CuI (30.9 mg, 162 μmol, 4.23 mol%) and NEt_3 (0.700 mL, 511 mg, 5.05 mmol). After 7.5 h at room temperature and workup, **15g** was isolated by column chromatography (silica gel, pentane/ethyl acetate 7:1 → 6:1 → 5:1) as a yellow-brown solid (879 mg, 3.46 mmol, 86%). ^{1}H NMR (300 MHz,

$CDCl_3$): $\delta = 1.92$ (t, $J = 2.3$ Hz, 3H; 2-CH_3), 2.29 (s, 6H; 3″-CH_3, 5″-CH_3), 2.43–2.48 (m, 2H; 5-H_2), 2.71 (tq, $J = 4.7$, 2.3 Hz, 2H; 4-H_2), 3.74 (s, 3H; 4″-OCH_3), 7.21 ppm (s, 2H; 2″-H, 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 9.69$ (2-CH_3), 15.91 (3″-CH_3, 5″-CH_3), 30.06 (C-4), 33.94 (C-5), 59.71 (4″-OCH_3), 84.15 (C-1′), 105.8 (C-2′), 117.2 (C-1″), 131.4 (C-3″, C-5″), 132.5 (C-2″, C-6″), 144.0 (C-3), 150.3 (C-2), 158.3 ppm (C-4″), 209.0 (C-1); HRMS (EI$^+$): m/z: calcd for $C_{17}H_{18}O_2$: 254.1307 $[M]^+$; found: 254.1307.

2-Methyl-3-[4-(trifluoromethyl)phenylethynyl]cyclopent-2-enone (15h): The title compound was synthesized according to General Procedure C from phenylacetylene **9h** (1.43 g, 8.41 mmol) dissolved in DMF (7.5 mL), vinyl iodide **7a** (1.78 g, 8.02 mmol) dissolved in DMF (10.0 mL), [Pd(PPh_3)$_2$$Cl_2$] (113 mg, 161 μmol, 2.01 mol%), CuI (61.5 mg, 323 μmol, 4.03 mol%), and NEt_3 (1.34 mL, 978 mg, 9.67 mmol). After 14.5 h at room temperature and workup, **15h** was isolated by column chromatography (silica gel, pentane/ethyl acetate 6:1) as a yellow-gray solid (1.81 g, 6.85 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.94$ (t, $J = 2.3$ Hz, 3H; 2-CH_3), 2.47–2.52 (m, 2H; 5-H_2), 2.76 (tq, $J = 4.7$, 2.3 Hz, 2H; 4-H_2), 7.64 ppm (s, 4H; 2″-H, 3″-H, 5″-H, 6″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 9.85$ (2-CH_3), 29.91 (C-4), 33.95 (C-5), 86.87 (C-1′), 103.2 (C-2′), 123.7 (q, $J = 273$ Hz, 4″-CF_3), 125.5 (q, $J = 3.9$ Hz, C-3″, C-5″), 125.8 (q, $J =$ 1.4 Hz, C-1″), 131.0 (q, $J = 33.0$ Hz, C-4″), 132.1 (C-2″, C-6″), 145.7 (C-3), 148.9 (C-2), 208.8 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{15}H_{11}F_3O$: 264.0762 $[M]^+$; found: 264.0762.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-methylcyclohex-2-enone (16a): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (4.83 g, 23.1 mmol), vinyl iodide **8a** (5.20 g, 22.0 mmol), [Pd(PPh_3)$_2$$Cl_2$] (232 mg, 331 μmol, 1.50 mol%), CuI (128 mg, 674 μmol, 3.06 mol%), and NEt_3 (3.72 mL, 2.71 g, 26.8 mmol) in DMF (23.0 mL). After 26 h at room temperature and workup, **16a** was isolated by column chromatography (silica gel, pentane/ethyl acetate 9:1) as a red oil (5.73 g, 18.1 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.38 (s, 9H; 4″-$OC(CH_3)_3$), 1.98–2.07 (m, 2H; 5-H_2), 2.07 (t, $J = 1.9$ Hz, 3H; 2-CH_3), 2.48 (dd, $J = 7.3$, 6.1 Hz, 2H; 6-H_2), 2.59 (m, 2H; 4-H_2), 6.88 (dd, $J = 8.6$, 2.3 Hz, 1H; 5″-H), 7.08 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.41 ppm (d, $J = 8.6$ Hz, 1H; 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.08$ (2-CH_3), 22.69 (C-5), 28.79 (4″-$OC(CH_3)_3$), 30.95 (C-4), 37.91 (C-6), 80.22 (4″-$OC(CH_3)_3$), 92.39 (C-1′), 99.67 (C-2′), 116.8 (C-1″), 121.7 (C-5″), 124.1 (C-3″), 133.6 (C-6″), 136.4, 137.3, 139.1 (C-2, C-2″, C-3), 157.2 (C-4″), 198.5 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{15}H_{13}ClO_2$: 260.0604 $[M]^+$; found: 260.0604.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-ethylcyclohex-2-enone (16b): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (505 mg, 2.42 mmol), vinyl iodide **8b** (630 mg, 2.52 mmol), [Pd(PPh_3)$_2$$Cl_2$] (25.5 mg, 36.4 μmol, 1.50 mol%), CuI (14.5 mg, 76.2 μmol, 3.15 mol%), and NEt_3 (0.400 mL, 292 mg, 2.88 mmol) in DMF (6.0 mL). After 19 h at room temperature and workup, **16b** was isolated by column chromatography (silica gel, pentane/ethyl acetate 9:1) as a yellow solid (525 mg, 1.59 mmol, 66%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.5$ Hz, 3H; 2-CH_2CH_3), 1.39 (s, 9H; 4″-$OC(CH_3)_3$), 2.03 (quint., $J = 6.4$ Hz, 2H; 5-H_2), 2.47 (dd, $J = 7.3$ Hz, 6.1 Hz, 2H; 6-H_2), 2.54–2.64 (m, 4H; 4-H_2, 2-CH_2CH_3), 6.88 (dd, $J = 8.5$, 2.3 Hz, 1H; 5″-H), 7.08 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.40 ppm (d, $J = 8.5$ Hz, 1H; 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.51$ (2-CH_2CH_3), 21.64 (2-CH_2CH_3), 22.70 (C-5), 28.80 (4″-$OC(CH_3)_3$), 31.02 (C-4), 38.18 (C-6), 80.24 (4″-$OC(CH_3)_3$), 92.09 (C-1′), 99.12 (C-2′), 116.9 (C-1″), 121.8 (C-5″), 124.2 (C-3″), 133.6 (C-6″), 136.5, 136.9 (C-2″, C-3), 145.0 (C-2), 157.2 (C-4″), 197.9 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{20}H_{23}ClO_2$: 330.1387 $[M]^+$; found: 330.1389.

