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First direct synthesis of 3-hydroxy-pent-4-ynoic acids. Application to the synthesis of pyran-2-ones

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ABSTRACT

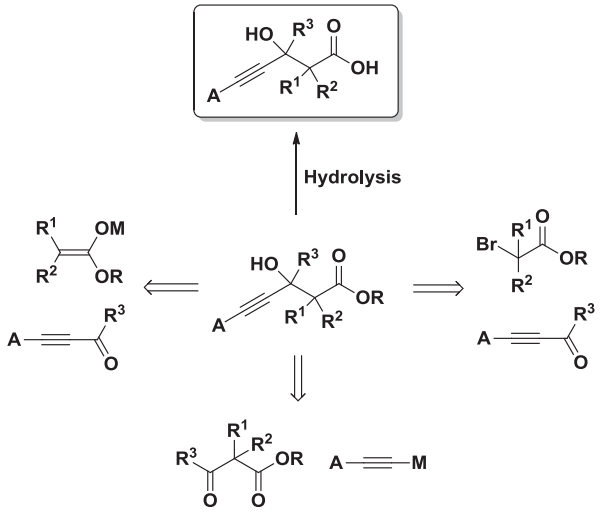
We describe a direct method for the synthesis of 3-hydroxy-pent-4-ynoic acids by the nucleophilic addition of bis-(TMS) ketene acetals to alkynones promoted by $BF_3{\cdot}Et_2O$. A systematic study involving electron withdrawing and electron donor groups (R^1=NO_2, CF_3, Br, Cl, H, Me, OMe) in the propargyl ketone reveals a strong dependence of electronic effects on the regiochemistry of the nucleophilic addition. Using a halolactonization protocol, we demonstrated the synthetic potential of these acids by their efficient transformation into new 5-bromo-3,4-dihydro-2*H*-pyran-2-ones.

1. Introduction

3-Hydroxy-pent-4-ynoic acids are interesting synthetic targets due to the presence of different functional groups on their structure, which could result in a huge range of compounds; by slightly changing the reaction conditions or the reagents used. Their use as synthetic intermediates has been sparsely reported and only some examples related to the synthesis of biologically active compounds, such as: ustiloxin D,[1] cyanobacterin,[2] (+)-phorboxazole,[3] and mevalonate derivatives[4] are reported, probably because a general method for the synthesis of these compounds is not available.

The 3-hydroxy-pent-4-ynoic acids can be prepared using α-haloesters and propargyl ketones or aldehydes via the Reformatsky reaction.[5] Another two complementary strategies are the nucleophilic addition of acetylide ions to 1,3-dicarbonyl esters,[6] or the addition of ester enolates to propargyl ketones or aldehydes[7] (Scheme 1). However in these complementary strategies, the hydrolysis of the ester formed is a required critical stage, and this reaction often proceeds with low yields due to undesirable side reactions, such as dehydration, decarboxylation or polymerization of the carboxylic acid.

On the other hand, the use of ketene acetals as potential 1,3-dinucleophiles,[8,9] in combination with different substrates,[10] has been an interesting strategy used in the synthesis of diverse compounds. In this context, we have envisaged a direct method for the synthesis of 3-hydroxy-pent-4-ynoic acids by the nucleophilic addition of bis-(trimethylsilyl) ketene acetals to acetylenic ketones in the presence of an appropriated Lewis acid (Scheme 2). The 3-hydroxy-pent-4-ynoic acids thus obtained can be used in the synthesis of new highly functional lactones.



Scheme 1.

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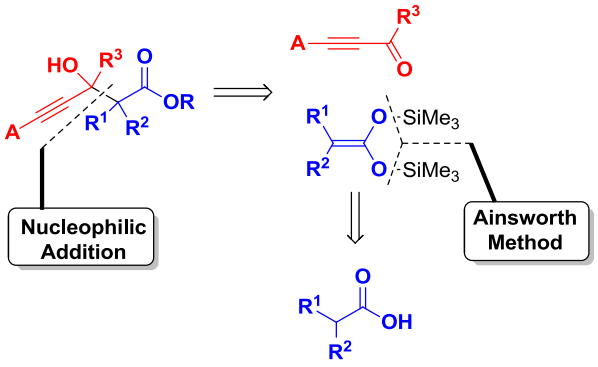
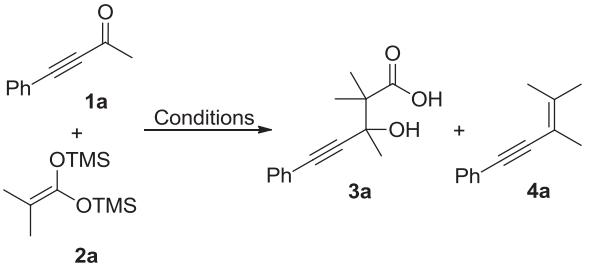


Scheme 2.

2. Results and discussion

We started the study with the reaction of 4-phenyl-3-butyn-2-one **1a** and the ketene acetal **2a** in CH_2Cl_2 (Table 1, entry 1). However after 24 h no product was observed; we therefore used an activating agent. We first tried with ^tBuOK and TBAF (Table 1, entries 2 and 3) to promote the cleavage of the silicon–oxygen bond in the ketene acetal releasing the corresponding anion, but this reaction did not afford good results.

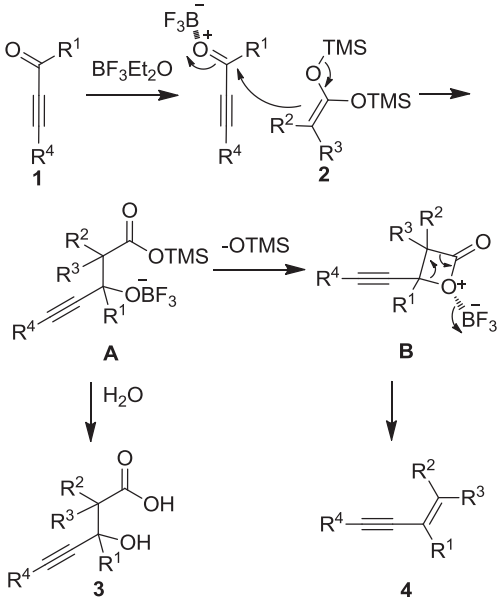
Table 1
Conditions for the reaction between acetylenic ketone and bis-(trimethylsilyl) ketene acetal



Entry	Activating agent	t (h)	Solvent	Molar ratio **3a**/**4a**	Global yield (%)
1[a]	Non	24	CH_2Cl_2	—	n.r
2[a]	TBAF	24	CH_2Cl_2	1:0	10
3[a]	^tBuOK	24	CH_2Cl_2	—	n.r
4[b]	$BF_3{\cdot}Et_2O$	4	CH_2Cl_2	3:2	80
5[a]	$InCl_3$	24	CH_2Cl_2	1:0	31
6[a]	$Cu(OTf)_2$	24	CH_2Cl_2	1:1	10
7[b]	$TiCl_4$	2	CH_2Cl_2	1:0	62
8[c]	$BF_3{\cdot}Et_2O$	4	Et_2O	10:1	96
9[c]	$TiCl_4$	2	Et_2O	1:0	49

[a] The reactions were carried out with **1a** (1.4 mmol), **2a** (1.2 equiv), and the activating agent (1.0 equiv) in 15 mL of dichloromethane, at room temperature.
[b] Same reaction condition, but the addition of Lewis acid took place at 0 °C.
[c] The reaction was carried out in diethyl ether 15 mL and the addition of Lewis acid took place at 0 °C.

Next, we used $BF_3{\cdot}Et_2O$ as Lewis acid to promote the addition of **1a** to the carbonyl group of **2a** (Table 1, entry 4), the reaction occurred with high conversion and we obtained a mixture of two products, **3a** and **4a** in a 3:2 ratio, respectively. The proposed pathway of this Mukaiyama-type aldol reaction conduces in a first step to the formation of intermediate **A** by the nucleophilic addition of ketene acetal **2** to the activated alkynone; the hydrolysis of intermediate **A** gives to the corresponding carboxylic acid **3**. Alternatively, **A** can cyclize to give β-lactone **B**. In according with literature,[11] the intermediate **B** can also undergo a decarboxylation leading the enyne **4** (Scheme 3).

