Synthesis A. Parida et al. Special Topic

Efficient Synthesis of 3-Alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones by a Stork–Danheiser Sequence from Vinylogous Esters and Terminal Alkynes

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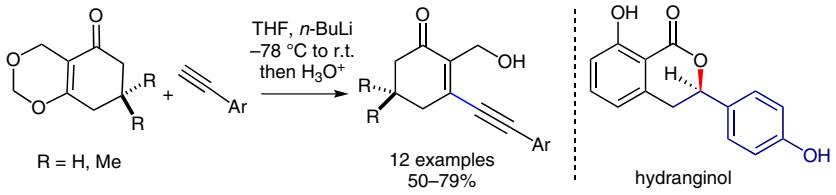

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Abstract An efficient Stork–Danheiser sequence has been developed for the preparation of a variety of 3-alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones in good to excellent yields from the corresponding 4,6,7,8-tetrahydro-5*H*-1,3-benzodioxin-5-ones and terminal alkynes. Several of the 3-alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-one products were catalytically cyclized to give the corresponding 3-aryl-1,5,6,7-tetrahydro-8*H*-isochromen-8-ones.

Key words alkynylations, Stork–Danheiser sequences, vinylogous esters, alkynes, cyclizations, chromenones

Naturally occurring dimeric bibenzyls containing one or two diaryl ether or biphenyl bonds have been found in liverworts of such genera as *Riccardia*, *Marchantia*, *Plagiochila*, *Preissia*, *Reboulia*, *Monoclea*, *Ricciocarpos*, and *Blasia*.[1] The compounds are secondary metabolites that show a wide range of cytotoxic, antibacterial, antifungual, and 5-lipoxygenase inhibitory activities.[2] Biogenically, dimeric bibenzyls are formed from lunularic acid (**1d**) or lunularin (**1a**) (Figure 1), which are widely distributed in leafy and thalloid liverworts.[1]

In 1983, Ohta and co-workers isolated prelunularic acid (**1c**) (Figure 1) from suspension-cultured cells of *Marchantia polymorpha*.[3a] The naturally occurring stilbene carboxylic acid lunularic acid (**1d**) has been isolated from the liverwort *Lunularia cruciate*, found in Israel.[3b,4] Hydrangeic acid 4′-*O*-β-D-glucopyranoside (**1e**) and 2-hydroxy-6-[2-(4-hydroxyphenyl)-2-oxoethyl]benzoic acid (**1f**) were isolated from the roots of viper's grass (*Scorzonera judaica*) from Jordan.[5]

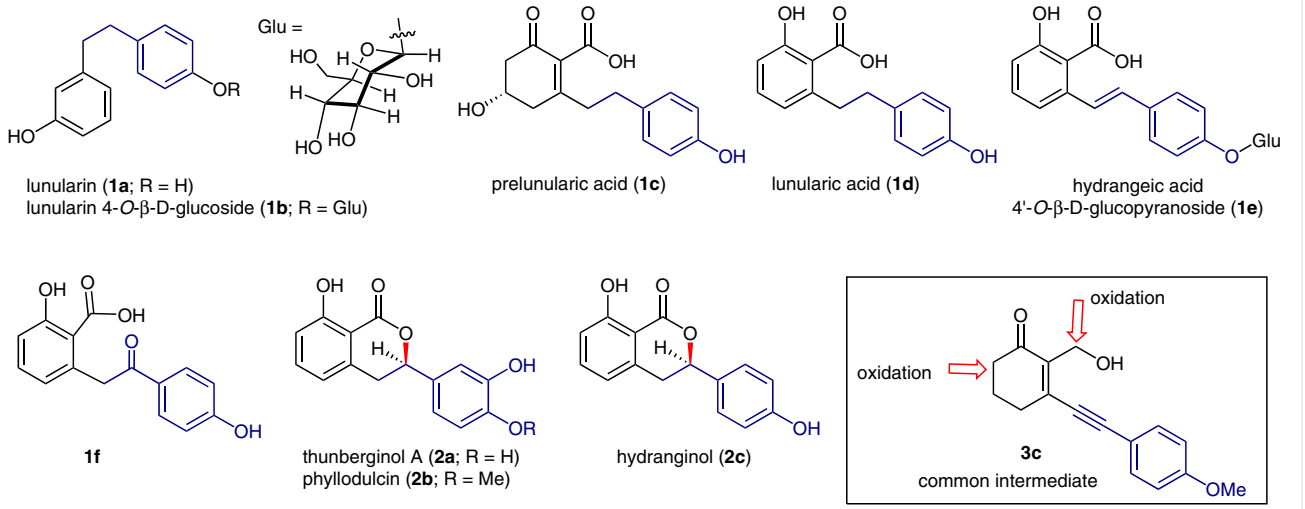
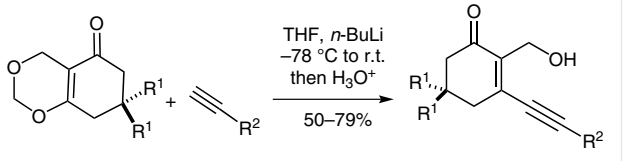