3-(4-*tert*-Butoxy-2-chlorophenylethynyl)-2-isopropylcyclohex-2-enone (16c): The title compound was synthesized according to General Procedure C from phenylacetylene **9a** (506 mg, 2.43 mmol), vinyl iodide **8c** (667 mg, 2.53 mmol), [Pd(PPh_3)$_2$$Cl_2$] (26.3 mg, 37.5 μmol, 1.54 mol%), CuI (14.3 mg, 75.1 μmol, 3.09 mol%), and NEt_3 (0.400 mL, 292 mg, 2.88 mmol) in DMF (6.0 mL). After 26.5 h at room temperature and workup, **16c** was isolated by column chromatography (silica gel, pentane/ethyl acetate 95:5) as a yellow solid (509 mg, 1.48 mmol, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (d, $J = 7.1$ Hz, 6H; 2-$CH(CH_3)_2$), 1.38 (s, 9H; 4″-$OC(CH_3)_3$), 1.94–2.04 (m, 2H; 5-H_2), 2.43 (dd, $J = 7.3$, 6.1 Hz, 2H; 6-H_2), 2.59 (t, $J = 6.1$ Hz, 2H; 4-H_2), 3.40 (sept., $J = 7.1$ Hz, 1H; 2-CH-$(CH_3)_2$), 6.88 (dd, $J = 8.5$ Hz, 2.3 Hz, 1H; 5″-H), 7.07 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.40 ppm (d, $J = 8.5$ Hz, 1H; 6″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 20.47$ (2-$CH(CH_3)_2$), 22.52 (C-5), 28.79 (4″-$OC(CH_3)_3$), 29.82 (2-CH-$(CH_3)_2$), 32.00 (C-4), 39.12 (C-5), 80.22 (4″-$OC(CH_3)_3$), 92.39 (C-1′), 99.96 (C-2′), 116.9 (C-1″), 121.8 (C-5″), 124.2 (C-3″), 133.5 (C-6″), 136.2, 136.4 (C-2″, C-3), 147.6 (C-2), 157.2 (C-4″), 198.1 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{21}H_{25}ClO_2$: 344.1543 $[M]^+$; found: 344.1542.

2-(2-Methyl-3-oxocyclohex-1-enylethynyl)-5-(triisopropylsilanyloxy)benzoic acid methyl ester (16e): The title compound was synthesized according to General Procedure C from a mixture of phenylacetylene **9c** and TIPSOH (1.18 g; **9c**/TIPSOH ratio 2.75:1, calculated from ^{1}H NMR data; 2.98 mmol) dissolved in a mixture of DMF (4.0 mL) and DMSO (2.0 mL), vinyl iodide **8a** (667 mg, 2.53 mmol), [Pd(PPh_3)$_2$$Cl_2$] (47.7 mg, 68.0 μmol, 2.28 mol%), CuI (27.1 mg, 142 μmol, 4.77 mol%), and NEt_3 (0.700 mL, 511 mg, 5.05 mmol) in DMF (6.0 mL). The reaction mixture was briefly heated to 50–60 °C with a heat gun. After 22 h at room temperature and workup, **16e** was isolated by column chromatography (silica gel, pentane/ethyl acetate 6:1 → pentane/ethyl acetate 4:1) as a reddish brown oil (658 mg, 1.49 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.11 (d, $J = 7.1$ Hz, 18H; 3×SiCH(CH_3)$_2$), 1.18–1.37 (m, 3H; 3×SiCH-$(CH_3)_2$), 2.04 (quint, $J = 6.4$ Hz, 2H; 5″-H_2), 2.08 (t, $J = 1.8$ Hz, 3H; 2″-CH_3), 2.48 (t, $J = 6.4$ Hz, 2H; 4″-H_2), 2.61 (tq, $J = 6.4$, 1.8 Hz, 2H; 6″-H_2), 3.93 (s, 3H; 1-$COOCH_3$), 7.01 (dd, $J = 8.6$, 2.7 Hz, 1H; 4-H), 7.47 (d, $J =$ 8.6 Hz, 1H; 3-H), 7.48 ppm (d, $J = 2.7$ Hz, 1H; 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.56$ (3×SiCH(CH_3)$_2$), 14.00 (2″-CH_3), 17.79 (3×SiCH(CH_3)$_2$), 22.69 (C-5″), 31.04 (C-6″), 37.90 (C-4″), 52.32 (1-COOCH_3), 91.41 (C-2′), 102.1 (C-1′), 115.1 (C-2), 121.9 (C-6), 123.5 (C-4), 133.1 (C-1), 135.7 (C-3), 137.9, 138.7 (C-1″, C-2″), 156.8 (C-5), 166.1 (1-COOCH$_3$), 198.6 ppm (C-3″); HRMS (EI$^+$): m/z: calcd for $C_{26}H_{32}O_4Si$: 440.2383 $[M]^+$; found: 440.2383.