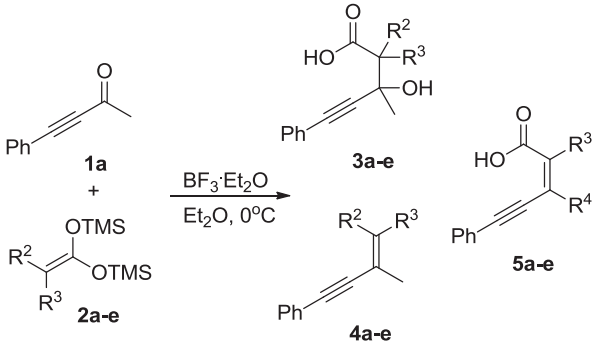


Scheme 3. Proposed pathway for the formation of 3-hydroxy-pent-4-ynoic acid **3** and enyne **4**.

In view of these results, we then tested several Lewis acids (entries 5–7) to enhance the selectivity of the reaction; however, in all cases, a low yield of **3a** was obtained. The reaction was finally improved using diethyl ether as solvent. Under these conditions and by using $BF_3{\cdot}Et_2O$ as activating agent (entry 8, Table 1) the reaction provided a 10:1 mixture of **3a** and **4a** in 96% yield.

Having established the best reaction conditions, we decided to test the reactivity of the acetylenic ketone **1a**, against different bis-(trimethylsilyl) ketene acetals (Table 2).

Table 2
Reaction between acetylenic ketone and different bis-(trimethylsilyl) ketene acetals



Entry		R^2	R^3	Molar ratio **3**/**4**/**5**	Global yield (%)
1	**2a**	Me	Me	10:1:0	96
2	**2b**	$-(CH_2)_4-$		5:2:0	92
3	**2c**	Ph	H	9:0:1	93
4	**2d**	Me	H	9:1:2	94
5	**2e**	H	H	4:0:2	72

All the reactions were carried out with **1a** (3.5 mmol), **2** (1.2 equiv), and $BF_3{\cdot}Et_2O$ (1.0 equiv) in 25 mL of diethyl ether, at 0 °C, while stirring for 4 h.

In all cases examined the reaction provided good yields, but when the unsubstituted ketene acetal **2e** was used the yield decreased and the relative amount of the corresponding dehydration product **5e** increased.

With the aim of knowing the substrate scope, we first tested the reaction of ketene acetal **2a** toward phenylpropargyl aldehyde (**1b**)

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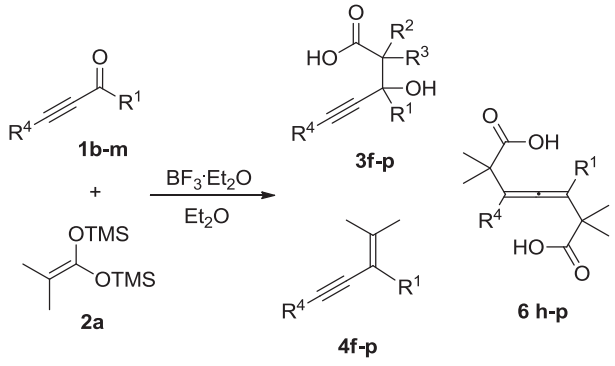
and 2-octynal (**1c**), we found that carboxylic acids **3f** and **3g** were produced with excellent yields (Table 3, entries 1 and 2). Next, we examined the reaction with alkynones bearing a trimethylsilyl, alkyl or phenyl group on the alkyne moiety. We found that the reaction proceeded without decarboxylation (entries 3–5), getting the carboxylic acids **3h**, **3i**, and **3j** in 98%, 91%, and 70% yield, respectively. Then, our attention was turned to the evaluation of the electronic influence of the substituent attached to the carbonyl group, we thus replaced the substituent R^1 with different phenyl groups *p*-substituted (Table 3, entries 6–12). The reaction proceeded with both excellent yield and selectivity, when R^1 is a phenyl group *p*-substituted with a withdrawing group gave the compound **3** almost exclusively (Table 3, entries 6–8). Nevertheless, we found that when R^1 is a *p*-ClPh, the starting material is completely consumed, but in addition to **3**, we obtained allene **6**, which is formed by addition of two units of bis-(trimethylsilyl) ketene acetal to acetylenic ketone (Table 3, entry 9). With the purpose of improving the yield of allene **6**, we performed another reaction by adding 2 equiv of bis-(trimethylsilyl) ketene acetal, and after purification we mostly isolated allene **6** (Table 3, entry 10). On the other hand, when R^1 is a phenyl group *p*-substituted with an electron releasing group (Table 3, entries 11 and 12), the main product is allene **6**. The structure of **6p** was fully established by means of X-ray diffraction analysis (Fig. 1). Data on the crystals and the refining of this compound are summarized in Table 4.

Table 3
Synthesis of 3-hydroxy-pent-4-ynoic acids



Entry	R^1	R^4	*t* (h)	Product	Molar ratio **3**/**4**/**6**	Global yield (%)
1[a]	H	Ph	2	**f**	1:0:0	98
2[a]	H	$CH_3(CH_2)_4$	1	**g**	1:0:0	99
3[a]	Me	$SiMe_3$	2	**h**	1:0:0	98
4[a]	Ph	$CH_3(CH_2)_3$	4	**i**	1:0:0	91
5[a]	Ph	Ph	4	**j**	1:0:0	70
6[a]	*p*-NO_2 Ph	Ph	1	**k**	1:0.2:0	91
7[a]	*p*-BrPh	Ph	1	**l**	1:0.3:0	99
8[a]	*p*-CF_3Ph	Ph	1	**m**	1:0:0	90
9[a]	*p*-ClPh	Ph	4	**n**	11:3:6	95
10[b]	*p*-ClPh	Ph	4	**n**	9:1:13	99
11[b]	*p*-OMePh	Ph	5	**o**	0:2:9	49
12[b]	*p*-MePh	Ph	16	**p**	0:0:1	30

[a] The reactions were carried out with **1** (3.5 mmol), **2** (1.2 equiv), and $BF_3{\cdot}Et_2O$ (1.0 equiv) in 25 mL of diethyl ether, at 0 °C.
[b] The reactions were carried out with 2 equiv of the ketene acetal **2a**.

To explain the formation of allene **6**, we propose the following pathway. This compound could come from the previously described β-lactone intermediate (**B**), which can be opened generating the transient propargylic carbocation **C** stabilized by resonance, then the nucleophilic attack of a second molecule of ketene acetal takes place giving **E**, which hydrolyzes leading the corresponding allene **6** (Scheme 4). This explains why electron donating substituents that will stabilize a cation increase the amount of compound **6**.