Figure 1 Lunularic acid (**1d**) and related compounds (**1a**–**c**,**e**,**f**), dihydroisocoumarins **2a**–**c**, and the common intermediate **3c**

Dihydroisocoumarins are widespread secondary metabolites that have been isolated from various organisms and have some interesting biological activities. Several dihydroisocoumarins are being examined as lead drugs in pharmaceutical research.[6,7] Thunberginol A (**2a**), phyllodulcin (**2b**), and hydrangenol (**2c**) (Figure 1) have been isolated from the leaves of *Hydrangea macrophylla* var. *thunbergii*. These compounds promote adipogenesis of 3T3-L1 cells and exhibit antidiabetic properties.[8,9] Various other naturally occurring dihydroisocoumarin derivatives isolated from various species show gastroprotective,[10a] antibiotic, antimicrobial, or antibacterial activities and some suppress inflammation or the activity of ulcers. Some congeners of this family are active against Gram-positive bacteria.[10b]

The carbon–carbon triple bond is among the most important functional groups in organic chemistry, and it has been used in advanced intermediates in natural-product synthesis as well as in syntheses of functionalized materials.[10] Recently, significant progress has been made in the construction of heterocyclic rings through intramolecular annulation of carboxylic acids, amides, alcohols, or amines to a variety of carbon–carbon triple bonds.[11] We surmised that natural products containing a 3-alkynylcyclohex-2-en-1-one structure[12] might be obtained by a Stork–Danheiser sequence from the vinylogous esters **4a**,**b** and the appropriate terminal alkynes. Here, we report an efficient Stork–Danheiser sequence[13] that uses lithium acetylides prepared in situ by the reaction of a terminal aralkyne and *n*-butyllithium (Scheme 1).



Scheme 1 Stork–Danheiser sequence from **4a**,**b**

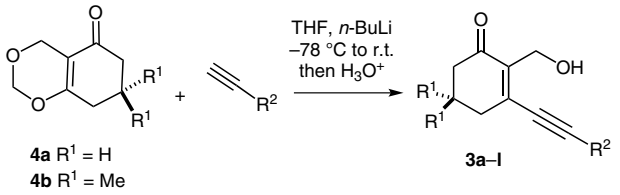
We treated one equivalent of the vinylogous ester **4a** or **4b**[14] with a lithium acetylide, prepared in situ by adding 1.3 equivalents of *n*-butyllithium to 1.2 equivalents of the appropriate terminal alkyne in tetrahydrofuran at –78 °C, to give the corresponding 3-alkynyl-(2-hydroxymethyl)cyclohex-2-en-1-ones **3a**–**l** in up to 79% yield (Table 1). Compounds **3a**–**f**, which have a hydroxymethyl group in the 2-position, are potentially useful as advanced intermediates for the synthesis of various lunularic acid derivatives or dihydroisocoumarins through synthetic elaboration of the triple bond and hydroxymethyl functionalities.

We were also interested in activating the triple-bond functionality of the 3-alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones **3** in the presence of a Lewis acid with aim of synthesizing core structures of naturally occurring dihydroisocoumarins.[15] We initially chose compound **3g** as a model substrate and examined the activation of its alkyne functionality with various catalysts (Table 2). We hoped that a Lewis acid might activate the carbonyl carbon to form the tetrahydroisochromenone **5b** by a 6-*endo*-*dig* cyclization rather than the less-preferred 5-*exo*-*dig* cyclization.