[4-(2-Methyl-3-oxocyclohex-1-enylethynyl)phenyl]carbamic acid *tert*-butyl ester (16g): The title compound was synthesized according to General Procedure C from phenyl acetylene **9g** (682 mg, 3.14 mmol) in DMF (3.0 mL), vinyl iodide **8c** (710 mg, 3.01 mmol) in DMF (4.0 mL), [Pd(PPh_3)$_2$$Cl_2$] (42.1 mg, 60.0 μmol, 1.99 mol%) and CuI (24.1 mg, 127 μmol, 4.20 mol%) in DMF (0.50 mL), and NEt_3 (0.650 mL, 475 mg, 4.69 mmol). After 43 h at room temperature and workup, **16g** was isolated by column chromatography (silica gel, pentane/ethyl acetate/NEt_3 90:30:1 → 90:60:1) as a yellow-brown solid (758 mg, 2.33 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (s, 9H; $C(CH_3)_3$), 2.02 (quint, $J = 6.3$ Hz, 2H; 5″-H_2), 2.04 (t, $J = 1.7$ Hz, 3H; 2″-CH_3), 2.48 (t, $J = 6.3$ Hz, 2H; 4″-H_2), 2.57 (tq, $J = 6.3$, 1.7 Hz, 2H; 6″-H_2), 6.89 (brs, 1H; NH), 7.41 ppm (s, 4H; 2-H, 3-H, 5-H, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.97$ (2″-CH_3), 22.62 (C-5″), 28.21 ($C(CH_3)_3$), 31.05 (C-6″), 37.82 (C-4″), 80.91 (C-$(CH_3)_3$), 87.72 (C-2′), 103.5 (C-1′), 116.4 (C-4), 118.0 (C-2, C-6), 132.6 (C-3, C-5), 137.9, 138.3, 139.5 (C-1, C-1″, C-2“), 152.3 (*C*O*O*t*Bu), 198.6 ppm (C-3″); HRMS (ESI): m/z: calcd for $C_{20}H_{23}NO_3$: 326.17507 $[M+H]^+$; found: 326.17515.

3-(4-Methoxyphenylethynyl)-2-methylcyclohex-2-enone (16h): The title compound was synthesized according to General Procedure C from phenylacetylene **9f** (2.10 g, 15.9 mmol) in DMF (13.5 mL), vinyl iodide **8a** (3.57 g, 15.1 mmol) in DMF (22.0 mL), [Pd(PPh_3)$_2$$Cl_2$] (212 mg, 302 μmol, 2.00 mol%) and CuI (115 mg, 604 μmol, 4.00 mol%) in DMF (2.50 mL), and NEt_3 (2.52 mL, 1.84 g, 15.1 mmol). After 15 h at room temperature and workup, **16h** was isolated by column chromatography (silica gel, CH_2Cl_2) as a light brown solid (2.69 g, 11.2 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (quint., $\delta = 6.4$ Hz, 2H; 5-H_2), 2.04 (t, $J =$ 1.8 Hz, 3H; 2-CH_3), 2.47 (t, $J = 6.4$ Hz, 2H; 6-H_2), 2.57 (tq, $J = 6.4$, 1.8 Hz, 2H; 4-H_2), 3.83 (s, 3H; 4″-OCH_3), 6.85–6.92 (m, 2H; 3″-H, 5″-H), 7.40–7.46 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 13.95 (2-CH_3), 22.66 (C-5), 31.09 (C-4), 37.85 (C-6), 55.28 (4″-OCH_3), 87.40 (C-1′), 103.6 (C-2′), 114.1 (C-3″, C-5″), 114.5 (C-I″), 133.3 (C-2″, C-6″), 137.9, 138.1 (C-2, C-3), 160.3 (C-4″), 198.4 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{16}H_{16}O_2$: 240.1150 $[M]^+$; found: 240.1143.

3-(4-Methoxy-3,5-dimethylphenylethynyl)-2-methylcyclohex-2-enone (16i): The title compound was synthesized according to General Proce-

dure C from phenylacetylene **9e** (662 g, 4.13 mmol) in DMF (4.0 mL), vinyl iodide **8a** (929 mg, 3.93 mmol) in DMF (5.0 mL), $[Pd(PPh_3)_2Cl_2]$ (55.2 mg, 78.6 μmol, 2.00 mol%) and CuI (30.0 mg, 158 μmol, 4.01 mol%) in DMF (1.0 mL), and NEt_3 (0.700 mL, 511 mg, 5.051 mmol). After 18.5 h at room temperature and workup, **16i** was isolated by column chromatography (silica gel, pentane/ethyl acetate 8:1 → 6:1) as a yellow-green solid (863 mg, 3.22 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (quint., $J = 6.4$ Hz, 2H; 5-H_2), 2.04 (t, $J = 1.9$ Hz, 3H; 2-CH_3), 2.28 (s, 6H; 3″-CH_3, 5″-CH_3), 2.47 (t, $J = 6.4$ Hz, 2H; 6-H_2), 2.56 (tq, $J = 6.4$, 1.9 Hz, 2H; 4-H_2), 3.73 (s, 3H; 4″-OCH_3), 7.17 ppm (s, 2H; 2″-H, 6″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 13.99$ (2-CH_3), 15.93 (3″-CH_3, 5″-CH_3), 22.68 (C-5), 31.10 (C-4), 37.88 (C-6), 59.75 (4″-OCH_3), 87.42 (C-1′), 103.4 (C-2′), 117.7 (C-1″), 131.4 (C-3″, C-5″), 132.3 (C-2″, C-6″), 137.8, 138.5 (C-2, C-3), 158.1 (C-4″), 198.5 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{18}H_{20}O_2$: 268.1463 $[M]^+$; found: 268.1463.