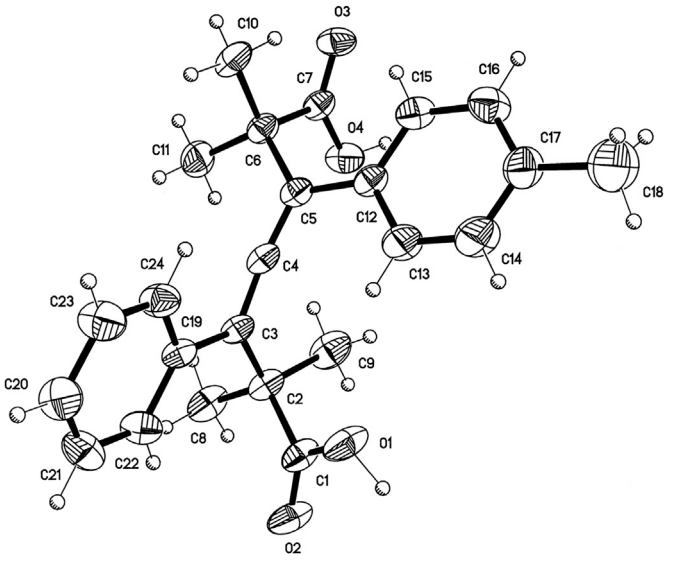


Fig. 1. ORTEP representation of allene **6p**. Thermal ellipsoids at 30% probability level. Selected bond length (Å) and bond angles (°): O(1)–C(1), 1.276(4); O(2)–C(1), 1.238(4); O(3)–C(7), 1.221(4); O(4)–C(7), 1.297(4); C(1)–C(2), 1.519(5); C(2)–C(3), 1.537(4); C(3)–C(4), 1.314(5); C(3)–C(19), 1.507(4); C(4)–C(5), 1.300(5); C(5)–C(12) 1.490(5); C(5)–C(6), 1.546(4); C(6)–C(7), 1.513(5); C(3)–C(19), 1.507(4); C(5)–C(12), 1.490(5); O(2)–C(1)–O(1), 123.3(3); O(2)–C(1)–C(2), 121.3(3); O(1)–C(1)–C(2), 115.3(3); C(1)–C(2)–C(3), 109.2(3); C(4)–C(3)–C(19), 119.0(3); C(4)–C(3)–C(2), 118.9(3); C(19)–C(3)–C(2), 122.0(3); C(5)–C(4)–C(3), 172.8(3); C(4)–C(5)–C(12), 119.0(3); C(4)–C(5)–C(6), 119.5(3); C(12)–C(5)–C(6), 121.5(3); C(7)–C(6)–C(11), 106.7(3); C(7)–C(6)–C(5), 109.6(3); O(3)–C(7)–O(4), 123.0(3); O(3)–C(7)–C(6), 123.3(3); O(4)–C(7)–C(6), 113.7(3), C(4)–C(3)–C(19), 119.0(3); C(19)–C(3)–C(2), 122.0(3); C(4)–C(5)–C(12), 119.0(3); C(12)–C(5)–C(6), 121.5(3).

Table 4
X-ray data collection and structure refinement details for compounds **6p**, **7d**, and **7k**

Compound	**6l**	**7d**	**7k**
Formula	$C_{24}H_{26}O_4$	$C_{19}H_{16}BrNO_5$	$C_{13}H_{13}BrO_3$
MW g^{-1} mol^{-1}	378.45	418.24	297.14
Crystal size (mm^3)	0.464×0.104×0.068	0.396×0.168×0.118	0.418×0.138×0.126
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
a/Å	13.562(2)	10.330(2)	6.285(1)
b/Å	11.964(2)	6.3346(9)	11.520(2)
c/Å	13.353(2)	26.551(4)	17.479(2)
α/(°)	90	90	90
β/(°)	92.779(2)	96.037(2)	90
γ/(°)	90	90	90
Volume/Å^3	2164.0(5)	1727.7(4)	1265.5(3)
Z	4	4	4
d_c/Mg m^{-3}	1.162	1.608	1.560
Θ/°	2.27–25.40	1.98–25.38	2.12–25.32
Index ranges	$-16\le h\le 16$ $-14\le k\le 14$ $-16\le l\le 16$	$-10\le h\le 12$ $-7\le k\le 7$ $-31\le l\le 32$	$-7\le h\le 7$ $-13\le k\le 8$ $-20\le l\le 17$
Reflections collected	22,698	9853	4040
Independent reflections	3967 [*R*(int)=0.0792]	3170 [*R*(int)=0.0353]	2310 [*R*(int)=0.0244]
Data/parameters	3967/264	3170/240	2310/160
Final *R* indices [$I>2\sigma(I)$]	*R*1=0.0760 *wR*2=0.1601	*R*1=0.0304 *wR*2=0.0709	*R*1=0.0368 *wR*2=0.0712
R indices (all data)	*R*1=0.1395 *wR*2=0.1834	*R*1=0.0392 *wR*2=0.0750	*R*1=0.0475 *wR*2=0.0751
GoF(F^2)	1.077	1.022	0.994
Absorptions corrections	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents

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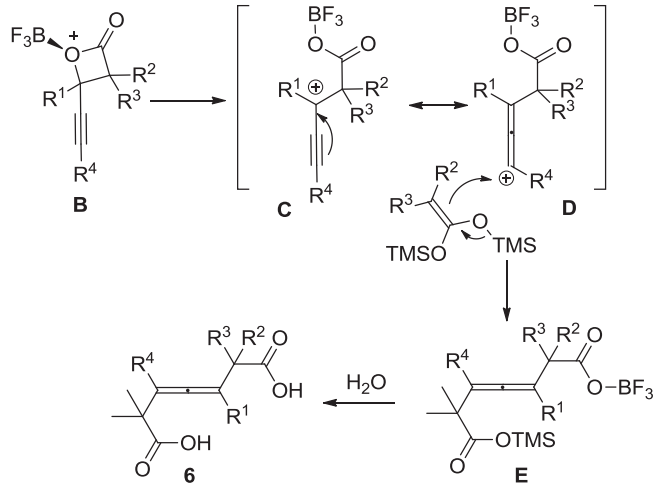
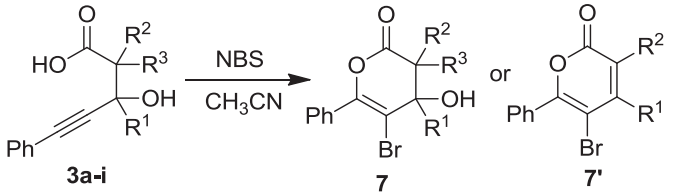


Scheme 4. Proposed pathway for allene formation (R=*p*-OMePh, *p*-MePh, *p*-ClPh).

Having established a method for synthesizing 3-hydroxy-pent-4-ynoic acids, we tested the synthetic efficacy of these compounds in the preparation of lactones via an intramolecular electrophilic annulation[12] using *N*-bromosuccinimide as halogenating agent[13] (Table 5). This reaction leads to the regioselective formation of **7** in good yields. Nevertheless, when R^3=H (Table 5: entries 4 and 6), formation of the 2*H*-pyran-2-ones **7d′** and **7e′** is observed, which could be due to the dehydration of the tertiary alcohol **7**, promoted by a slight increase in temperature. The structure of lactones **7d** and **7f** was fully established by means of X-ray diffraction analysis (Figs. 2 and 3.). Data on the crystals and the refining of these compounds are summarized in Table 4.

Table 5
Synthesis of 5-bromo-3,4-dihydro-2*H*-pyran-2-ones



Entry	3	R^1	R^2	R^3	*T* (°C)	*t* (h)	Product	Yield (%)
1	**3a**	Me	Me	Me	0	2	**7a**	75
2	**3b**	Me	$-(CH_2)_4-$		0	2	**7b**	94
3	**3d**	Me	Me	H	0	2	**7d**	76
4	**3d**	Me	Me	H	25	4	**7d′**	73
5	**3e**	Me	H	H	0	2	**7e**	58
6	**3e**	Me	H	H	25	4	**7e′**	54
7	**3j**	Ph	Me	Me	0	2	**7j**	66
8	**3k**	*p*-NO_2Ph	Me	Me	0	2	**7k**	74
9	**3l**	*p*-BrPh	Me	Me	0	4	**7l**	77
10	**3n**	*p*-ClPh	Me	Me	0	3	**7n**	71

All reactions were carried out with **3** (0.3 g), NBS (1.2 equiv), in 10 mL of CH_3CN.