We found that 10 mol% of bismuth(III) triflate[16] in various solvents gave tetrahydroisochromenone **5b** in yields of up to 30% (Table 2, entries 1–5), whereas 10 mol% of scandium(III) triflate gave **5b** in 50% yield (entry 6). Interestingly, 10 mol% of iron(III) chloride was a better Lewis acid catalyst, giving **5b** in 72% yield when the reaction was carried out in dichloromethane (entry 7). On changing the catalysts from a Lewis acid to a transition metal,[17] we found that 10 mol% of palladium(II) acetate gave product **5b** in up to 82% yield at room temperature (entries 8–11).

Similar treatment of the 3-alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones **3c**, **3i**, and **3j** under the optimized conditions gave the corresponding to dihydroisocoumarin **5a**, **5c**, and **5d**, respectively, in 63–84% isolated yield (Table 3).

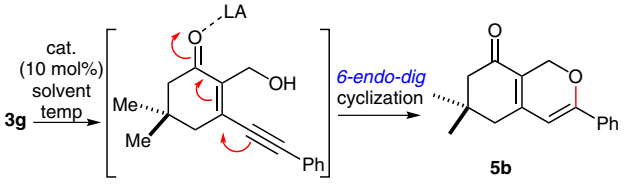
Table 1 Substrate Scope of Bicyclic Vinylogous Esters **4a**,**b**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H	Ph	**3a**	76
2	H	4-Tol	**3b**	50
3	H	4-$MeOC_6H_4$	**3c**	72
4	H	4-$F_3CC_6H_4$	**3d**	58
5	H	3,4-$(MeO)_2C_6H_3$	**3e**	78
6	H	3-*i*-Pr-4-$MeOC_6H_3$	**3f**	75
7	Me	Ph	**3g**	69
8	Me	4-Tol	**3h**	71
9	Me	4-$MeOC_6H_4$	**3i**	67
10	Me	4-$F_3CC_6H_4$	**3j**	62
11	H	Bu	**3k**	75
12	H	*c*-Pr	**3l**	79

[a] Reaction conditions: **4a**,**b** (1.5 mmol), THF (10 mL), –78 °C to r.t., 10 h then 4 M aq HCl, 0 °C, 2 h.
[b] Isolated yield after column chromatography.

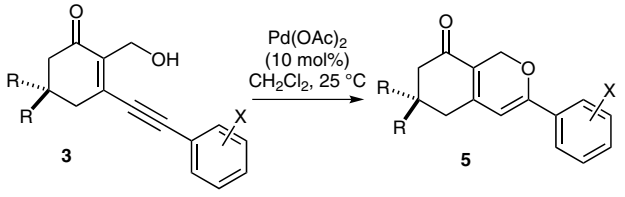
Table 2 Optimization of the Cyclization of 2-(Hydroxymethyl)-5,5-dimethyl-3-(phenylethynyl)cyclohex-2-en-1-one (**3g**)[a]



Entry	Catalyst	Solvent	Temp (°C)	Time	Yield[b,c] (%)
1	$Bi(OTf)_3$	DCE	80	3 h	21
2	$Bi(OTf)_3$	DMF	110	6 h	–
3	$Bi(OTf)_3$	MeCN	80	24 h	10
4	$Bi(OTf)_3$	F_3CCH_2OH	25	10 h	30
5	$Bi(OTf)_3$	CH_2Cl_2	40	15 h	22
6	$Sc(OTf)_3$	CH_2Cl_2	40	40 min	50
7	$FeCl_3$	CH_2Cl_2	40	10 h	72
8	$Pd(OAc)_2$	EtOH	25	18 h	66
9	$Pd(OAc)_2$	DCE	25	24 h	64
10	**$Pd(OAc)_2$**	**CH_2Cl_2**	**25**	**24 h**	**82**
11	$Pd(OAc)_2$	F_3CCH_2OH	25	24 h	63

[a] Reactions were carried out with 0.2 mmol of **3g** in 2 mL of solvent.
[b] Isolated yield after column chromatography.
[c] 10–52% of the starting material **3g** was recovered as a result of incomplete reaction.