General Procedure D—Deprotection of estrogen analogues 15 and 16: CF_3COOH was added at room temperature to a solution of the ether **15** or **16** in CH_2Cl_2. After completion of the reaction the solvent was removed in vacuo.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-methylcyclopent-2-enone (3a): The *tert*-butyl ether **15a** was deprotected according to General Procedure D with **15a** (460 mg, 1.52 mmol) and CF_3COOH (1.50 mL) in CH_2Cl_2 (15.0 mL). After the mixture had been stirred for 75 min at room temperature, **3a** was isolated as a yellow-green solid (354 mg, 1.43 mmol, 94%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.82$ (t, $J = 2.0$ Hz, 3H; 2-CH_3), 2.36–2.42 (m, 2H; 5-H_2), 2.64–2.72 (m, 2H; 4-H_2), 6.81 (dd, $J = 8.5$, 2.3 Hz, 1H; 5″-H), 6.97 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.50 (d, $J = 8.5$ Hz, 1H; 6″-H), 10.55 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 9.42$ (2-CH_3), 29.33 (C-4), 33.52 (C-5), 88.19 (C-1′), 102.0 (C-2′), 111.2 (C-1″), 115.1 (C-5′), 116.3 (C-3″), 134.9 (C-6″), 135.9 (C-2″), 143.3, 148.8 (C-2, C-3), 159.9 (C-4″), 207.5 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{14}H_{11}ClO_2$: 246.0448 $[M]^+$; found: 246.0437.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-ethylcyclopent-2-enone (3b): The *tert*-butyl ether **15b** was deprotected according to General Procedure D with **15b** (392 mg, 1.24 mmol) and CF_3COOH (1.20 mL) in CH_2Cl_2 (12.0 mL). After the mixture had been stirred for 15 min at room temperature, **3b** was isolated as a light yellow solid (283 mg, 1.09 mmol, 88%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.02$ (t, $J = 7.5$ Hz, 3H; 2-CH_2CH_3), 2.30 (q, $J = 7.5$ Hz, 2H; 2-CH_2CH_3), 2.35–2.41 (m, 2H; 5-H_2), 2.63–2.70 (m, 2H; 4-H_2), 6.80 (dd, $J = 8.6$ Hz, 2.3 Hz, 1H; 5″-H), 6.96 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.47 (d, $J = 8.6$ Hz, 1H; 6″-H), 10.55 ppm (brs, 1H; 4“-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 12.20$ (2-CH_2CH_3), 17.42 (2-CH_2CH_3), 29.39 (C-4), 33.76 (C-5), 88.01 (C-1′), 101.9 (C-2′), 111.3 (C-1″), 115.1 (C-5″), 116.3 (C-3″), 134.9 (C-6″), 136.0 (C-2″), 148.6 (C-2, C-3), 159.9 (C-4″), 207.3 ppm (C-1); HRMS (ESI): m/z: calcd for $C_{15}H_{13}ClO_2$: 261.06768 $[M+H]^+$; found: 261.06767.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-isopropylcyclopent-2-enone (3c): The *tert*-butyl ether **15c** was deprotected according to General Procedure D with **15c** (418 mg, 1.27 mmol) and CF_3COOH (1.30 mL) in CH_2Cl_2 (13.0 mL). After the mixture had been stirred for 15 min at room temperature, **3c** was isolated as a light yellow solid (349 mg, 1.27 mmol, quant.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.20$ (d, $J = 7.0$ Hz, 6H; 2-CH-(CH_3)$_2$), 2.33–2.40 (m, 2H; 5-H_2), 2.62–2.70 (m, 2H; 4-H_2), 2.92 (sept., $J = 7.0$ Hz, 1H; 2-CH(CH$_3$)$_2$), 6.82 (dd, $J = 8.5$ Hz, 2.3 Hz, 1H; 5″-H), 6.96 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.47 (d, $J = 8.5$ Hz, 1H; 6″-H), 10.61 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 19.98$ (2-CH-(CH_3)$_2$), 25.04 (2-CH(CH$_3$)$_2$), 29.85 (C-4), 33.99 (C-5), 88.21 (C-1′), 102.4 (C-2′), 111.3 (C-1″), 115.1 (C-5″), 116.3 (C-3″), 134.8 (C-6″), 136.0 (C-2″), 147.5 (C-3), 151.3 (C-2), 159.9 (C-4″), 207.2 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{16}H_{15}ClO_2$: 274.0761 $[M]^+$; found: 274.0759.

3-(4-Hydroxyphenylethynyl)-2-methylcyclopent-2-enone (3d)—Procedure a: A solution of BBr_3 (1.0 M in CH_2Cl_2, 3.50 mL, 3.50 mmol) was added dropwise at −78 °C to a solution of **15f** (227 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL). The reaction mixture was slowly warmed to room temperature over 14 h, and a saturated solution of NH_4Cl (20 mL) and H_2O (5 mL) was then added. The mixture was stirred for 15 min at room temperature and then extracted with ethyl acetate (30 mL, 2×20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$, and the solvent was evaporated after addition of silica gel (4 g). The product was isolated by column chromatography (silica gel, pentane/ethyl acetate 2.5:1 → 1:1) and subsequent HPLC (Kromasil 100 C18 (7 μm, 250×20 mm), CH_3CN/H_2O 45:55, flow 12 mL min^{-1}) as a yellow solid (69.0 mg, 325 μmol, 33%).