3. Conclusions

In conclusion, we have developed a direct method for the synthesis of good yields of 3-hydroxy-pent-4-ynoic acids, by the nucleophilic addition of bis-(trimethylsilyl) ketene acetals to acetylenic ketones and aldehydes. The formation of allene **6** as side-product is observed, when the carbonyl group has as substituent an electron donating group. The 3-hydroxy-pent-4-ynoic acids obtained by this new method were efficiently transformed into new

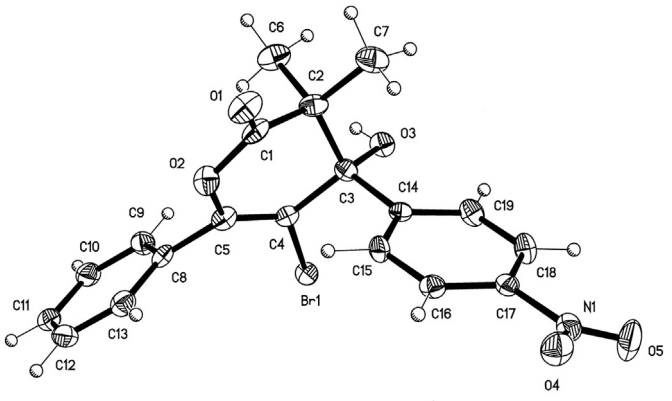


Fig. 2. ORTEP representation of **7f**. Thermal ellipsoids at 30% probability level. Selected bond length (Å) and bond angles (°) : Br(1)–C(4), 1.894(2); O(1)–C(1), 1.200(3); O(2)–C(1), 1.365(3); O(2)–C(5), 1.409(3); O(3)–C(3), 1.417(3); C(1)–C(2), 1.514(4); C(2)–C(3), 1.567(3); C(3)–C(4), 1.513(3); C(4)–C(5), 1.327(3); C(1)–O(2)–C(5), 120.1(2); O(1)–C(1)–O(2), 116.8(2); O(1)–C(1)–C(2), 125.6(2); O(2)–C(1)–C(2), 117.4(2); C(1)–C(2)–C(3), 110.5(2); O(3)–C(3)–C(4), 111.7(2); O(3)–C(3)–C(2), 109.3(2); C(4)–C(3)–C(2), 107.8(2); C(5)–C(4)–C(3), 124.1(2); C(5)–C(4)–Br(1), 119.2(2); C(3)–C(4)–Br(1), 116.7(2); C(4)–C(5)–O(2), 121.0(2).

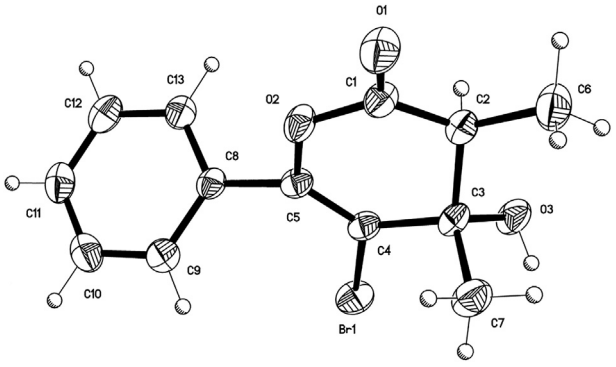


Fig. 3. ORTEP representation of **7d**. Thermal ellipsoids at 30% probability level. Selected bond length (Å) and bond angles (°) : Br(1)–C(4), 1.899(4); O(1)–C(1), 1.201(4); O(2)–C(1), 1.362(5); O(2)–C(5), 1.397(4); C(1)–C(2), 1.505(5); C(2)–C(3), 1.533(5), C(3)–C(4), 1.519(5); C(4)–C(5), 1.319, C(1)–O(2)–C(5), 121.4(3); O(1)–C(1)–O(2), 116.7(3); O(1)–C(1)–C(2), 126.2(4); O(2)–C(1)–C(2), 117.0(3); C(1)–C(2)–C(3), 111.3(3); O(3)–C(3)–C(2), 105.1(3); C(4)–C(3)–C(2), 106.9(3); C(5)–C(4)–C(3), 122.9 (3); C(5)–C(4)–Br(1), 119.1(3); C(3)–C(4)–Br(1), 117.6; C(4)–C(5)–O(2), 120.3(3).

5-bromo-3,4-dihydro-2*H*-pyran-2-ones using a halolactonization protocol. Finally, we are still working on the development of the stereoselective synthesis of 3-hydroxy-pent-4-ynoic acids and their annulation using different electrophiles.

4. Experimental section

4.1. General considerations

All reagents and solvents were obtained from commercial sources and used without further purification. All compounds were characterized by IR spectra, recorded on a Bruker Tensor 27 spectrophotometer, by KBr or film techniques, and all data are expressed in wave numbers (cm^{-1}). Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a Bruker Advance III, 300 MHz using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are in parts per million (δ), relative to TMS. The following abbreviations are used: s=singlet, d=doublet, t=triplet, dd=double doublet, m=multiplet. The MS-EI spectra were obtained with a JEOL JMSAX505 HA using 70 eV as ionization energy and for MS-FAB a JEOL JMS-SX102A using

nitrobenzyl alcohol and ethylene glycol as a matrix. Elemental analysis was measured with an Elemental analyzer External Analytical Inc. CE 440. Starting materials: bis-(trimethylsilyl) ketene acetals **2a**–**e** were prepared according to published method[9] and alkynones (**1b**–**m**) were prepared following the literature reported method.[14]

4.2. Structure determination by X-ray crystallography

Suitable X-ray quality crystals of **7d** were grown through slow evaporation of a dichloromethane/*n*-hexane solvent mixture at −5 °C, and crystals of **6p** and **7k** were grown through slow evaporation of an ethyl acetate/*n*-hexane solvent mixture at room temperature. Single white crystals of compounds **6p**, **7d**, and **7k** were mounted on a glass fiber at room temperature. The crystals were then placed on a Bruker SMART APEX CCD diffractometer, equipped with Mo Kα radiation; decay was negligible in both cases. Details of crystallographic data collected on compounds **6p**, **7d**, and **7k** are provided in Table 4. Systematic absences and intensity statistics were used in space group determinations. The structures were determined using direct methods.[15] Anisotropic structure refinements were achieved using full-matrix, least-squares techniques on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times the value of the attached atom. Structure solutions and refinements were performed using SHELXTL v 6.10.[16]

4.3. General procedure for the synthesis of the 3-hydroxy-pent-4-ynoic acids 3(a–n)

At 0 °C under argon atmosphere we added $BF_3 \cdot Et_2O$ (0.44 mL, 3.47 mmol) to a solution of 4-phenyl-3-butyn-2-one (**1a**) (0.5 g, 3.47 mmol) in anhydrous diethyl ether (20 mL), and stirred this for 3 min. Then we slowly added bis-(trimethylsilyl) ketene acetal **2a** (0.96 mL, 4.1 mmol) at 0 °C. The reaction was stirred for 4 h at room temperature. The reaction mixture was washed with water (15 mL) and extracted with dichloromethane (2×15 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuum. The crude was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent.

*4.3.1. 3-Hydroxy-2,2,3-trimethyl-5-phenylpent-4-ynoic acid (**3a**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 60–62 °C. IR (Film, cm^{-1}) ν_{max}: 3081, 2987, 2234, 1700. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.52 (s, COO*H*), 7.39 (d, C*H*), 7.37 (d, C*H*), 7.27 (d, C*H*), 7.25 (s, C*H*), 1.58 (s, CH_3), 1.45 (s, CH_3), 1.37 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=182.8 (C=O), 131.7 (CH), 128.4 (CH), 128.2 (CH), 122.4 (C), 90.5 (C), 84.4 (C), 72.6 (C), 50.4 (C), 24.7 (CH_3), 22.1 (CH_3), 20.8 (CH_3). MS (FAB^+) *m*/*z* (%): 233 (10) [M^++1], 215 (20) [M^+−OH], 187 (40) [M^+−COOH]. MS calcd for $C_{14}H_{16}O_3$: calculated 232.1099, found 232.1097.

