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Sonogashira cross-coupling of 3-bromo-1,2-diones: an access to 3-alkynyl-1,2-diones

Anne Paju [a], Tõnis Kanger [a], Aleksander-Mati Müürisepp [a], Tiina Aid [a], Tõnis Pehk [b], Margus Lopp [a,*]

[a] Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia
[b] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia

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ABSTRACT

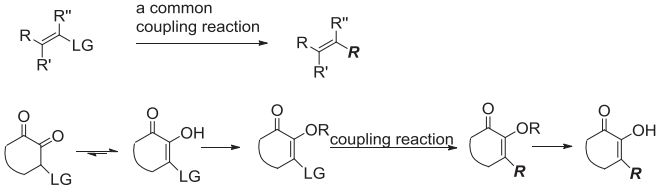
A new general method for the synthesis of enols of cyclic 3-alkynyl-substituted 1,2-diketones is developed. Sonogashira cross-coupling of silyl enolates of cyclic 3-bromo-cyclopentane- and 3-bromo-cyclohexane-1,2-diones with variety of substituted acetylenes afforded enols of cyclic 3-alkynyl-1,2-diones with good yields (up to 93%) in a short reaction time. The starting 3-bromo-1,2-diones are easily obtainable by direct bromination of 1,2-diones with NBS.

1. Introduction

Cross-coupling reactions are among the most frequently used tools for creating new C–C bonds of organic molecule skeletons.[1] Vinyl halides and other functionalized alkenes are the common substrates for these transformations. Thus, the vinylic α- and β-leaving groups (halide, triflate, etc.) at the double bond of α,β-unsaturated carbonyl compounds can be replaced by alkyl, alkenyl, alkynyl or aryl groups.[2] There are some examples in the literature of the replacement of enol ester groups and 2-halides of enol ethers of ketones by the cross-coupling reaction.[3] Also, there are references on the substitution of 2-halides (Br, I) of enol ethers of 1,3-dicarbonyl compounds by alkynyl groups in Sonogashira coupling.[4]

To the best of our knowledge, there are only a few specific references on the cross-coupling reactions of enol ethers of 1,2-dicarbonyl compounds having leaving groups (LG) in position 3: iodine replacement in 2-hydroxy-3-iodo-1,4-naphthoquinone by Heck reaction,[5] bromine and iodine replacement in 2-hydroxy-1,4-naphthoquinone-3-halides by Sonogashira coupling,[6] bromine replacement in 3-bromoisotetronic acid by Suzuki coupling,[7] and 3-triflate replacement in 2-arylchromones by Stille coupling.[8]

LG-substituted enolates of 1,2-diketones have not been used as the substrates in cross-coupling reactions, although 3-substituted 1,2-dicarbonyl compounds are useful intermediates for the synthesis of different valuable compounds.[9] To find a simple approach to 3-substituted 1,2-diketones a possibility to use the enolate of 3-LG-1,2-diketone as substrate for cross-coupling reaction needs to be investigated (Scheme 1).



Scheme 1. Cross-coupling reaction of generated from 1,2-diketones vinylic compounds to form 3-substituted 1,2-dicarbonyl compounds.

We decided first to study Sonogashira coupling of 3-bromo-cyclopentane- and cyclohexane-1,2-diones with alkynes in order to prepare cyclic 3-alkynyl-substituted 1,2-diones. These compounds are very rare: there is only one reference on the formation of 3-alkynylcyclopentane-1,2-diones by Au-catalyzed Nazarov cyclization.[2g] 3-Alkynyl-cyclohexane-1,2-diketones have not been described in literature so far.

2. Results and discussion

In the present work Sonogashira coupling of the enolate of 3-bromo-cyclopentane-1,2-dione **1**, of silyl enolate of 3-bromo-cyclopentane-1,2-dione **2**, and of silyl enolate of

* Corresponding author. E-mail addresses: margus.lopp@ttu.ee, lopp@chemnet.ee (M. Lopp).

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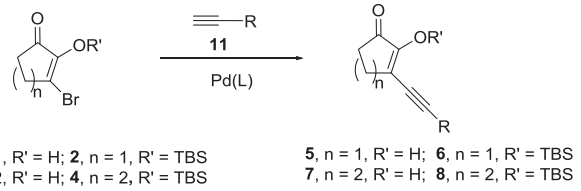
3-bromo-cyclohexane-1,2-dione **4** with acetylenic compounds **11** was studied (Scheme 2).

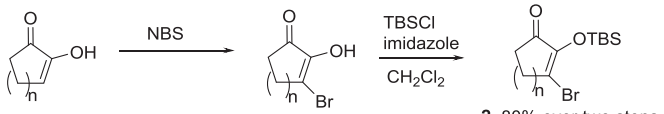


1, n = 1, R' = H; **2**, n = 1, R' = TBS
3, n = 2, R' = H; **4**, n = 2, R' = TBS

5, n = 1, R' = H; **6**, n = 1, R' = TBS
7, n = 2, R' = H; **8**, n = 2, R' = TBS

Scheme 2. Sonogashira cross-coupling reaction of cyclic 3-bromo-1,2-dicarbonyl compounds.