Table 3 Substrate Scope of the Isomerization of Enones **3**[a]



R	X	Product	Yield[b] (%)
H	4-$MeOC_6H_4$	**5a**	84
Me	Ph	**5b**	82
Me	4-$MeOC_6H_4$	**5c**	79
Me	4-$F_3CC_6H_4$	**5d**	63

[a] Reaction conditions: **3** (0.2 mmol), CH_2Cl_2 (2 mL), r.t.
[b] Isolated yield after column chromatography.

In conclusion, we have developed an efficient Stork–Danheiser sequence starting from vinylogous esters and terminal alkynes. The resulting 3-alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones **3** might be useful as building blocks for synthesis of the isocoumarin skeleton. We also believe that a Corey–Bakshi–Shibata reduction[18] of the 3-alkynylcyclohex-2-en-1-ones **3** should give an enantioenriched intermediate that might be useful in organic synthesis. Further studies on applications of our method in the syntheses of natural products are currently underway in our laboratory.

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. All other solvents such as DCE, DMF, 2,2,2-trifluoroethanol and reagents were used as received.

Thin-layer chromatography was performed using Merck Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain and other stains. Silica gel from Merck (100–200 mesh) was used for flash chromatography. Melting points were recorded on a digital melting point apparatus from Jyoti Scientific (AN ISO 9001:2000) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 and 500 MHz spectrometers with ^{13}C operating frequencies of 100 and 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on an FT-IR system (Spectrum BX) from PerkinElmer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-resolution mass spectral data were obtained from the Central Instrumentation Facility (CIF) at IISER Bhopal.

3-Alkynyl-2-(hydroxymethyl)cyclohex-2-en-1-ones 3; General Procedure

A 2.0 M soln of *n*-BuLi in cyclohexane (1.95 mmol, 1.3 equiv) was added to a stirred solution of the appropriate terminal alkyne (1.8 mmol, 1.2 equiv) in THF (5 mL) at – 78 °C, and the mixture was stirred for 1 h. A solution of vinylogous ester **4** (1.5 mmol, 1.0 equiv) in THF (5 mL) was then slowly added over 5 min. The mixture was allowed to warm to r.t. and stirred for 10 h. The reaction was then quenched with 4 M aq HCl (5 mL) at 0 °C and the mixture was stirred for 2 h. The resulting mixture was extracted with EtOAc (3 × 25 mL) and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a crude product that was purified by column chromatography.

2-(Hydroxymethyl)-3-(phenylethynyl)cyclohex-2-en-1-one (3a)

Yellow oil; yield: 258 mg (76%; 1.5 mmol scale); R_f = 0.39 (30% EtOAc–hexanes).

IR (film): 3432, 2928, 2197, 1661, 1643, 1361, 1311, 1187, 1010, 759 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.48 (m, 2 H), 7.34–7.37 (m, 3 H), 5.20 (br s, 1 H), 4.59 (s, 2 H), 2.61 (t, *J* = 6.02 Hz, 2 H), 2.49 (t, *J* = 6.44 Hz, 2 H), 2.02–2.07 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 140.13, 140.10, 131.9, 129.7, 128.6, 121.9, 104.7, 86.7, 60.2, 37.9, 31.3, 22.3.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_2$: 249.0886; found: 249.0905.

2-(Hydroxymethyl)-3-(4-tolylethynyl) cyclohex-2-en-1-one (3b)

Yellow oil; yield: 180 mg (50%; 1.5 mmol scale); mp 55–58 °C; R_f = 0.52 (30% EtOAc–hexane).

IR (film): 3401, 1647, 922, 745 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.07 Hz, 2 H), 7.19 (d, *J* = 8.03 Hz, 2 H), 4.63 (s, 2 H), 3.00 (br s, 1 H), 2.65 (t, *J* = 6.02 Hz, 2 H), 2.52 (t, *J* = 6.45 Hz, 2 H), 2.40 (s, 3 H), 2.0–2.11 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.1, 140.4, 140.2, 139.7, 131.9, 129.4, 118.8, 105.3, 86.3, 60.3, 37.9, 31.3, 22.3, 21.7.

2-(Hydroxymethyl)-3-[(4-methoxyphenyl)ethynyl]cyclohex-2-en-1-one (3c)

Yellow solid; yield: 276 mg (72%; 1.5 mmol scale); mp 89–95 °C; R_f = 0.38 (30% EtOAc–hexane).