*4.3.2. 1-(2-Hydroxy-4-phenylbut-3-yn-2-yl)cyclohexanecarboxylic acid (**3b**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 130–131 °C. IR (KBr, cm^{-1}) ν_{max}: ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.43–7.40 (m, C*H*), 7.30–7.25 (m, C*H*), 2.37 (d, *J*=12 Hz, CH_2), 2.23 (d, *J*=12 Hz, CH_2), 1.75–1.65 (m, CH_2), 1.59 (s, CH_3), 1.46–1.34 (m, CH_2), 1.21–1.13 (m, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=181.0 (C), 131.7 (CH), 128.5 (CH), 128.3 (CH), 122.3 (C), 90.4 (C), 85 (C), 73.3 (C), 55.8 (C), 29.7 (CH_2), 29.5 (CH_2), 25.48 (CH_2), 25.42 (CH_3), 23.5 (CH_2), 23.4 (CH_2). MS (FAB^+) *m*/*z* (%): 273 (2) [M^++1], 255 (40) [M^+−OH], 227 (20) [M^+−COOH]. HRMS: calcd for $C_{17}H_{19}O_2$: calculated 255.1385, found 255.1390.

*4.3.3. 3-Hydroxy-3-methyl-2,5-diphenylpent-4-ynoic acid (**3c**).* Obtained as brown solid, chromatography column (hexane/ethyl acetate). Mp 155–157 °C. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.13, H, 5.60. IR (KBr, cm^{-1}) ν_{max}: 3596, 3055, 2990, 2234, 1682, 1222. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.33–7.29 (m, C*H*), 7.24–7.18 (m, C*H*), 7.14–7.07 (m, C*H*), 3.82 (m, C*H*), 1.24 (m, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=178.1 (C), 132.7 (C), 131.7 (CH), 130.0 (CH), 128.59 (CH), 128.54 (CH), 128.4 (CH), 128.2 (CH), 122.2 (C) 91.5 (C), 84.1 (C), 68.5 (C), 60.6 (CH), 26.7 (CH_3). MS (FAB^+) *m*/*z* (%): 281 (3) [M^++1].

*4.3.4. 3-Hydroxy-2,3-dimethyl-5-phenylpent-4-ynoic acid (**3d**).* Obtained as pale yellow oil, chromatography column (hexane/ethyl acetate). IR (Film, cm^{-1}) ν_{max}: 3408, 3082, 2987, 2235, 1709. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.41–7.39 (m, C*H*), 7.29–7.26 (m, C*H*), 2.79 (q, *J*=9 Hz, C*H*), 2.17 (s, O*H*), 1.65 (s, CH_3), 1.43 (d, *J*=9 Hz, CH_3), 1.45 (s, CH_3), 1.37 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=179.9 (C), 131.7 (2CH), 128.5 (CH), 128.2 (CH), 122.3 (C), 89.5 (C), 84.6 (C), 69.7 (C), 50.0 (CH), 28.4 (CH_3), 13.3 (CH_3). MS (EI) *m*/*z* (%): 218 (10) [M^+], 201 (20) [M^+−OH], 171 (19) [M^+−COOH]. HRMS: calcd for $C_{13}H_{14}O_3$: calculated 218.0943, found 218.0950.

*4.3.5. 3-Hydroxy-3-methyl-5-phenylpent-4-ynoic acid (**3e**).* Obtained as red oil, chromatography column (hexane/ethyl acetate). IR (Film, cm^{-1}) ν_{max}: 3260, 3060, 2986, 2232, 1713. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.39 (d, C*H*), 7.37 (s, C*H*), 7.27 (d, C*H*), 7.25 (d, C*H*), 7.01 (s, COO*H*), 2.88 (d, *J*=15 Hz, CH_2), 2.75 (d, *J*=15 Hz, CH_2), 2.65 (s, O*H*), 1.64 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=175.6 (C), 131.7 (CH), 128.4 (CH), 128.2 (CH), 122.3 (C), 91.0 (C), 83.2 (C), 65.6 (C), 46.6 (CH_2), 29.5 (CH_3). MS (EI) *m*/*z* (%): 204 (10) [M^+], 187 (70) [M^+−OH]. HRMS $C_{12}H_{12}O_3$ [M^+]: calculated 204.0786, found 204.0791.

*4.3.6. 3-Hydroxy-2,2-dimethyl-5-phenylpent-4-ynoic acid (**3f**).* Obtained as pale yellow solid, chromatography column (hexane/ethyl acetate), mp 72–74 °C. IR (KBr, cm^{-1}) ν_{max}: 3431, 2977, 2221, 1690. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.42 (m, C*H*), 7.30 (m, C*H*), 7.04 (s, COO*H*), 4.77 (s, C*H*), 1.39 (s, CH_3), 1.36 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=182.3 (C), 131.7 (CH), 128.5 (CH), 128.2 (CH), 122.3 (C), 86.5 (C), 86.4 (C), 68.5 (C), 47.7 (C), 22.7 (CH_3), 19.4 (CH_3). MS (I.E) *m*/*z* (%): 218 (5) [M^+], 201 (6) [M^+−OH], 131 (100) [M^+−$C_4H_7O_2$]. HRMS: calcd for $C_{13}H_{14}O_3$: calculated 218.0943, found 218.0944.

*4.3.7. 3-Hydroxy-2,2-dimethyldec-4-ynoic acid (**3g**).* Obtained as orange oil, filtration over silica gel with a mixture of hexane/ethyl acetate. IR (Film, cm^{-1}) ν_{max}: 3490, 2934, 2229, 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.87 (s, COO*H*), 4.52 (s, C*H*), 2.32 (t, CH_2), 1.50 (t, CH_2), 1.30 (s, CH_3), 1.28 (s, CH_3), 0.89 (t, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=182.6 (C), 87.3 (C), 77.6 (C), 68.2 (CH), 47.6 (C), 30.9 (CH_2), 28.1 (CH_2), 22.6 (CH_3), 22.1 (CH_2), 19.2 (CH_3), 18.5 (CH_2), 13.9 (CH_3). MS (I.E) *m*/*z* (%): 213 (5) [M^++1], 195 (18) [M^+−OH]. HRMS: calcd for $C_{12}H_{21}O_3$: calculated 213.1491, found 213.1495.

*4.3.8. 3-Hydroxy-2,2,3-trimethyl-5-(trimethylsilyl)pent-4-ynoic acid (**3h**).* Obtained as white solid, filtration over silica gel with a mixture of hexane/ethyl acetate, mp 57–59 °C. IR (KBr, cm^{-1}) ν_{max}: 3344, 2964, 2790, 2171, 1716. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.44 (s, CH_3), 1.34 (s, CH_3), 1.44 (s, CH_3), 0.105 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=182.9 (C), 106.8 (C), 88.7 (CH), 72.1 (C), 50.1 (C), 24.3 (CH_3), 21.8 (CH_3), 20.5 (CH_3), −0.29 (CH_3). MS (I.E) *m*/*z* (%): 228 (2) [M^+], 311 (30) [M^+−OH], 141 (100) [M^+−$C_4H_7O_2$]. HRMS: calcd for $C_{11}H_{19}O_2Si$: calculated 211.1154, found 211.1161.

*4.3.9. 3-Hydroxy-2,2-dimethyl-3-phenylnon-4-ynoic acid (**3i**).* Obtained as pale yellow solid, chromatography column (hexane/ethyl acetate), mp 65–67 °C. IR (KBr, cm^{-1}) ν_{max}: 3489, 2929, 2234, 1706, 1664. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.67 (m, C*H*), 7.36 (m, C*H*), 2.32 (t, CH_2), 1.55 (m, CH_2), 1.49 (m, CH_2), 1.30 (s, CH_3), 1.25

(s, CH_3), 0.96 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=183.1 (C), 139.1 (C), 127.8 (CH), 127.2 (CH), 87.2 (C), 81.1 (C), 76.4 (C), 51.5 (C), 30.4 (CH_2), 22.0 (CH_3), 21.8 (CH_2), 22.4 (CH_3), 18.2 (CH_2), 13.4 (CH_3). MS (I.E) *m*/*z* (%): 273 (3) [M^+-1], 257 (68) [M^+-OH], 187 (100) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{17}H_{21}O_3$: calculated 273.1491, found 273.1490.