The substrate for coupling, 3-bromo enol **1**, had been previously prepared by bromination of cylcopentanone with Br_2 followed by hydrolysis in 47% yield in two steps.[10] Bromoenol **3** was prepared from 2-bromo-cyclohexanone by α-oxidation with DMSO in 34% yield,[11] and by a direct bromination of 1,2-cyclohexanedione in up to 90% yield.[11,12] We prepared 3-bromo enol **1** by direct bromination of dione **9** with NBS in a 4:1 mixture of acetone/water, in 89% yield, using a slightly modified procedure for the halogenation of vinylic ethers.[13] Protection of the enol hydroxyl group might not be necessary for the cross-coupling reaction. Therefore both, enols (**1**, **3**) and *tert*-butyldimethylsilyl enolates (**2**, **4**), were prepared. The enol hydroxyl group was converted to *tert*-butyldimethylsilyl enol ether **2** in 90% yield. 1,2-Cyclohexanedione **10** was brominated with NBS in a 4:1 mixture of CH_2Cl_2/MeOH. The isolated yield of 3-bromo cylohexane-1,2-dione enol derivative **4** was slightly lower: 62% for two steps (Scheme 3).



9, n=1
10, n=2

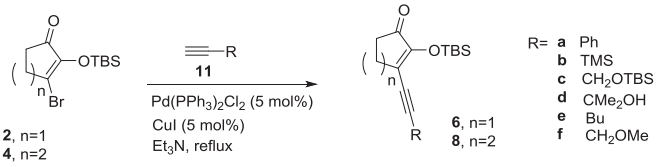
1, n = 1
3, n = 2

2, 80% over two steps
4, 62% over two steps

Scheme 3. Synthesis of cyclic 3-bromo-1,2-diones.

In order to find optimal conditions for Sonogashira cross-coupling[14] of cyclic 3-bromo-1,2-diones its reaction with acetylenic compounds **11a** and **11b** was investigated (Table 1). Phenylacetylene **11a** and trimethylsilylacetylene **11b** with unprotected substrate **1** gave a low yield of acetylenic compound **5** (13% for **5a** and 15% for **5b**, Table 1, entries 1 and 2; 5 mol % of $Pd(PPh_3)_2Cl_2$, in the presence of 5 mol % of CuI for **11a**, and of 5 mol % of $Pd(PPh_3)_4$ for **11b**). Always, a considerable amount of reduction product **9** (33% and 20%, correspondingly) was isolated. At the same time, the bromide of silyl enol ether **2** reacted smoothly with phenylacetylene **11a** and trimethylsilylacetylene **11b** in the same reaction conditions, affording **6a** in 90% and **6b** in 83% yield (Table 1, entries 3 and 4). Therefore, in the following experiments only protected substrates **2** and **4** were used in cross-coupling experiments.

Table 2
Cross-coupling reaction of cyclic 3-bromo-1,2-diketones with alkynes



2, n=1
4, n=2

6, n=1
8, n=2

No	Substrate	**11** (equiv)	Product	Yield %
1	**2**	**a** (3)	**6a**	93
2	**4**	**a** (2)	**8a**	91
3	**2**	**b** (3)	**6b**	83
4	**2**	**c** (3)	**6c**	64
5[a]	**2**	**c** (3)	**6c**	83
6	**2**	**d** (2)	**6d**	93
7	**4**	**d** (2)	**8d**	80
8	**2**	**e** (3)	**6e**	59
9[a]	**2**	**e** (3)	**6e**	68
10	**2**	**f** (3)	**6f**	85
11	**4**	**f** (3)	**8f**	59
12[a]	**4**	**f** (3)	**8f**	70

[a] $Pd(PPh)_3Cl_2$ (10 mol %); CuI (10 mol %).

The presence of a base is essential for the cross-coupling reaction.[14] The most common bases are secondary and tertiary amines and carbonates of alkali metals. In many cases, the bases (e.g., amines) also act as reaction media.[14,15] When using a mixture of THF/Et_3N, we found that the yield of the reaction depended only slightly on the Et_3N and THF ratio (Table 1, entries 3 and 6 for **11a**; 4 and 8 for **11b**). The reaction temperature had a significant effect on the yield: at room temperature even in long reaction times, the yields of coupling for **11a** remained low (Table 1, entries 5 and 7). Alkyne **11b** is more reactive at room temperature, so the temperature increase did not have a notable effect on the yield, but only had an effect on the reaction rate (Table 1, entry 4 and 8). Stable yields for both reagents, **11a** and **11b**, were obtained by using boiling Et_3N as a reaction medium. Although a boiling mixture of THF/Et_3N afforded a similar yield of the products (Table 1, entry 6), in the following experiments Et_3N at reflux was used (Table 1, entries 3, 4, 9–11; all entries of Table 2).

The presence of copper (CuI) in a reaction medium supported the reaction (compare Table 1, entries 4 and 9). There are many different Pd sources and ligands used for Sonogashira coupling.[14] The most common Pd catalysts are $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(PPh_3)_2(OAc)_2$. In our case these catalysts worked almost equally well for the coupling reaction (Table 1, entries 3, 10–11). Twofold and threefold excess of acetylenic compound **11** to substrate **2** was found to result in stable good yields of **6**.