Procedure b: CsF (1.40 g, 9.22 mmol) was added at 0 °C to a solution of **15d** (1.09 g, 2.96 mmol) in CH_3CN (29.0 L). After 1 min a yellow precipitate had formed. The ice bath was removed, and the mixture was stirred for 1.5 h at room temperature. The mixture was then poured into a saturated solution of $NaHCO_3$ (150 mL) and extracted with Et_2O (50 mL) and ethyl acetate (2×50 mL). The combined organic layers were washed with brine (2×30 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The product was isolated by column chromatography (silica gel, pentane/ethyl acetate 4:1 → pentane/ethyl acetate 1:2 → acetone) as a bright yellow solid (555 mg, 2.61 mmol, 88%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.79$ (t, $J = 2.2$ Hz, 3H; 2-CH_3), 2.34–2.39 (m, 2H; 5-H_2), 2.66 (tq, $J = 4.7$, 2.2 Hz, 2H; 4-H_2), 6.79–6.85 (m, 2H; 3″-H, 5″-H), 7.37–7.43 (m, 2H; 2″-H, 6″-H), 10.09 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 9.40$ (2-CH_3), 29.58 (C-4), 33.50 (C-5), 83.74 (C-1′), 106.2 (C-2′), 111.3 (C-l″), 115.9 (C-3″, C-5″), 133.6 (C-2″, C-6″), 142.4 (C-3), 149.5 (C-2), 159.1 (C-4″), 207.5 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{14}H_{12}O_2$: 212.0837 $[M]^+$; found: 212.0837.

3-(4-Aminophenylethynyl)-2-methylcyclopent-2-enone (3e): The *tert*-butyl ether **15e** was deprotected according to General Procedure D with **15e** (687 mg, 2.21 mmol) and CF_3COOH (17 mL) in CH_2Cl_2 (40.0 mL). After the mixture had been stirred for 1.5 h at room temperature the solvent was evaporated, the residue was taken up in HCl (2 M, 5 mL) and toluene (50 mL), and the solvent was evaporated in vacuo. The procedure was repeated four times. The formed hydrochloride was dissolved in NaOH (10%, 50 mL) and ethyl acetate (50 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2×50 mL), and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave **3e** as a brown solid (456 mg, 2.15 mmol, 97%). ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 1.80$ (t, $J = 2.3$ Hz, 3H; 2-CH_3), 2.32–2.37 (m, 2H; 5-H_2), 2.67 (tq, $J = 4.8$, 2.3 Hz, 2H; 4-H_2), 5.29 (brs, 2H; 4″-NH_2), 6.66–6.72 (m, 2H; 3″-H, 5″-H), 7.24–7.30 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (75.5 MHz, [D$_4$]MeOH): $\delta = 9.61$ (2-CH_3), 31.32 (C-4), 34.88 (C-5), 84.36 (C-1′), 110.3, 110.6 (C-2′, C-1″), 115.4 (C-3″, C-5″), 134.7 (C-2″, C-6″), 142.5 (C-3), 151.7 (C-2), 154.3 (C-4″), 211.7 ppm (C-1); HRMS (EI$^+$): m/z: calcd for $C_{14}H_{13}NO$: 211.0997 $[M]^+$; found: 211.0997.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-methylcyclohex-2-enone (4a): The *tert*-butyl ether **16a** was deprotected according to General Procedure D with **16a** (5.33 g, 16.8 mmol) and CF_3COOH (16.7 mL) in CH_2Cl_2 (167 mL). After the mixture had been stirred for 80 min at room temperature, **4a** was isolated as a yellow solid (4.26 g, 16.3 mmol, 97%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.87$–1.98 (m, 5H; 5-H_2, 2-CH_3), 2.38 (t, $J = 6.6$ Hz, 2H; 6-H_2), 2.50–2.56 (m, 2H; 4-H_2), 6.77 (dd, $J = 8.6$, 2.3 Hz, 1H; 5″-H), 6.93 (d, $J = 2.3$ Hz, 1H; 3″-H), 7.43 (d, $J = 8.6$ Hz, 1H; 6″-H), 10.48 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 13.72$ (2-CH_3), 22.18 (C-5), 30.29 (C-4), 37.23 (C-6), 91.26 (C-1′), 99.83 (C-2′), 111.6 (C-1″), 115.0 (C-5″), 116.2 (C-3″), 134.8 (C-6″), 135.9, 136.8, 137.4 (C-2, C-2″, C-3), 159.6 (C-4″), 197.1 ppm (C-1); HRMS (ESI): m/z: calcd for $C_{15}H_{13}ClO_2$: 261.06768 $[M+H]^+$; found: 261.06781.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-ethylcyclohex-2-enone (4b): The *tert*-butyl ether **16b** was deprotected according to General Procedure D with **16b** (454 mg, 1.37 mmol) and CF_3COOH (1.36 mL) in CH_2Cl_2 (13.6 mL). After the mixture had been stirred for 80 min at room temperature, **4b** was isolated as a yellow solid (318 mg, 1.16 mmol, 84%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H; 2-CH_2CH_3), 1.87–1.98 (m, 2H; 5-H_2), 2.39 (t, $J = 6.7$ Hz, 2H; 4-H_2), 2.46 (q, $J = 7.5$ Hz, 2H; 2-CH_2CH_3), 2.53 (t, $J = 6.1$ Hz, 2H; 4-H_2), 6.79 (dd, $J = 8.6$, 2.4 Hz, 1H; 5″-H), 6.94 (d, $J = 2.4$ Hz, 1H; 3″-H), 7.44 (d, $J = 8.6$ Hz, 1H; 6″-H), 10.50 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 13.25$ (2-CH_2CH_3), 20.97 (2-CH_2CH_3), 22.17 (C-5), 30.31 (C-4), 37.43 (C-6), 90.82 (C-1′), 99.27 (C-2′), 111.6 (C-1″), 115.0 (C-5″), 116.2 (C-3″), 134.7 (C-6″), 135.9, 136.5 (C-2″, C-3), 143.3 (C-2), 159.6 (C-4″),