*4.3.10. 3-Hydroxy-2,2-dimethyl-3,5-diphenylpent-4-ynoic acid (**3j**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 108–110 °C. IR (KBr, cm^{-1}) ν_{max}: 3060, 2226, 1696. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.70 (d, C*H*), 7.45 (d, C*H*), 7.35–7.28 (m, C*H*), 1.29 (s, CH_3), 1.26 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=183.1 (C), 138.7 (C), 131.8 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 122.2 (C), 90.1 (C), 86.5 (C), 76.9 (C), 51.8 (C), 22.1 (CH_3), 20.5 (CH_3). MS (I.E) *m*/*z* (%): 293 (5) [M^+-1], 277 (18) [M^+-OH], 207 (100) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{19}H_{18}O_3$: calculated 294.1252, found 294.1256.

*4.3.11. 3-Hydroxy-2,2-dimethyl-3,5-diphenylpent-4-ynoic acid (**3k**).* Obtained as orange solid, chromatography column (hexane/ethyl acetate), mp 112–114 °C. IR (KBr, cm^{-1}) ν_{max}: 3411, 3080, 2227, 1700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.20 (d, C*H*), 7.89 (d, C*H*), 7.46–7.43 (m, C*H*), 7.35–7.30 (m, C*H*) 1.31 (s, CH_3), 1.26 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=182.9 (C), 147.7 (C), 146.0 (C), 131.8 (CH), 129.1 (CH), 128.4 (CH), 122.6 (CH), 121.6 (C), 88.9 (C), 87.3 (C), 76.5 (C), 51.7 (C), 21.9 (CH_3), 20.5 (CH_3). MS (I.E) *m*/*z* (%): 339 (2) [M^+], 339 (20) [M^+-OH], 294 (15) [M^+-COOH], 252 (100) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{19}H_{17}O_4N$: calculated 323.1158, found 323.1157.

*4.3.12. 3-(4-Bromophenyl)-3-hydroxy-2,2-dimethyl-5-phenylpent-4-ynoic acid (**3l**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 116–118 °C. IR (KBr, cm^{-1}) ν_{max}: 3059, 2227, 1697. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.56 (d, *J*=9 Hz, C*H*), 7.46 (d, *J*=9 Hz, C*H*), 7.44–7.41 (m, C*H*), 7.31–7.25 (m, C*H*) 1.27 (s, CH_3), 1.23 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=183.2 (C), 137.9 (C), 131.8.0 (CH), 130.6 (CH), 129.7 (CH), 128.9 (CH), 128.4 (CH), 122.5 (C), 121.9 (C), 89.6 (C), 86.7 (C), 76.5 (C), 51.6 (C), 22.0 (CH_3), 20.4 (CH_3). MS (FAB$^+$) *m*/*z* (%): 373 (2) [M^+], 355 (30) [M^+-OH], 287 (50) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{19}H_{16}O_2Br$: calculated 355.0334, found 355.0342.

*4.3.13. Hydroxy-2,2-dimethyl-5-phenyl-3-(4-trifluoromethyl)phenyl pent-4-ynoic acid (**3m**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 94–96 °C. IR (Film, cm^{-1}) ν_{max}: 3060, 2227, 1698. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.83 (d, *J*=9 Hz, C*H*), 7.61 (d, *J*=9 Hz, C*H*), 7.44 (dd, C*H*), 7.33–7.28 (m, C*H*), 1.30 (s, CH_3), 1.25 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=183.2 (C), 142.8 (C), 131.8 (CH), 130.6 (C), 130.2 (C), 128.9 (CH), 128.4 (2CH), 125.8 (C), 124.4 (C), 122.2 (C), 121.8 (C), 89.5 (C), 86.9 (C), 76.6 (C), 51.7 (C), 22.0 (CH_3), 20.4 (CH_3). MS (IE$^+$) *m*/*z* (%): 362 (1) [M^+], 345 (50) [M^+-OH], 275 (100) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{20}H_{16}O_2F_3$: calculated 345.1102, found 345.1100.

*4.3.14. 3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethyl-5-phenylpent-4-ynoic acid (**3n**).* Obtained as pale yellow oil, chromatography column (hexane/ethyl acetate). IR (Film, cm^{-1}) ν_{max}: 3081, 2227, 1698. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.62 (d, C*H*), 7.43 (dd, C*H*), 7.32–7.27 (m, C*H*), 1.27 (s, CH_3), 1.23 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=183.0 (C), 137.54 (C), 134.3 (C), 131.9 (CH), 129.4 (CH), 128.9 (CH), 128.4 (CH), 127.7 (CH), 122.0 (C), 89.8 (C), 86.7 (C), 76.6 (C), 51.8 (C), 22.12 (CH_3), 20.5 (CH_3). MS (FAB$^+$) *m*/*z* (%): 328 (2) [M^+], 311 (20) [M^+-OH], 241 (40) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{19}H_{16}O_2Cl$: calculated 311.0839, found 311.0836.

*4.3.15. (3-Cyclohexylidenebut-1-yn-1-yl)benzene (**4b**).* Obtained as orange oil, chromatography column (hexane). Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.62, H, 8.55. IR (Film, cm^{-1}) ν_{max}: 2933, 2857, 2202. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.38–7.28 (m, C*H*), 7.27–7.11 (m, C*H*), 2.41 (t, CH_2), 2.12 (t, CH_2), 1.78 (s, CH_3), 1.52–1.42 (*m*-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 148.12 (C), 131.2 (CH), 128.2 (CH), 127.4 (CH), 124.3 (C), 108.4 (C), 91.3 (C), 90.8 (C), 33.8 (CH_2), 30.1 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 26.5 (CH_2), 18.0 (CH_3). MS (I.E) *m*/*z*: 210 (10) [M^+].

*4.3.16. 1-(4-Methyl-1-phenylpent-3-en-1-yn-3-yl)-4-nitrobenzene (**4k**).* Obtained as orange oil, chromatography column (hexane). IR (Film, cm^{-1}) ν_{max}: 2952, 2853, 2199, 1596, 1518, 1345. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.21 (d, *J*=9 Hz, C*H*), 7.53 (d, *J*=9 Hz, C*H*), 7.43–7.42 (m, C*H*), 7.40 (d, *J*=3 Hz, C*H*), 7.31–7.30 (m, C*H*), 7.29 (d, *J*=3 Hz, C*H*), 2.24 (s, CH_3), 1.88 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.5 (C), 146.2 (C), 145.8 (C), 131.3 (CH), 130.1 (CH), 128.3 (CH), 128.1 (CH), 123.4 (2CH), 117.6 (C), 93.2 (C), 88.9 (C), 24.4 (CH_2), 21.7 (CH_3). MS (I.E) *m*/*z* (%): 277 (100) [M^+]. HRMS: calcd for $C_{18}H_{15}O_2N$: calculated 277.1103, found 277.1105.

*4.3.17. 1-Bromo-4-(4-methyl-1-phenylpent-3-en-1-yn-3-yl)benzene (**4l**).* Obtained as pale yellow oil, chromatography column (hexane). IR (Film, cm^{-1}) ν_{max}: 2926, 2198, 1485, 755. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.47 (d, *J*=9 Hz, C*H*), 7.42–7.39 (m, C*H*), 7.29–7.25 (m, C*H*), 7.23 (d, *J*=9 Hz, C*H*), 2.19 (s, CH_3), 1.83 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=143.8 (C), 138.3 (C), 131.3 (CH), 131.2 (CH), 130.9 (CH), 128.2 (CH), 127.8 (CH), 123.8 (C), 120.8 (C), 118.1 92.5 (C), 89.7 (C), 24.1 (CH_3), 21.6 (CH_3). MS (I.E) *m*/*z* (%): 310 (85) [M^+], 268 (100) [$M^+-C_3H_6$]. HRMS: calcd for $C_{18}H_{15}Br$: calculated 310.0357, found 310.0354.