IR (film): 3421, 2936, 2191, 1645, 1296, 1252, 1176, 1025, 835 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (m, 2 H), 6.89 (m, 2 H), 4.61 (s, 2 H), 3.83 (s, 3 H), 3.09 (br s, 1 H), 2.62 (t, *J* = 6.02 Hz, 2 H), 2.50 (m, 2 H), 2.03–2.08 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 160.8, 140.6, 139.3, 133.7, 114.2, 113.9, 105.4, 86.0, 60.2, 55.4, 37.9, 31.3, 22.3.

2-(Hydroxymethyl)-3-{[4-(trifluoromethyl)phenyl]ethynyl}cyclohex-2-en-1-one (3d)

Yellow solid; yield: 256 mg (58%; 1.5 mmol scale); mp 95–97 °C; R_f = 0.42 (30% EtOAc–hexane).

IR (film): 3399, 2097, 1660, 1648, 780 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.66 (m, 4 H), 4.62 (s, 2 H), 2.97 (br s, 1 H), 2.66 (t, *J* = 5.99 Hz, 2 H), 2.55 (m, 2 H), 2.07–2.13 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.0, 140.9, 139.1, 132.1, 131.3, 125.6 (m), 125.5 (q, *J* = 3.82 Hz), 122.6, 102.3, 88.4, 60.3, 37.9, 31.1, 22.3.

3-[(3,4-Dimethoxyphenyl)ethynyl]-2-(hydroxymethyl)cyclohex-2-en-1-one (3e)

Yellow gel; yield: 335 mg (78%; 1.5 mmol scale); R_f = 0.32 (30% EtOAc–hexanes).

IR (film): 3419, 2935, 2360, 2340, 2186, 1650, 1515, 1252, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 8.31, 1.65 Hz, 1 H), 6.93 (d, *J* = 1.53 Hz, 1 H), 6.81 (d, *J* = 8.31 Hz, 1 H), 4.58 (s, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.98 (t, *J* = 7.54 Hz, 1 H), 2.60 (t, *J* = 5.89 Hz, 2 H), 2.47 (t, *J* = 6.67 Hz, 2 H), 1.99–2.05 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 150.7, 148.8, 140.4, 139.4, 125.9, 114.3, 114.0, 111.1, 105.5, 85.8, 60.3, 56.0, 37.9, 31.3, 29.7, 22.3.

2-(Hydroxymethyl)-3-[(3-isopropyl-4-methoxyphenyl)ethynyl]cyclohex-2-en-1-one (3f)

Colorless gel; yield: 336 mg (75%; 1.5 mmol scale); R_f = 0.35 (30% EtOAc–hexanes).

IR (film): 3444, 2962, 2360, 2340, 2189, 1660, 1587, 1495, 1290, 1248, 1186, 1024, 816 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.31 (m, 2 H), 6.78 (d, *J* = 9.0 Hz, 1 H), 4.60 (s, 2 H), 3.83 (s, 3 H), 3.21–3.30 (m, 1 H), 2.95 (br s, 1 H), 2.60 (t, *J* = 5.92 Hz, 2 H), 2.47 (t, *J* = 6.55, 2 H), 1.99–2.06 (m, 2 H), 1.18 (d, *J* = 6.81, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 158.2, 140.7, 139.1, 137.6, 131.1, 130.0, 113.6, 110.3, 106.3, 85.7, 60.4, 55.4, 37.9, 31.4, 26.6, 22.4, 22.3.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{22}NaO_3$: 321.1461; found: 321.1459.

2-(Hydroxymethyl)-5,5-dimethyl-3-(phenylethynyl)cyclohex-2-en-1-one (3g)

Yellow gel; yield: 263 mg (69%; 1.5 mmol scale); R_f = 0.45 (20% EtOAc–hexanes).

IR (film): 3435, 2962, 2197, 1653, 1012, 759, 475 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.52 (m, 2 H), 7.35–7.41 (m, 3 H), 4.64 (s, 2 H), 3.03 (br s, 1 H), 2.53 (s, 2 H), 2.37 (s, 2 H), 1.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 139.1, 137.8, 131.9, 129.6, 128.6, 121.9, 104.1, 87.0, 60.0, 51.5, 44.9, 33.5, 28.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}NaO_2$: 277.1199; found: 277.1202.