196.7 ppm (C-1); HRMS(EI): *m/z*: calcd for $C_{16}H_{25}ClO_2$: 274.0761 $[M]^+$; found: 274.0761.

3-(2-Chloro-4-hydroxyphenylethynyl)-2-isopropylcyclohex-2-enone (4c): The *tert*-butyl ether **16c** was deprotected according to General Procedure D with **16c** (418 mg, 1.21 mmol) and CF_3COOH (1.21 mL) in CH_2Cl_2 (12.1 mL). After the mixture had been stirred for 75 min at room temperature, **4c** was isolated as a beige solid (337 mg, 1.17 mmol, 96%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.18 (d, J=7.1 Hz, 6H; 2-CH-(CH_3)$_2$), 1.83–1.94 (m, 2H; 5-H$_2$), 2.35 (dd, J=7.2, 6.1 Hz, 2H; 6-H$_2$), 2.54 (t, J=6.0 Hz, 2H; 4-H$_2$), 3.32 (sept., J=7.1 Hz, 1H; 2-C*H*(CH$_3$)$_2$), 6.79 (dd, J=8.6 Hz, 2.3 Hz, 1H; 5″-H), 6.94 (d, J=2.3 Hz, 1H; 3″-H), 7.42 (d, J=8.6 Hz, 1H; 6″-H), 10.49 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=20.27 (2-CH(*C*H$_3$)$_2$), 22.01 (C-5), 29.13 (2-*C*H(CH$_3$)$_2$), 31.29 (C-4), 38.39 (C-6), 91.06 (C-1′), 100.2 (C-2′), 111.7 (C-1″), 115.0 (C-5″), 116.3 (C-3″), 134.6 (C-6″), 135.8, 135.9 (C-2″, C-3), 146.0 (C-2), 159.6 (C-4″), 197.0 ppm (C-1); HRMS (EI$^+$): *m/z*: calcd for $C_{17}H_{17}C1O_2$: 288.0917 $[M]^+$; found: 288.0917.

3-(4-Hydroxyphenylethynyl)-2-methylcyclohex-2-enone (4d)—Procedure a: A solution of BBr_3 (1.0 M in CH_2Cl_2, 1.00 mL, 1.00 mmol) was added dropwise at −78 °C to a solution of **16h** (80.6 mg, 335 μmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred at −78 °C for 20 min and at room temperature for 2.25 h. The mixture was poured into H_2O (50 mL), brine (20 mL) was then added, and the mixture was extracted with ethyl acetate (4×20 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. KO*t*Bu (194 mg, 1.73 mmol) was added at room temperature to a solution of the crude product in *t*BuOH (4.0 mL). The mixture was stirred for 15 min at room temperature, then heated in a microwave for 20 min at 60 °C, and then poured into HCl (2 M, 40 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$, and the solvent was evaporated. The product was isolated by column chromatography (silica gel, pentane/ethyl acetate 1:1) as a yellow solid (49.1 mg, 217 μmol, 65%).

Procedure b: Sonogashira coupling was carried out according to General Procedure B with phenylacetylene **9d** (640 mg, 2.10 mmol) in DMF (1.6 mL), vinyl iodide **8a** (472 mg, 2.00 mmol) in DMF (3.0 mL), [Pd-(PPh$_3$)$_2$Cl$_2$] (21.4 mg, 30.5 μmol, 1.52 mol%) and CuI (12.2 mg, 64.1 μmol, 3.20 mol%) in DMF (0.40 mL), and NEt_3 (0.500 mL, 365 mg, 3.61 mmol). After 15.5 h at room temperature and workup, **16d** was purified by column chromatography (silica gel, pentane/ethyl acetate 15:1 → 12:1). TBAF·3H$_2$O (1.26 g, 3.99 mmol) in THF (15 mL) was added at room temperature to a solution of the intermediate product in THF (25 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for another 30 min, and was then diluted with H_2O (80 mL) and extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine (3×20 mL) and dried over Na_2SO_4, and the solvent was evaporated after addition of silica gel (5 g). The product **4d** was isolated by column chromatography (silica gel, pentane/ethyl acetate 3:1 → 1:1) as a light yellow solid (381 mg, 1.68 mmol, 84% over two steps). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.91 (t, J=1.9 Hz, 3H; 2-CH$_3$), 1.92 (quint., J=6.4 Hz, 2H; 5-H$_2$), 2.38 (t, J=6.4 Hz, 2H; 6-H$_2$), 2.51 (tq, J=6.4, 1.9 Hz, 2H; 4-H$_2$), 6.77–6.83 (m, 2H; 3″-H, 5″-H), 7.32–7.38 (m, 2H; 2″-H, 6″-H), 10.03 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=13.65 (2-CH$_3$), 22.19 (C-5), 30.46 (C-4), 37.23 (C-6), 86.83 (C-1′), 103.8 (C-2′), 111.7 (C-1″), 115.8 (C-3″, C-5″), 133.3 (C-2″, C-6″), 136.7, 137.3 (C-2, C-3), 158.9 ppm (C-4″), 197.1 (C-1); HRMS (EI$^+$): *m/z*: calcd for $C_{15}H_{14}O_2$: 226.0994 $[M]^+$; found: 226.1017.