*4.3.18. 1-Chloro-4-(4-methyl-1-phenylpent-3-en-1-yn-3-yl)benzene (**4n**).* Obtained as yellow oil, chromatography column (hexane). IR (Film, cm^{-1}) ν_{max}: 2908, 2726, 2198, 1594, 1486, 1092. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.42–7.39 (m, C*H*), 7.31–7.25 (m, C*H*), 2.19 (s, CH_3), 1.83 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=143.8 (C), 137.9 (C), 132.6 (C), 131.3 (CH), 130.6 (CH), 128.3 (CH), 127.8 (CH), 123.8 (C), 118.0 (C), 92.5 (C), 89.8 (C), 24.1 (CH_3), 21.6 (CH_3). MS (I.E) *m*/*z* (%): 266 (100) [M^+]. HRMS: calcd for $C_{18}H_{15}Cl$: calculated 266.0862, found 266.0864.

*4.3.19. 1-Methoxy-4-(4-methyl-1-phenylpent-3-en-1-yn-3-yl)benzene (**4o**).* Obtained as orange oil, chromatography column (hexane). IR (Film, cm^{-1}) ν_{max}: 2907, 2838, 2196, 1605, 1509, 1247. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.41 (dd, C*H*), 7.28 (d, *J*=9 Hz, C*H*), 7.26–7.24 (m, C*H*), 6.87 (d, *J*=9 Hz, C*H*), 3.78 (s, CH_3), 2.18 (s, CH_3), 1.84 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=158.3 (C), 142.5 (C), 131.7 (C), 131.1 (CH), 130.2 (CH), 128.1 (CH), 127.5 (CH), 124.0 (CH), 118.4 (C), 113.3 (C), 91.9 (C), 90.4 (C), 55.1 (CH_3), 24.0 (CH_3), 21.5 (CH_3). MS (I.E) *m*/*z*: 262 (100) [M^+]. HRMS: calcd for $C_{19}H_{18}O$: calculated 262.1358, found 262.1361.

*4.3.20. 3-(4-Chlorophenyl)-2,2,6,6-tetramethyl-5-phenylhepta-3,4-dienedioic acid (**6n**).* Obtained as white solid, chromatography column (hexane/ethyl acetate), mp 161–163 °C. IR (KBr, cm^{-1}) ν_{max}: 3056, 2984, 1739, 1695. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=10.61 (s, COOH), 7.38–7.25 (m, C*H*), 1.53 (d, 2CH_3), 1.48 (s, 2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=204.4 (C), 183.88 (C), 183.82 (C), 134.53 (C), 133.42 (C), 133.13 (C), 128.73 (CH), 128.62 (CH) 127.46 (CH), 115.22 (C), 113.99 (C), 45.52 (C), 45.39 (C), 26.25 (CH_3), 26.08 (CH_3), 25.91 (CH_3), 25.77 (CH_3). MS (FAB$^+$) *m*/*z* (%): 398 (3) [M^+], 353 (15) [M^+-COOH], 311 (100) [$M^+-C_4H_7O_2$]. HRMS: calcd for $C_{22}H_{22}O_2Cl$: calculated 353.1308, found 353.1314.

*4.3.21. 1-(4-Methoxyphenyl)-2,2,6,6-tetramethyl-5-phenylhepta-3,4-dienedioic acid (**6o**).* Obtained as white solid (recrystallized from hexane/ethyl acetate), mp 200–202 °C. IR (KBr, cm^{-1}) ν_{max}:

3062, 2980, 1699, 1603. ^{1}H NMR (300 MHz, DMSO): δ (ppm)= 7.36–7.26 (m, C*H*), 7.19 (t, C*H*), 6.86 (d, C*H*), 3.69 (s, CH_3), 1.36 (s, 4CH_3). ^{13}C NMR (75 MHz, DMSO): δ (ppm)=203.3 (C), 178.0 (C), 177.98 (C), 158.2 (C), 135.2 (C), 128.3 (CH), 128.0 (CH), 127.0 (C), 126.8 (CH), 114.5 (C), 114.4 (C), 113.8 (CH), 55.0 (CH_3), 44.46 (C), 44.40 (C), 26.18 (CH_3), 26.13 (CH_3), 25.6 (CH_3), 25.5 (CH_3). MS (FAB$^+$) *m*/*z* (%): 394 (3) [M$^+$], 350 (10) [M$^+$–COO], 307 (65) [M$^+$–$C_4H_7O_2$]. HRMS: calcd for $C_{23}H_{27}O_3$: calculated 351.1960, found 351.1967.

*4.3.22. 2,2,6,6-Tetramethyl-3-phenyl-5-(p-tolyl)hepta-3,4-dienedioic acid (**6p**).* Obtained as white solid (recrystallized from hexane/ethyl acetate), mp 162 °C. IR (KBr, cm^{-1}) ν_{max}: 3060, 2987, 1699 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ (ppm)=12.54 (s, COO*H*), 7.38–7.16 (m, C*H*), 7.10 (d, C*H*), 2.23 (s, CH_3), 1.39–1.37 (m, 4CH_3). ^{13}C NMR (75 MHz, DMSO): δ (ppm)=203.5 (C), 177.8 (C), 177.7 (C), 136.2 (C), 135.2 (C), 132.1 (C), 128.9 (CH), 128.3 (CH), 126.8 (2CH), 114.8 (C), 114.7 (C), 44.44 (C), 44.41 (C), 26.2 (CH_3), 26.1 (CH_3), 25.7 (CH_3), 25.6 (CH_3), 20.5 (CH_3). MS (I.E) *m*/*z* (%): 377 (12) [M$^+$], 332 (25) [M$^+$–COOH], 291 (100) [M$^+$–$C_4H_7O_2$]. HRMS: calcd for $C_{24}H_{25}O_4$: calculated 377.1753, found 377.1753.

4.4. General procedure for the synthesis of the 5-bromo-3,4-dihydro-2*H*-pyran-2-ones 7(a–n)

At 0 °C we added *N*-bromosuccinimide (0.15 g, 8.6 mmol) to a solution of the 3-hydroxy-2,2,3-trimethyl-5-phenylpent-4-ynoic acid (**2a**) (0.2 g, 8.6 mmol) in 5 mL of acetonitrile, the reaction was stirred for 2 h at 0 °C, after that the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and then washed with distilled water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuum. The crude was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate as eluent.

*4.4.1. 5-Bromo-4-hydroxy-3,3,4-trimethyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7a**).* Obtained as white solid (0.2 g, 75%) chromatography column (hexane/ethyl acetate), mp 110–112 °C. IR (KBr, cm^{-1}) ν_{max}: 3476, 2989, 1753. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.63–7.62 (m, C*H*), 7.40–7.39 (m, C*H*), 2.33 (s, O*H*), 1.43 (s, CH_3), 1.40 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=172.7 (C), 145.3 (C), 134.3 (C), 132.2 (CH), 129.9 (CH), 128.9 (CH), 128.1 (CH), 111.3 (C), 74.6 (C), 46.7 (C), 23.9 (CH_3), 20.2 (CH_3), 19.5 (CH_3). MS (EI) *m*/*z* (%): 310 (10) [M$^+$]. HRMS: calcd for $C_{14}H_{15}O_3Br$: calculated 310.0213, found 310.0205.

*4.4.2. 4-Bromo-5-hydroxy-5-methyl-3-phenyl-2-oxaspiro[5.5]undec-3-en-1-one (**7b**).* Obtained as white solid (0.24 g, 94%) (recrystallized from hexane/dichlorometane), mp 98–100 °C. IR (KBr, cm^{-1}) ν_{max}: 3494, 2941, 1738. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.69–7.66 (m, C*H*), 7.45–7.41 (m, C*H*), 2.33 (s, O*H*), 2.13 (d, *J*=12 Hz, CH_2), 1.74 (d, *J*=12 Hz, CH_2), 1.42 (s, CH_3), 1.24–1.15 (m, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=171.1 (C), 132.0 (C), 129.7 (CH), 128.8 (CH), 128.0 (CH), 49.9 (C), 27.5 (C), 25.2 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 22.6 (CH_3). MS (EI) *m*/*z* (%): 350 (10) [M$^+$–1], 333 (30) [M$^+$–OH], 307 (15) [M$^+$–COO]. HRMS: calcd for $C_{17}H_{19}O_3Br$: calculated 351.0596, found 351.0606.