2-(Hydroxymethyl)-5, 5-dimethyl-3-(4-tolylethynyl)cyclohex-2-en-1-one (3h)

Colorless solid; yield: 286 mg (71%; 1.5 mmol scale); mp 90–92 °C; R_f = 0.51 (20% EtOAc–hexane).

IR (film): 3396, 2190, 1641, 1364, 780 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.06 Hz, 2 H), 7.18 (d, *J* = 7.94 Hz, 2 H), 4.64 (s, 2 H), 3.05 (br s, 1 H), 2.52 (s, 2 H), 2.39 (s, 3 H), 2.37 (s, 2 H), 1.11 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3, 140.1, 138.7, 138.0, 131.9, 129.3, 118.9, 104.7, 86.6, 60.1, 51.5, 45.0, 33.5, 28.0, 21.6.

HRMS (ESI): *m/z* $[M + K]^+$ calcd for $C_{18}H_{20}KO_2$: 307.1095; found: 307.1110.

2-(Hydroxymethyl)-3-[(4-methoxyphenyl)ethynyl]-5,5-dimethylcyclohex-2-en-1-one (3i)

Yellow solid; yield: 286 mg (67%; 1.5 mmol scale); mp 95–100 °C; R_f = 0.39 (20% EtOAc–hexane).

IR (film): 3470, 2960, 2187, 1645, 1592, 1511, 1365, 1292, 1253, 1021, 835 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (m, 2 H), 6.90 (m, 2 H), 4.63 (s, 2 H), 3.85 (s, 3 H), 3.08 (br s, 1 H), 2.52 (s, 2 H), 2.36 (s, 2 H), 1.10 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.3, 160.8, 138.3, 138.2, 133.7, 114.3, 113.9, 105.0, 86.4, 60.1, 55.4, 51.5, 45.0, 33.5, 28.1.

HRMS (ESI): *m/z* $[M + K]^+$ calcd for $C_{18}H_{20}KO_3$: 323.1044; found: 323.1031.

2-(Hydroxymethyl)-5,5-dimethyl-3-{[4-(trifluoromethyl)phenyl]ethynyl}cyclohex-2-en-1-one (3j)

Yellow solid; yield: 300 mg (62%; 1.5 mmol scale); mp 70–72 °C; R_f = 0.40 (20% EtOAc–hexane).

IR (film): 3425, 1647, 1322, 1130, 844 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.66 (m, 4 H), 4.63 (s, 2 H), 2.95 (br s, 1 H), 2.55 (s, 2 H), 2.40 (s, 2 H), 1.13 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 139.9, 136.8, 132.1, 132.1, 131.3, 125.6 (m), 125.5 (q, *J* = 3.7 Hz), 101.8, 88.8, 60.1, 51.5, 44.7, 33.5, 28.0.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{17}F_3NaO_2$: 345.1073; found: 345.1073.

3-Hex-1-yn-1-yl-2-(hydroxymethyl)cyclohex-2-en-1-one (3k)

Brown liquid; yield: 232 mg (75%; 1.5 mmol scale); R_f = 0.50 (20% EtOAc–hexane).

IR (film): 3440, 2935, 2874, 2213, 1655, 1360, 1015 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (s, 2 H), 2.97 (br s, 1 H), 2.51 (t, *J* = 5.96 Hz, 2 H), 2.47 (m, 4 H), 1.97–2.04 (m, 2 H), 1.55–1.62 (m, 2 H), 1.41–1.50 (m, 2 H), 0.95 (t, *J* = 7.35 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3, 141.3, 139.6, 107.7, 78.7, 60.2, 37.9, 31.6, 30.3, 22.2, 22.0, 19.7, 13.5.

3-(Cyclopropylethynyl)-2-(hydroxymethyl)cyclohex-2-en-1-one (3l)

Yellow gel; yield: 225 mg (79%; 1.5 mmol scale); R_f = 0.32 (20% EtOAc–hexane).

IR (film): 3400, 3013, 2945, 2875, 2205, 1649, 1595, 1371, 1219, 1188, 1110, 1011, 942 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (s, 2 H), 3.00 (br s, 1 H), 2.38–2.44 (m, 4 H), 1.91–1.97 (m, 2 H), 1.41–1.47 (m, 1 H), 0.89–0.94 (m, 2 H), 0.76–0.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 141.4, 139.3, 111.2, 74.1, 59.9, 37.8, 31.5, 22.2, 9.6, 0.8.