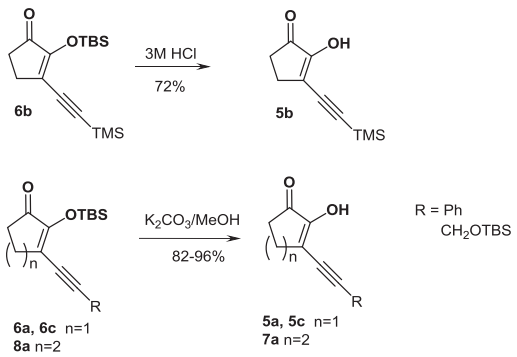
Table 1
Investigation of reaction conditions for the cross-coupling reaction

No	Substrate	Alkyne **11**	Catalyst (5 mol %)	THF/Et_3N (molar ratio)	Temp	Time h	Yield % **6**
1	**1**	**a** (2)	$Pd(PPh_3)_2Cl_2$/CuI	Et_3N	Reflux	1	13[a]
2	**1**	**b** (3)	$Pd(PPh_3)_4$	Et_3N	Reflux	3	15[b]
3	**2**	**a** (2)	$Pd(PPh)_3Cl_2$/CuI	Et_3N	Reflux	1	90
4	**2**	**b** (3)	$Pd(PPh)_3Cl_2$/CuI	Et_3N	Reflux	1	83
5	**2**	**a** (2)	$Pd(PPh_3)_2Cl_2$/CuI	THF/Et_3N (3.6:1)	rt	24	28
6	**2**	**a** (2)	$Pd(PPh_3)_2Cl_2$/CuI	THF/Et_3N (3.6:1)	Reflux	1	79
7	**2**	**a** (2)	$Pd(PPh_3)_2Cl_2$/CuI	Et_3N	rt	21	7
8	**2**	**b** (2)	$Pd(PPh_3)_2Cl_2$/CuI	THF/Et_3N (3.6:1)	rt	24	85
9	**2**	**b** (3)	$Pd(PPh_3)_4$	Et_3N	Reflux	1	54
10	**2**	**a** (2)	$Pd(PPh_3)_2(OAc)_2$/CuI	Et_3N	Reflux	1	83
11	**2**	**a** (2)	$Pd(PPh_3)_4$/CuI	Et_3N	Reflux	1	88

[a] 33% of enol **9** was isolated.
[b] 20% of enol **9** was isolated.

To elucidate the scope of the method different terminal alkynes **11** were subjected to cross-coupling reactions with protected enol 3-bromides of cyclopentane- and cylohexane-1,2-diones **2** and **4** in boiling triethyl amine using $Pd(PPh)_3Cl_2$/CuI as a catalyst. A smooth reaction afforded 3-substituted cyclopentane- and cylohexane-1,2-diones **6** and **8** up to 93% isolated yield, although cyclopentane-1,2-diones **2** gave slightly better yields than the corresponding cyclohexane substrates **4** (Table 2). The less reactive alkynes **11c** and **11e** demanded higher catalyst loadings to afford acceptable yields (Table 2, entries 5 and 9).

Desilylation of silyl enol ethers was performed with K_2CO_3/MeOH affording enols **5** in almost quantitative yield (96% for **5a** and 94% for **7a**). For the disilyl products **6b** and **6c**, a problem of selective mono-desilylation arises because the enol–TBS group is both, acid- and base-sensitive and acetylenic and propargylic TBS groups have different sensitivities to acid. For silyl acetylene **6b** mono-desilylation was achieved in acidic conditions with 3 M HCl in THF, affording silyl acetylene derivative **5b** in 72% yield. For **6c** a selective mono-desilylation of the enol ether moiety succeeded only by using basic treatment with K_2CO_3/MeOH, affording mono silyl derivative **5c** in 82% yield, while in acidic conditions both silyl groups cleaved (Scheme 4).



Scheme 4. Desilylation of silyl enol ethers.

3. Conclusions

A simple and efficient Sonogashira cross-coupling reaction of cyclic 3-bromo-1,2-diketones **2** and **4** with substituted acetylenes **11** was developed. The protocol affords enols of 3-alkynyl-substituted 1,2-diketones **6** and **8** in a short reaction time with good yield. Easy access of the starting bromoenols **1** and **3** from available compounds makes the whole approach convenient and practical. The use of 3-bromo-1,2-diketones in other coupling reactions is currently under study.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded in deuterated solvents on a 400 MHz spectrometer. Deuterated solvent peaks were used as references. 2D FT methods were used for the full assignment of ^1H and ^{13}C chemical shifts. Mass spectra were measured on a GC–MS spectrometer using EI (70 eV). TLC was performed using $60F_{254}$ silica gel plates. For column chromatography 40–100 μm and 100–160 μm silica gel was used. All reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. THF was distilled from $LiAlH_4$ before use. CH_2Cl_2 was distilled from CaH_2.