*4.4.3. 5-Bromo-4-hydroxy-3,4-dimethyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7d**).* Obtained as white solid (0.2 g 76%), chromatography column (hexane/ethyl acetate), mp: 84–86 °C. IR (KBr) ν_{max}: 3471, 2992, 1744, 1666. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.64–7.62 (m, C*H*), 7.4 (s, C*H*), 3.11 (q, *J*=6 Hz, C*H*), 2.42 (s, O*H*), 1.42 (d, *J*=6 Hz, CH_3), 1.36 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=169.5 (C), 145.5 (C), 132.1 (C), 129.9 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 112.5 (C), 72.8 (C), 45.7 (C), 22.2 (CH_3), 20.2 (CH), 9.8 (CH_3). MS (EI) *m*/*z* (%): 296 (15) [M$^+$–1]. HRMS: calcd for $C_{13}H_{14}O_3Br$: calculated 297.0125, found 297.0126.

*4.4.4. 5-Bromo-3,4-dimethyl-6-phenyl-2H-pyran-2-one (**7d′**).* Obtained as white solid (0.18 g, 73%), chromatography column (hexane/ethyl acetate), mp 104–106 °C. IR (KBr, cm^{-1}) ν_{max}: 2993, 1744, 1669. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.73–7.70 (m, C*H*), 7.45–7.43 (m, C*H*), 2.36 (s, CH_3), 2.20 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=162.1 (C), 154.4 (C), 150.0 (C), 132.6 (C), 130.2 (CH), 129.3 (CH), 128.1 (CH), 121.2 (C), 104.4 (C), 20.7 (CH_3), 14.1 (CH_3). MS (EI) *m*/*z* (%): 278 (48) [M$^+$–1]. HRMS: calcd for $C_{13}H_{12}O_2Br$: calculated 279.0013, found 279.0021.

*4.4.5. 5-Bromo-4-hydroxy-4-methyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7e**).* Obtained as white solid (0.16 g, 58%), chromatography column (hexane/ethyl acetate), mp 124 °C. IR (KBr, cm^{-1}) ν_{max}: 3444, 1737, 1660. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.63–7.59 (m, C*H*), 7.39 (d, C*H*), 7.37 (d, C*H*), 3.11 (d, *J*=15 Hz, CH_2), 2.99 (d, *J*=15 Hz, CH_2), 2.31 (s, O*H*), 1.54 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=166.1 (C), 147.1 (C), 132.2 (C), 130.0 (CH), 129.1 (CH), 128.1 (CH), 110.5 (C), 70.6 (C), 43.4 (CH_2), 28.4 (CH_3). MS (EI) *m*/*z* (%): 283 (30) [M$^+$]. HRMS: calcd for $C_{12}H_{11}O_3Br$: calculated 281.9891, found 281.9889.

*4.4.6. 5-Bromo-4-methyl-6-phenyl-2H-pyran-2-one (**7e′**).* Obtained as white solid (0.14 g, 54%), chromatography column (hexane/ethyl acetate), mp 99–100 °C. IR (KBr, cm^{-1}) ν_{max}: 1719, 1611. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.78–7.74 (m, C*H*), 7.50–7.45 (m, C*H*), 6.25 (q, *J*=3 Hz, C*H*), 2.35 (d, *J*=3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=160.6 (C), 157.5 (C), 156.4 (C), 132.0 (C), 130.5 (CH), 129.2 (CH), 128.0 (CH), 112.8 (CH), 103.3 (C), 23.8 (CH_3). MS (EI) *m*/*z* (%): 264 (50) [M$^+$]. HRMS: calcd for $C_{12}H_{10}O_2Br$: calculated 264.9864, found 264.9870.

*4.4.7. 5-Bromo-4-hydroxy-3,3-dimethyl-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (**7j**).* Obtained as white solid (0.17 g, 66%), chromatography column (hexane/ethyl acetate), mp 168–170 °C. IR (KBr, cm^{-1}) ν_{max}: 3481, 2989, 1751, 1670. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.74 (d, C*H*), 7.44–7.32 (m, C*H*), 2.78 (s, O*H*), 1.59 (s, CH_3), 1.06 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=172.0 (C), 146.5 (C), 139.8 (C), 132.0 (C), 130.2 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 125.6 (CH), 110.9 (C), 79.3 (C), 47.9 (C), 22.5 (CH_3), 19.5 (CH_3). MS (EI) *m*/*z* (%): 374 (10) [M$^+$]. HRMS: calcd for $C_{19}H_{17}O_3Br$: calculated 374.0339, found 374.0341.

*4.4.8. 5-Bromo-4-hydroxy-3,3-dimethyl-4-(4-nitrophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7k**).* Obtained as white solid (0.18 g, 74%), chromatography column (hexane/ethyl acetate), mp 190–191 °C. IR (KBr, cm^{-1}) ν_{max}: 3488, 2985, 1752, 1655, 1518, 1348. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.24 (d, *J*=9 Hz, C*H*), 7.73 (dd, C*H*), 7.64 (d, *J*=9 Hz, C*H*), 7.49–7.46 (m, C*H*), 2.95 (s, O*H*), 1.60 (s, CH_3), 1.07 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=171.2 (C), 148.0 (C), 147.5 (C), 147.4 (C), 131.5 (C), 130.2 (CH), 128.9 (CH), 128.4 (CH), 127.03 (CH), 123.8 (CH), 109.0 (C), 79.2 (C), 47.7 (C), 22.3 (CH_3), 19.9 (CH_3). MS (EI) *m*/*z* (%): 417 (10) [M$^+$]. HRMS: calcd for $C_{19}H_{16}BrO_5N$: calculated 417.0212, found 417.0209.

*4.4.9. 5-Bromo-4-(4-bromophenyl)-4-hydroxy-3,3-dimethyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7l**).* Obtained as white solid (0.18 g, 77%), chromatography column (hexane/ethyl acetate), mp: 180–182 °C. IR (KBr, cm^{-1}) ν_{max}: 3493, 2986, 1750, 1656. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.73–7.72 (m, C*H*), 7.50 (d, *J*=6 Hz, C*H*), 7.49–7.32 (m, C*H*), 7.30 (d, *J*=6 Hz, C*H*), 2.81 (s, O*H*), 1.57 (s, CH_3), 1.06 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=171.6 (C), 146.8 (C), 139.0 (C), 130.2 (CH), 128.9 (CH), 128.2 (CH), 127.4 (CH), 122.7

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(C), 110.0 (C), 78.9 (C), 47.7 (C), 22.3 (CH_3), 19.9 (CH_3). MS (EI) *m*/*z* (%): 452 (10) [M^+]. HRMS: calcd for $C_{19}H_{16}O_3Br_2$: calculated 451.9446, found 451.9460.

*4.4.10. 5-Bromo-4-(4-chlorophenyl)-4-hydroxy-3,3-dimethyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (**7n**).* Obtained as white solid (0.18 g, 71%), chromatography column (hexane/ethyl acetate), mp: 178 °C. IR (KBr, cm^{-1}) ν_{max}: 3493, 2967, 1750, 1654. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.75–7.72 (m, C*H*), 7.46–7.43 (m, C*H*), 7.39–7.32 (m, C*H*), 2.81 (s, O*H*), 1.57 (s, CH_3), 1.07 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=171.7 (C), 146.8 (C), 138.5 (C), 134.6 (C), 131.8 (C), 130.3 (CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.2 (CH), 110.2 (C), 79.0 (C), 47.8 (C), 22.3 (CH_3), 19.9 (CH_3). MS (IE) *m*/*z* (%): 406 (10) [M^+-1]. HRMS: calcd for $C_{19}H_{16}BrClO_3$: calculated 407.0050, found 407.0042.

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Supplementary data

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