3-Aryl-1,5,6,7-tetrahydro-8*H*-isochromen-8-ones 5; General Procedure

$Pd(OAc)_2$ (0.02 mmol, 0.1 equiv) was added to a stirred solution of enone **3** (0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at r.t. under an inert atmosphere. When the starting material had been consumed (TLC), most of the volatiles were evaporated in a rotary evaporator under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc–hexane).

3-(4-Methoxyphenyl)-1,5,6,7-tetrahydro-8*H*-isochromen-8-one (5a)

Yellow oil; yield: 43 mg (84%; 0.2 mmol scale); R_f = 0.65 (30% EtOAc–hexane).

IR (film): 3445, 2100, 1642, 1254, 1176, 835 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.70 (m, 2 H), 6.92–6.95 (m, 2 H), 5.88 (s, 1 H), 5.05 (s, 2 H), 3.87 (s, 3 H), 2.48 (t, *J* = 6.08 Hz, 2 H), 2.44–2.47 (m, 2 H), 2.04–2.09 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.3, 161.6, 160.6, 152.6, 127.9, 125.3, 116.2, 113.9, 99.4, 64.2, 55.4, 37.5, 28.4, 22.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}O_3$: 257.1172; found: 257.1182.

6,6-Dimethyl-3-phenyl-1,5,6,7-tetrahydro-8*H*-isochromen-8-one (5b)

Yellow oil; yield: 42 mg (82%; 0.2 mmol scale); R_f = 0.5 (15% EtOAc–hexane).

IR (film): 3314, 3054, 3023, 2959, 2874, 1661, 1617, 1406, 1049, 1022, 809, 753, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (m, 2 H), 7.34–7.38 (m, 2 H), 7.22 (t, *J* = 7.40 Hz, 1 H), 5.67 (m, 1 H), 5.25 (m, 2 H), 2.40 (t, *J* = 2.25 Hz, 2 H), 2.39 (s, 2 H), 1.62 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.6, 159.2, 151.6, 135.5, 135.3, 128.5, 128.4, 126.7, 102.7, 74.7, 52.0, 35.5, 35.1, 28.5.

HRMS (ESI): *m/z* [M – H]$^+$ calculated for $C_{17}H_{17}O_2$: 253.1223; found: 253.1213.

3-(4-Methoxyphenyl)-6,6-dimethyl-1,5,6,7-tetrahydro-8*H*-isochromen-8-one (5c)

Yellow oil; yield: 45 mg (79%; 0.2 mmol scale); R_f = 0.70 (20% EtOAc–hexane).

IR (film): 2930, 1664, 1251, 1177, 1033, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.72 Hz, 2 H), 6.90 (d, *J* = 8.80 Hz, 2 H), 5.63 (s, 1 H), 5.23 (m, 2 H), 3.84 (s, 3 H), 2.39 (s, 2 H), 2.38 (s, 2 H), 1.15 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 158.4, 157.6, 151.7, 134.6, 129.8, 128.1, 114.0, 112.6, 74.5, 55.3, 51.9, 35.4, 35.1, 28.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{21}O_3$: 285.1485; found: 285.1475.

6,6-Dimethyl-3-[4-(trifluoromethyl)phenyl]-1,5,6,7-tetrahydro-8*H*-isochromen-8-one (5d)

Yellow oil; yield: 41 mg (63%; 0.2 mmol scale); R_f = 0.72 (20% EtOAc–hexane).

IR (film): 2945, 1664, 1328, 1115, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.23 Hz, 2 H), 7.58 (d, *J* = 8.36 Hz, 2 H), 5.67 (s, 1 H), 5.28 (m, 2 H), 2.43 (t, *J* = 2.29 Hz, 2 H), 2.42 (s, 2 H), 1.18 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 160.9, 151.0, 138.8 (d, *J* = 1.38 Hz), 136.7, 128.3, 125.3 (q, *J* = 3.83 Hz, CF_3), 101.0, 75.1, 52.0, 35.5, 35.1, 28.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}F_3O_2$: 323.1253; found: 323.1260.

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Supporting Information

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