4.2. 3-Bromo-2-hydroxy-cyclopent-2-enone (1)

To a solution of 1,2-cyclopentanedione **9** (98 mg, 1 mmol) in acetone (4 mL) and water (1 mL) NBS (214 mg, 1.2 mmol) was added and the mixture was stirred for 16 h at room temperature. Water (4 mL) was then added, acetone was removed under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (1×8 mL and 4×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, heptanes/EtOAc 10:2) gave compound **1** as a white solid (158 mg, 89%); mp 151–153 °C; [Found: C, 34.02; H, 2.90. $C_5H_5BrO_2$ requires C, 33.93; H, 2.85]; ν_{max} (KBr, cm^{-1}): 3205, 2921, 1703, 1657, 1372, 1301, 1261, 1228, 1135, 875; δ_H (400 MHz, $CDCl_3$) 6.40 (s, 1H, OH), 2.86–2.84 (m, 2H, H-4), 2.60–2.58 (m, 2H, H-5); δ_C (101 MHz, $CDCl_3$) 198.7 (C-1), 151.2 (C-2), 127.8 (C-3), 33.8 (C-5), 30.0 (C-4). *m/z* (EI) 178 and 176 (M^+, 39.9 and 41.6), 97 (94.0), 69 (100).

4.3. 3-Bromo-2-hydroxy-cyclohex-2-enone (3)

To a solution of 1,2-cyclohexanedione **10** (162 mg, 1.45 mmol) in MeOH (5.8 mL) and CH_2Cl_2 (1.45 mL) NBS (310 mg, 1.74 mmol) was added and the mixture was stirred for 3 h at room temperature. Then a solution of $Na_2S_2O_3$ (2%, 6.5 mL) was added and the mixture was extracted with CH_2Cl_2 (4×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, heptanes/EtOAc 10:1 to 10:1.5) gave compound **3** as a white solid (183 mg, 66%), which physical and spectroscopic properties correspond to the literature data,[11,12a] (see ^1H and ^{13}C NMR spectra in Supplementary data).

4.4. 3-Bromo-2-(*tert*-butyl-dimethyl-silanyloxy)-cyclopent-2-enone (2)

To a solution of 3-bromocyclopentane-1,2-dione **1** (446 mg, 2.52 mmol) and imidazole (343 mg, 5.04 mmol) in CH_2Cl_2 (12.5 mL) TBDMSCl (571 mg, 3.78 mmol) was added. After stirring at room temperature for 30 min, water (25 mL) was added, CH_2Cl_2 layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, heptanes/EtOAc 60:1 to 50:1) to give target compound **2** as a white solid (662 mg, 90%); mp 54–55 °C; [Found: C, 45.40; H, 6.58. $C_{11}H_{19}BrO_2Si$ requires C, 45.36; H, 6.621]. δ_H (400 MHz, $CDCl_3$): 2.82–2.80 (m, 2H, H-4), 2.51–2.49 (m, 2H, H-5), 0.98 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 198.6 (C-1), 151.9 (C-2), 136.1 (C-3), 34.1 (C-5), 30.0 (C-4), 25.7 ($C(CH_3)_3$), 18.5 ($C(CH_3)_3$), −3.9 ($Si(CH_3)_2$). ν_{max} (KBr, cm^{-1}): 2929, 2859, 1706, 1632, 1474, 1408, 1332, 1156, 844, 785. *m/z* (EI) 277 and 275 (M^+–15, 1.6 and 1.5), 235 and 233 (M^+–57, 100 and 99.3), 154 (14.0), 139 (10.8), 137 (10.4).

4.5. 3-Bromo-2-(*tert*-butyl-dimethyl-silanyloxy)-cyclohex-2-enone (4)

To a solution of 3-bromocyclohexane-1,2-dione **3** (275 mg, 1.44 mmol) and imidazole (196 mg, 2.88 mmol) in CH_2Cl_2 (7.2 mL) TBDMSCl (326 mg, 2.16 mmol) was added. After stirring at room temperature for 1 h, water (15 mL) was added and the work-up was performed as described for bromoenone **2**, resulting in the target compound **4** as a white solid (413 mg, 94%); mp 60–61 °C; [Found: C, 47.25; H, 6.95. $C_{12}H_{21}BrO_2Si$ requires C, 47.21; H, 6.93]. ν_{max} (KBr, cm^{-1}): 2932, 2856, 1678, 1616, 1473, 1335, 1311, 1249, 1206, 1179, 939, 840, 783. δ_H (400 MHz, $CDCl_3$) 2.89 (t, *J*=6.1 Hz, 2H. H-4), 2.48 (dd, *J*=7.4, 6.0 Hz, 2H, H-6), 2.03–1.97 (m, 2H, H-5), 0.98 (s, 9H, $C(CH_3)_3$), 0.20 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 192.0 (C-1), 146.9 (C-2), 128.3 (C-3), 38.0 (C-6), 35.8 (C-4), 26.0 ($C(CH_3)_3$), 23.0

(C-5), 19.1 ($C(CH_3)_3$), −3.7 ($Si(CH_3)_2$). *m/z* (EI) 291 and 289 (M^+−15, 3.7 and 3.8), 249 and 247 (M^+−57, 100 and 99.3), 167 (14.8), 139 (45.2), 137 (45.9).