5-Hydroxy-2-(2-methyl-3-oxocyclohex-1-enylethynyl)benzoic acid methyl ester (4e): TBAF·3H$_2$O (1.35 g, 4.28 mmol) was added at 0 °C to a solution of **16e** (629 mg, 1.43 mmol) in THF (25 mL). The solution was stirred for 30 min at 0 °C and for 35 min at room temperature, and was then diluted with H_2O (50 mL) and brine (30 mL) and extracted with ethyl acetate (4×50 mL). The combined organic layers were washed with brine (2×30 mL) and dried over $MgSO_4$, and the solvent was evaporated after addition of silica gel (5 g). The product **4e** was isolated by column chromatography (silica gel, pentane/ethyl acetate 1.5:1) as a light yellow solid (379 mg, 1.33 mmol, 93%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.93 (t, J=1.6 Hz, 3H; 2″-CH$_3$), 1.94 (quint., J=6.2 Hz, 2H; 5″-H$_2$), 2.39 (t, J=6.2 Hz, 2H; 4″-H$_2$), 2.53 (tq, J=6.2, 1.6 Hz, 2H; 6″-H$_2$), 3.83 (s, 3H; 1-COOCH$_3$), 7.01 (dd, J=8.5, 2.7 Hz, 1H; 4-H), 7.29 (d, J=2.7 Hz, 1H; 6-H), 7.48 (d, J=8.5 Hz, 1H; 3-H), 10.44 ppm (brs, 1H; 5-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=13.66 (2″-CH$_3$), 22.21 (C-5″), 30.40 (C-6″), 37.25 (C-4″), 52.17 (1-COO*C*H$_3$), 90.41 (C-2′), 102.1 (C-1′), 111.7 (C-2), 116.8 (C-6), 119.4 (C-4), 133.2 (C-1), 135.8 (C-3), 137.3, 137.4 (C-1″, C-2″), 158.5 (C-5), 165.6 (1-*C*OOCH$_3$), 197.3 ppm (C-3″); HRMS (EI$^+$): *m/z*: calcd for $C_{17}H_{16}O_4$: 284.1049 $[M]^+$; found: 284.1049.

3-(2-Bromo-4-hydroxyphenylethynyl)-2-methylcyclohex-2-enone (4f): Sonogashira coupling was carried out according to General Procedure C with phenylacetylene **9b** (400 mg, 1.42 mmol) in DMF (1.2 mL), vinyl iodide **8a** (279 mg, 1.18 mmol) in DMF (1.5 mL), [Pd(PPh$_3$)$_2$Cl$_2$] (12.6 mg, 18.0 μmol, 1.50 mol%) and CuI (7.10 mg, 37.0 μmol, 3.20 mol%) in DMF (0.30 mL), and NEt_3 (0.260 mL, 190 mg, 1.88 mmol). After 20 h at room temperature and workup, **16f** was purified by column chromatography (silica gel, pentane/ethyl acetate/NEt_3 15:1 → 100:20:1). The intermediate product **16f** was deprotected according to General Procedure C with CH_2Cl_2 (20 mL) and CF_3COOH (2.0 mL) at room temperature. After the mixture had been stirred at room temperature for 30 min and the solvent had been evaporated, the product **4f** was isolated by recrystallization from THF/cyclohexane as a yellow solid (204 mg, 668 μmol, 57% over two steps). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.94 (quint., J=6.3 Hz, 2H; 5-H$_2$), 1.95 (t, J=1.7 Hz, 3H; 2-CH$_3$), 2.39 (t, J=6.3 Hz, 2H; 6-H$_2$), 2.54 (tq, J=6.3, 1.7 Hz, 2H; 4-H$_2$), 6.83 (dd, J=8.6, 2.4 Hz, 1H; 5″-H), 7.11 (d, J=2.4 Hz, 1H; 3″-H), 7.45 (d, J=8.6 Hz, 1H; 6″-H), 10.50 ppm (brs, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=13.84 (2-CH$_3$), 22.19 (C-5), 30.30 (C-4), 37.23 (C-6), 90.51 (C-1′), 101.6 (C-2′), 113.8 (C-1″), 115.4 (C-5″), 119.3 (C-3″), 125.7 (C-2″), 134.9 (C-6″), 136.8, 137.4 (C-2, C-3), 159.5 (C-4″), 197.2 ppm (C-1); HRMS (EI$^+$): *m/z*: calcd for $C_{15}H_{13}BrO_2$: 304.0099 $[M]^+$; found: 304.0099.