4.6. General procedure for the coupling of cyclic 3-bromo-1,2-diketones with terminal alkynes

A mixture of bromo-diketone (**2** or **4**; 0.3 mmol), $Pd(PPh_3)_2Cl_2$ (10.5 mg, 0.015 mmol), and CuI (2.9 mg, 0.015 mmol) in 10-mL flask equipped with septum was flushed with argon for 10 min. Triethyl amine (6 mL) was then added and the flask flushed again with argon for 10 min. Finally, alkyne **11** (0.6–0.9 mmol) was added and the reaction mixture was heated at reflux for 1 h. Subsequently, saturated NH_4Cl solution (12 mL) was added to the cooled mixture and extracted with EtOAc (2×10 mL). The extracts were washed with brine (5 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, heptanes/EtOAc or heptanes/toluene) to give target compounds.

4.7. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylethynyl-cyclopent-2-enone (6a)

Obtained as a white solid (87 mg, 93%); mp 103–105 °C; [Found: C 73.05; H, 7.77. $C_{19}H_{24}O_2Si$ requires C, 73.03; H, 7.74.]. ν_{max} (KBr, cm^{-1}): 3058, 2928, 2855, 2195, 1698, 1613, 1591, 1488, 1380, 1308, 1249, 1165, 1109, 856, 788, 755, 688. δ_H (400 MHz, $CDCl_3$) 7.50–7.47 (m, 2H, *o*-Ph), 7.37–7.35 (m, 3H, m, *p*-Ph), 2.68–2.65 (m, 2H, H-4), 2.44–2.42 (m, 2H, H-5), 1.03 (s, 9H, $C(CH_3)_3$), 0.26 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 202.9 (C-1), 155.7 (C-2), 131.8 (2C, *o*-Ph), 131.2 (C-3), 129.2 (1C, *p*-Ph), 128.6 (2C, *m*-Ph), 122.7 (*s*-Ph), 104.4 (C-2′) 84.7 (C-1′), 32.3 (C-5), 25.7 ($C(CH_3)_3$), 25.65 (C-4), 18.5 ($C(CH_3)_3$), −4.0 ($Si(CH_3)_2$). *m/z* (EI) 297 (M^+−15, 1.3), 255 (M^+−57, 100).

4.8. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-trimethylsilanylethynyl-cyclopent-2-enone (6b)

Obtained as a white solid (77 mg, 83%); mp 64–66 °C. [Found: C 62.33; H, 9.10. $C_{16}H_{28}O_2Si_2$ requires C, 62.28; H, 9.15]. ν_{max} (KBr, cm^{-1}): 2954, 2934, 2858, 2139, 1713, 1613, 1474, 1365, 1250, 1198, 1125, 845, 786, 758, 693. δ_H (400 MHz, $CDCl_3$) 2.56–2.54 (m, 2H, H-4), 2.37–2.35 (m, 2H, H-5), 0.98 (s, 9H, $C(CH_3)_3$), 0.22 (s, 9H, $Si(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 203.2 (C-1), 156.6 (C-2), 130.7 (C-3), 111.0 (C-2′), 99.6 (C-1′) 32.2 (C-5), 25.7 ($C(CH_3)_3$), 25.5 (C-4), 18.5 ($C(CH_3)_3$), −0.16 ($Si(CH_3)_3$), −4.0 ($Si(CH_3)_2$). *m/z* (EI) 293 (M^+−15, 3.3), 251 (M^+−57, 100).

4.9. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-prop-1-ynyl-cyclopent-2-enone (6c)

Obtained as a white solid (95 mg, 83%); mp 86–88 °C. [Found: C 63.18; H, 9.50, $C_{20}H_{36}O_3Si_2$ requires C, 63.10; H, 9.53]. ν_{max} (KBr, cm^{-1}): 2930, 2858, 1705, 1620, 1474, 1409, 1374, 1256, 1140, 1085, 849, 784. δ_H (400 MHz, $CDCl_3$) 4.54 (s, 2H, H-3′), 2.56–2.54 (m, 2H, H-4), 2.38–2.36 (m, 2H, H-5), 0.97 (s, 9H, $C(CH_3)_3$), 0.91 (s, 9H, $C(CH_3)_3$), 0.21 (s, 6H, $Si(CH_3)_2$) 0.13 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 203.1 (C-1), 155.7 (C-2), 130.9 (C-3), 103.3 (C-2′), 79.8 (C-1′) 52.4 (C-3′) 32.2 (C-5), 25.9 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 25.6 (C-4), 18.46 ($C(CH_3)_3$), 18.44 ($C(CH_3)_3$), −3.9 ($Si(CH_3)_2$), −5.0 ($Si(CH_3)_2$). *m/z* (EI) 365 (M^+−15, 2.5), 323 (M^+−57, 100).

4.10. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-hydroxy-3-methyl-but-1-ynyl)-cyclopent-2-enone (6d)

Obtained as a white solid (82 mg, 93%); mp 110–112 °C. [Found: C, 65.33; H, 8.91, $C_{16}H_{26}O_3Si$ requires C, 65.26; H, 8.90]. ν_{max} (KBr, cm^{-1}): 2930, 3470, 2953, 2933, 2859, 2205, 1708, 1693, 1610, 1472, 1374, 1248, 1184, 1126, 958, 847, 782. δ_H (400 MHz, $CDCl_3$) 2.55–2.53 (m, 2H, H-4), 2.39–2.36 (m, 2H, H-5), 2.05 (s, 1H, OH), 1.58 (s, 6H, $(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 203.0 (C-1), 155.9 (C-2), 130.7 (C-3), 108,9 (C-2′), 77.4 (C-1′) 66.0 (C-3′) 32.2 (C-5), 31.4 $(CH_3)_2$, 25.7 ($C(CH_3)_3$), 25.6 (C-4), 18.5 ($C(CH_3)_3$), −4.0 ($Si(CH_3)_2$). *m/z* (EI) 279 (M^+−15, 1.6), 237 (M^+−57, 100), 219 (26.0).

4.11. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-hex-1-ynyl-cyclopent-2-enone (6e)

Obtained as a colorless oil (60 mg, 68%); [Found: C, 69.71; H, 9.65, $C_{17}H_{28}O_2Si$ requires C, 69.81; H, 9.65]. ν_{max} (neat, cm^{-1}): 2932, 2859, 2215, 1711, 1615, 1462, 1372, 1252, 1216, 1134, 845, 787. δ_H (400 MHz, $CDCl_3$): 2.52–2.50 (m, 2H, H-4), 2.45 (t, *J*=7.0 Hz, 2H, H-3′), 2.36–2.33 (m, 2H, H-5), 1.60–1.52 (m, 2H, H-4′) 1.49–1.40 (m, 2H, H-5′) 0.97 (s, 9H, $C(CH_3)_3$), 0.92 (t, *J*=7.3 Hz, 3H, H6′), 0.20 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 203.2 (C-1), 155.1 (C-2), 132.8 (C-3), 107.0 (C-2′), 76.1 (C-1′) 32.2 (C-5), 30.6 (C-4′) 26.0 (C-4), 25.7 ($C(CH_3)_3$), 22.1 (C-5′) 19.9 (C-3′) 18.4 ($C(CH_3)_3$), 13.7 (C-6′), −4.0 ($Si(CH_3)_2$). *m/z* (EI) 277 (M^+−15, 2.0), 235 (M^+−57, 100).

4.12. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-methoxy-prop-1-ynyl)-cyclopent-2-enone (6f)

Obtained as a white solid (71 mg, 85%); mp 42–43 °C; [Found: C, 64.36, H, 8.68, $C_{15}H_{24}O_3Si$ requires C, 64.24; H, 8.63]. ν_{max} (KBr, cm^{-1}): 2928, 2857, 1703, 1622, 1472, 1367, 1251, 1214, 1132, 1100, 844, 788. δ_H (400 MHz, $CDCl_3$) 4.34 (s, 2H, H-3′), 3.42 (s, 3H, OCH_3), 2.58–2.55 (m, 2H, H-4), 2.39–2.37 (m, 2H, H-5), 0.97 (s, 9H, $C(CH_3)_3$), 0.21 (s, 6H, $Si(CH_3)_2$) δ_C (101 MHz, $CDCl_3$) 203.0 (C-1), 156.1 (C-2), 130.4 (C-3), 100.3 (C-2′), 81.5 (C-1′), 60.6 (C-3′), 57.9 (OCH_3), 32.2 (C-5), 25.64 ($C(CH_3)_3$), 25.57 (C-4), 18.4 ($C(CH_3)_3$), −4.0 ($Si(CH_3)_2$). *m/z* 265 (M^+−15, 1.7), 223 (M^+−57, 100), 208 (7.1), 193 (22.8), 179 (11.5), 155 (26.9).

4.13. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylethynyl-cyclohex-2-enone (8a)

Obtained as a white solid (86 mg, 88%); mp 84–86 °C. [Found: C, 73.64; H, 8.05, $C_{20}H_{26}O_2Si$ requires C, 73.57; H, 8.03]. ν_{max} (KBr, cm^{-1}): 2936, 2854, 2186, 1676, 1601, 1586, 1488, 1471, 1367, 1205, 1179, 929, 831, 779, 755. δ_H (400 MHz, $CDCl_3$) 7.49–7.45 (m, 2H, *o*-Ph), 7.36–7.33 (m, 3H, *m*, *p*-Ph), 2.62 (t, *J*=6.0 Hz, 2H, H-4), 2.51 (dd, *J*=7.4, 5.9 Hz, 2H, H-6), 2.04–1.98 (m, 2H, H-5), 1.02 (s, 9H, $C(CH_3)_3$), 0.23 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 194.1 (C-1), 150.4 (C-2), 131.7 (2C, *o*-Ph), 128.9 (*p*-Ph), 128.5 (2C, *m*-Ph), 123.2 (*s*-Ph), 120.6 (C-3), 102.6 (C-2′) 87.6 (C-1′), 38.5 (C-6), 30.4 (C-4), 26.0 ($C(CH_3)_3$), 22.8 (C-5), 19.0 ($C(CH_3)_3$), −3.9 ($Si(CH_3)_2$). *m/z* (EI) 311 (M^+−15, 32.6), 269 (M^+−57, 100).