3-(4-Aminophenylethynyl)-2-methylcyclohex-2-enone (4g): A solution of **16g** (735 mg, 2.26 mmol) in CF_3COOH (4.0 mL) and CH_2Cl_2 (40 mL) was stirred for 20 min at room temperature. The solvent was evaporated and the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ (2×20 mL) and brine (20 mL) and dried over $MgSO_4$, and the solvent was evaporated. Compound **4g** was isolated by column chromatography (silica gel, pentane/ethyl acetate 2.5:1 → pentane/ethyl acetate/NEt_3 60:40:1) as a yellow solid (271 mg, 1.20 mmol, 53%). Starting material **16g** was also isolated (179 mg, 550 μmol, 24%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.00 (quint., J=6.3 Hz, 2H; 5-H$_2$), 2.03 (t, J=1.8 Hz, 3H; 2-CH$_3$), 2.46 (t, J=6.3 Hz, 2H; 6-H$_2$), 2.56 (tq, J=6.3, 1.8 Hz, 2H; 4-H$_2$), 3.96 (brs, 2H; 4″-NH$_2$), 6.59–6.67 (m, 2H; 3″-H, 5″-H), 7.25–7.34 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.90 (2-CH$_3$), 22.68 (C-5), 31.19 (C-4), 37.87 (C-6), 87.03 (C-1′), 105.0 (C-2′), 111.5 (C-1″), 114.6 (C-3″, C-5″), 132.3 (C-2″, C-6″), 137.4, 138.5, 147.6 (C-2, C-3, C-4″), 198.6 ppm (C-1); HRMS (EI$^+$): *m/z*: calcd for $C_{15}H_{15}NO$: 225.1154 $[M]^+$; found: 225.1154.

2-Methyl-3-(4-triisopropylsilanyloxyphenylethynyl)cyclopent-2-enol (17): Compound **15d** (921 mg, 2.50 mmol), dissolved in MeOH (10 mL), was added at room temperature to a stirred solution of $CeCl_3$·7H$_2$O (3.22 g, 8.64 mmol) in MeOH (25 mL). Et_2O (10 mL) was then added and stirring was continued for 20 min. $NaBH_4$ (114 mg, 3.01 mmol) was added portionwise every 5 min over 20 min, and the reaction mixture was stirred for 110 min at room temperature. After addition of another portion of $NaBH_4$ (58 mg, 1.5 mmol) and stirring for another 60 min a third portion of $NaBH_4$ (82 mg, 2.2 mmol) was added, and the mixture was stirred for 60 min at room temperature. The mixture was poured into H_2O (150 mL), stirred for 15 min, and extracted with Et_2O (4×50 mL). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo after addition of silica gel (6 g). Column chromatography (silica gel, pentane/ethyl acetate 7:1) gave **17** as a yellow oil (801 mg, 2.16 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.09 (d, J=7.4 Hz, 18H; 3×SiCH(CH$_3$)$_2$), 1.21–1.30 (m, 3H; 3×SiCH(CH$_3$)$_2$), 1.51 (brs, 1H; 1-OH), 1.67–1.75 (ddt, 1H; 5-H$_A$), 1.94–1.96 (brm, 3H; 2-CH$_3$), 2.31–2.40 (m, 1H; 5-H$_B$), 2.39–2.47 (brm, 1H; 4-

H_A), 2.59–2.67 (m, 1H; 4-H_B), 4.66–4.71 (br m, 1H; 1-H), 6.80–6.85 (m, 2H; 3″-H, 5″-H), 7.30–7.35 ppm (m, 2H; 2″-H, 6″-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 12.63$ ($3\times SiCH(CH_3)_2$), 13.14 (2-CH_3), 17.85 ($3\times SiCH(CH_3)_2$), 33.04 (C-5), 33.71 (C-4), 80.17 (C-1), 84.47 (C-1′), 94.37 (C-2′), 115.8 (C-1″), 120.0 (C-3″, C-5″), 121.5 (C-3), 132.9 (C-2″, C-6″), 147.0 (C-2), 156.3 ppm (C-4″); HRMS (EI$^+$): m/z: calcd for $C_{23}H_{34}O_2$: 370.2328 $[M]^+$; found: 370.2328.

3-(4-Hydroxyphenylethynyl)-2-methylcyclopent-2-enol (5): CsF (836 mg, 5.50 mmol) was added at 0 °C to a stirred solution of **17** (757 mg, 2.04 mmol) in CH_3CN (20 mL). Stirring was continued for 5 h at room temperature, CsF (800 mg, 5.27 mmol) was again added, and stirring was continued for another 13.5 h. The mixture was then poured into a saturated solution of NaCl (100 mL) and extracted with ethyl acetate ($2\times$ 50 mL), dichloromethane (50 mL), and Et_2O (3×50 mL). The combined organic layers were washed with brine (2×30 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The product was isolated by column chromatography (silica gel, Et_2O) as a bright yellow solid (249 mg, 1.16 mmol, 57%). ^{1}H NMR (500 MHz, [D_6]acetone): $\delta = 1.62$–1.70 (m, 1H; 5-H_A), 1.87–1.89 (br m, 3H; 2-CH_3), 2.21–2.28 (m, 1H; 5-H_B), 2.29–2.38 (br m, 1H; 4-H_A), 2.47–2.55 (m, 1H; 4-H_B), 4.01 (br s, 1H; 1-OH), 4.59–465 (br m, 1H; 1-H), 6.80–6.85, 2H; 3″-H, 5″-H), 7.27–7.32 (m, 2H; 2″-H, 6″-H), 8.75 ppm (br s, 1H; 4″-OH); ^{13}C NMR (75.5 MHz, [D_6]acetone): $\delta = 13.34$ (2-CH_3), 33.54 (C-5), 34.23 (C-4), 79.59 (C-1), 84.96 (C-1′), 94.62 (C-2′), 115.2 (C-1″), 116.4 (C-3″, C-5″), 120.6 (C-3), 133.7 (C-2″, C-6″), 148.9 (C-2), 158.5 ppm (C-4″); HRMS (EI$^+$): m/z: calcd for $C_{14}H_{14}O_2$: 214.0990 $[M]^+$; found: 212.0990.

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