4.14. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-hydroxy-3-methyl-but-1-ynyl)-cyclohex-2-enone (8d)

Obtained as a white solid (74 mg, 80%); mp 99–101 °C; [Found: C, 66.20; H, 9.14, $C_{17}H_{28}O_3Si$ requires C, 66.19; H, 9.15]. ν_{max} (KBr, cm^{-1}): 3419, 2928, 2854, 2209, 1656, 1586, 1462, 1372, 1259, 1210, 1182, 1148, 936, 830. δ_H (400 MHz, $CDCl_3$) 2.50–2.45 (m, 4H, H-4, H-6), 2.01–1.92 (m, 3H, H-5, OH), 1.56 (s, 6H, $(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 194.2 (C-1), 150.4 (C-2), 119.8 (C-3), 106,9 (C-2′), 80.2 (C-1′) 66.0 (C-3′) 38.4 (C-6), 31.4 $(CH_3)_2$, 30.4 (C-4), 26.0 ($C(CH_3)_3$), 22.7 (C-5), 18.9 ($C(CH_3)_3$), −3.9 ($Si(CH_3)_2$). *m/z* (EI) 293 (M^+−15, 2.4), 251 (M^+−57, 85.9), 233 (100), 193 (19.1), 177 (12.2).

4.15. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-(3-methoxy-prop-1-ynyl)-cyclohex-2-enone (8f)

Obtained as a colorless oil (62 mg, 70%). [Found: C, 65.31; H, 8.88, $C_{16}H_{26}O_3Si$ requires C, 65.26; H, 8.90]. ν_{max} (neat, cm^{-1}): 2931, 2857, 1683, 1592, 1464, 1364, 1252, 1175, 1102, 1006, 936, 841. δ_H (400 MHz, $CDCl_3$): 4.29 (s, 2H, H-3′), 3.39 (s, 3H, OCH_3), 2.52–2.45 (m, 4H, H-4, H-6), 1.98–1.92 (m, 2H, H-5), 0.96 (s, 9H, $C(CH_3)_3$), 0.18 (s, 6H, $Si(CH_3)_2$); δ_C (101 MHz, $CDCl_3$) 194.2 (C-1), 150.9 (C-2), 119.8 (C-3), 98.3 (C-2′), 84.3 (C-1′), 60.7 (C-3′), 57.9 (OCH_3), 38.4 (C-6), 30.1 (C-4), 25.8 ($C(CH_3)_3$), 22.7 (C-5), 18.8 ($C(CH_3)_3$), −4.0 ($Si(CH_3)_2$). *m*/*z* (EI) 279 (M^+−15, 2.5), 237 (M^+−57, 100), 222 (33.3), 207 (18.7), 193 (5.7), 169 (17.2).

4.16. Procedure for cross-coupling in a mixture of THF/Et_3N

A mixture of bromo diketone (**2** or **4**; 1 mmol), $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol), and CuI (9.5 mg, 0.05 mmol) in a 10-mL flask, equipped with septum was flushed with argon for 10 min. Then, THF (5 mL), Et_3N (1.39 mL, 10 mmol), and alkyne **11** (2 mmol) were added and the mixture was stirred for 24 h for **6b** or refluxed for 1 h for **6a**. Then saturated NH_4Cl solution (30 mL) and EtOAc (30 mL) were added, the layers were separated, the organic phase was washed with brine (15 mL), dried (Na_2SO_4) and the solvents evaporated. The residue was purified by flash chromatography.

4.17. Procedure for deprotection of silyl enol ethers in basic conditions

To a solution of **6a** or **6c** or **8a** (0.1–0.2 mmol) in MeOH (1.5–3 mL) K_2CO_3 (0.1–0.4 mmol) was added and the mixture was stirred for 2 h at room temperature. Then water was added, the mixture was acidified with 1 N HCl to pH ~ 3 and extracted with EtOAc (1×10 mL and 2×5 mL). The extracts were washed with brine (5 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (heptane/acetone 10:2) giving the target compound.

4.18. 2-Hydroxy-3-phenylethynyl-cyclopent-2-enone (5a)

Obtained from **6a** (54 mg, 0.17 mmol) and K_2CO_3 (26 mg, 0.19 mmol) in MeOH (2.2 mL) as a white solid (33 mg, 96%); mp 163–166 °C. [Found: C, 78.69; H, 5.19, $C_{13}H_{10}O_2$ requires C, 78.77; H, 5.09]. ν_{max} (KBr, cm^{-1}): 3285, 2924, 2193, 1680, 1631, 1489, 1407, 1391, 1341, 1240, 1142, 1114, 777, 688. δ_H (400 MHz, DMSO-d_6) 10.31 (s, 1H, OH), 7.53–7.51 (m, 2H, *o*-Ph), 7.44–7.42 (m, 3H, *m*, *p*-Ph), 2.58–2.56 (m, 2H, H-4), 2.41–2.39 (m, 2H, H-5); δ_C (101 MHz, DMSO-d_6) 202.3 (C-1), 156.3 (C-2), 131.3 (2C, *o*-Ph), 129.2 (*p*-Ph), 128.9 (2C, *m*-Ph), 122.1 (*s*-Ph), 121.4 (C-3), 102.4 (C-2′), 84.9 (C-1′), 31.9 (C-5), 25.0 (C-4). *m*/*z* (EI) 198 (M^+ 93.9), 170 (7.1), 141 (38.4), 128 (100).

4.19. 3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-prop-1-ynyl]-2-hydroxy-cyclopent-2-enone (5c)

Obtained from **6c** (38 mg, 0.1 mmol) and K_2CO_3 (15 mg, 0.11 mmol) in MeOH (1.5 mL) as a white solid (22 mg, 83%); mp 107–109 °C; [Found: C, 63.12; H, 8.27, $C_{14}H_{22}O_3Si$ requires C, 63.12; H, 8.32]. ν_{max} (KBr, cm^{-1}): 3275, 2929, 2857, 1689, 1646, 1455, 1389, 1085, 838, 776. δ_H (400 MHz, $CDCl_3$): δ 6.29 (s, 1H, OH), 4.57 (s, 2H, H-3′), 2.60–2.58 (m, 2H, H-4), 2.47–2.45 (m, 2H, H-5), 0.92 (s, 9H, $C(CH_3)_3$), 0.15 (s, 6H, $Si(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 202.7 (C-1), 154.4 (C-2), 122.9 (C-3), 103.9 (C-2′), 78.8 (C-1′) 52.6 (C-3′) 31.7 (C-5), 26.0 ($C(CH_3)_3$), 25.7 (C-4), 18.4 ($C(CH_3)_3$), −5.0 ($Si(CH_3)_2$). *m*/*z* (EI) 251 (M^+−15, 1.8), 209 (M^+−57, 100), 193 (10.5), 179 (41.3).

4.20. 2-Hydroxy-3-phenylethynyl-cyclohex-2-enone (7a)

Obtained from **8a** (65 mg, 0.2 mmol) and K_2CO_3 (61 mg, 0.44 mmol) in MeOH (3 mL) as a white solid (40 mg, 94%); mp 106–109 °C. [Found: C, 79.42; H, 5.78, $C_{14}H_{12}O_2$ requires C, 79.22; H, 5.70]. ν_{max} (KBr, cm^{-1}): 3390, 2946, 2185, 1651, 1607, 1489, 1378, 1166, 1133, 887, 756, 690. δ_H (400 MHz, $CDCl_3$) 7.54–7.49 (m, 2H, *o*-Ph), 7.36–7.31 (m, 3H, *m*, *p*-Ph), 6.63 (s, 1H, OH), 2.63–2.57 (m, 4H, H-4, H-6), 2.08–2.02 (m, 2H, H-5); δ_C (101 MHz, $CDCl_3$) 193.9 (C-1), 149.5 (C-2), 131.9 (2C, *o*-Ph), 129.1 (*p*-Ph), 128.5 (2C, *m*-Ph), 122.8 (*s*-Ph), 112.4 (C-3), 103.5 (C-2′), 85.6 (C-1′) 36.2 (C-6), 29.3 (C-4), 22.8 (C-5). *m*/*z* (EI) 212 (M^+ 79.1), 197 (3.2), 184 (15.7), 156 (11.4), 141 (19.3), 128 (100).

4.21. 2-Hydroxy-3-trimethylsilanylethynyl-cyclopent-2-enone (5b)

To a solution of **6b** (62 mg, 0.2 mmol) in THF (2 mL) a solution of HCl (3 N, 0.8 mL) was added and the mixture was stirred for 25 h at room temperature. Then water (6 mL) was added, the mixture was extracted with EtOAc (2×10 mL), the extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (heptane/acetone 15:1 to 10:1) giving compound **5b** as a white solid (28 mg, 72%); mp 135–137 °C. [Found: C, 61.84; H, 7.28, $C_{10}H_{14}O_2Si$ requires C, 61.81; H, 7.26]. ν_{max} (KBr, cm^{-1}): 3324, 2962, 2127, 1690, 1640, 1380, 1249, 1121, 847, 689. δ_H (400 MHz, $CDCl_3$) 6.43 (s, 1H, OH), 2.61–2.59 (m, 2H, H-4), 2.46–2.44 (m, 2H, H-5), 0.24 (s, 9H, $Si(CH_3)_3$); δ_C (101 MHz, $CDCl_3$) 203.0 (C-1), 154.8 (C-2), 123.1 (C-3), 111.8 (C-2′), 98.0 (C-1′) 31.8 (C-5), 25.9 (C-4), −0.1 ($Si(CH_3)_3$). *m*/*z* (EI) 194 (M^+ 34.7), 179 (100), 151 (14.2).

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Supplementary data

^1H, ^{13}C NMR and IR spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.037.

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