Research Article

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Wolff rearrangement of β-alkynyl-α-diazo-β-ketoesters: light-induced acetylene–allene isomerization and its use for activation of enediynes

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Irradiation of β-phenylethynyl-α-diazo-β-ketoester with 300 or 350 nm light results in efficient and regioselective Wolff rearrangement producing only the product of alkynyl group migration. Addition of alcohols to the resulting α-oxoketene yields α-phenylethynyl-β-diester, which undergoes rapid ($\tau < 1$ min) tautomerization to 1,1-dicarbalkoxyallene. The latter then adds second molecule of alcohol in Michael fashion to form the final product, 2-(1-alkoxy-2-phenylvinyl)malonic ester. α-Phenylethynyl-β-ketoacid produced from the ketene in aqueous solutions does not isomerize to an allene but rather undergoes decarboxylation to give β,γ-acetylenic ester. Introduction of *o*-(3-hydroxy-1-propynyl) fragment in the structure of the parent α-diazo-β-ketoester allowed us to achieve two goals simultaneously: ring closure by intramolecular nucleophilic attack of propargyl alcohol on photo-generated ketene and the subsequent acetylene–allene rearrangement. The resulting enyne–allene undergoes spontaneous Myers–Saito cycloaromatization generating 1,4-biradical. In alcohol solutions, however, ketene reaction with solvent outcompetes the intramolecular process. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: acetylene–allene rearrangement; diazo compounds; Myers–Saito cyclization; photochemistry; Wolff rearrangement

INTRODUCTION

The extreme cytotoxicity of natural enediyne antibiotics[1] is attributed to the ability of the (*Z*)-3-hexene-1,5-diyne (enediyne)[2] and (*Z*)-1,2,4-heptatrien-6-yne (enyne–allene)[3–5] fragments to cyclize, producing DNA-damaging aromatic biradicals.[1,6–9] From a mechanistic point of view, enediyne cycloaromatization, known as the Bergman cyclization, permits access to the unique family of σ,σ-1,4-biradicals, *p*-benzynes. A similar cyclization of (*Z*)-hexa-1,2,4-heptatrien-6-ynes yields σ,π-1,4-biradicals (Myers–Saito cyclization).[3–5] Although natural enediynes are very powerful dDNA-cleaving machines, the lack of anti-tumor selectivity results in a very high general toxicity, which hampers clinical applications of natural enediyne antibiotics.[10–19] Photo-triggering of the cycloaromatization reaction opens the possibility for the selective treatment of cancerous tissues in a fashion similar to photodynamic therapy.[20–22] Our group has developed several strategies for the photochemical activation of enediynes.[23] We have designed enediyne precursors, which are stable in the dark but are efficiently converted into reactive form upon irradiation with UV–Vis[22–26] or near-infrared (NIR)[27] light. However, the rate of the Bergman cyclization of even highly strained nine-membered ring enediynes ($\tau_{25°C} \sim 2$ h)[22] is not fast enough to allow for the spatial resolution of *p*-benzyne generation in biological systems. In order to enhance the rate of the formation of cytotoxic 1,4-diradicals, we turned our attention to enyne–allenes. Acyclic enyne–allenes usually undergo spontaneous cyclization under ambient conditions.[28] Cyclic enyne–allenes are virtually unknown, apparently because of their ability to undergo very rapid cycloaromatization.[25,29,30] We have developed two methods for the photochemical activation of 10-membered ring enyne–allenes: unmasking of a triple bond in precursor **1**[31] and Wolff rearrangement of acetylenic α-diazo-β-diketone **5**[25] (Scheme 1).

Enyne–allene **2** undergoes facile spontaneous cyclization under ambient conditions but produces diradical intermediate only in non-polar solvents. In water or alcohols, it yields O–H insertion product **4**, apparently via a polar intermediate (e.g., **3**).[31] Cycloaromatization of β-ketoester **6a** proceeds via rate-limiting tautomerization to enyne–allene **7**, which rapidly cyclizes ($\tau_{25°C} < 0.1$ s) to produce 1,4-biradical **8** even in alcohol or aqueous solutions.[25] The complete suppression of O–H insertion in this case is apparently explained by the destabilization of the polar intermediate (analogous to **3**) by electron-withdrawing carbonyl groups. Unfortunately, the enyne–allene producing β-ketoester **6a** is only a minor isomer formed in the Wolff rearrangement of α-diazo-β-diketone **5**. The major β-ketoester **6b** undergoes relatively slow Bergman cyclization.[25]

We hypothesized that with proper selection of substituents at the α-diazo-β-dicarbonyl fragment, we can achieve selective formation of the tautomerizable regioisomer of acetylenic β-oxoester. Because the migratory aptitude of oxygen in the

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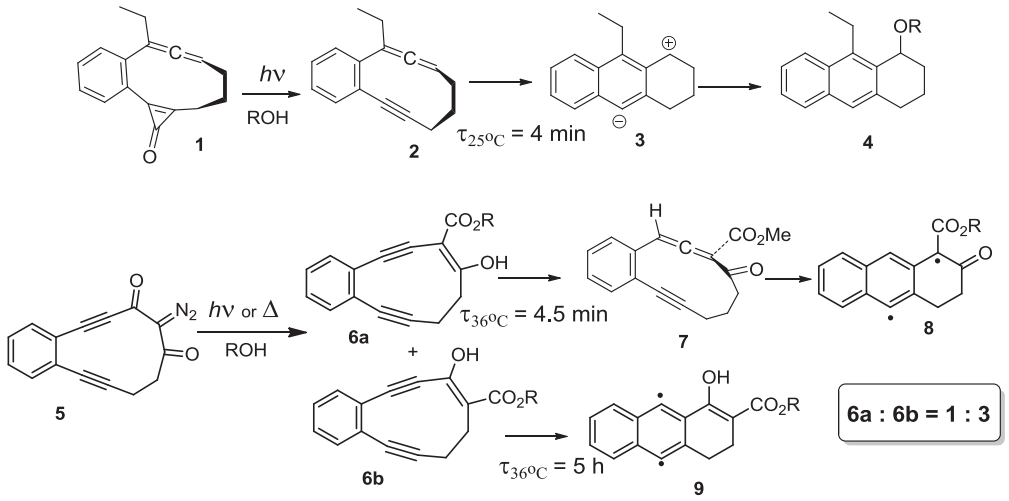


Scheme 1. Photochemical generation of cyclic eneyne-allenes

photochemical Wolff rearrangment is much lower than that of the carbon atom,[32,33] irradiation of acetylenic α-diazo-β-ketoester **10** is expected to induce exclusive or predominant migration of alkynyl substituent to give ketene **11**. It would rapidly add alcohol-producing β-diester **12**, which, in turn, should isomerize into allene **13** (Scheme 2).

We also planned to explore whether nucleophilic addition of alcohol to ketene **11** can be achieved intramolecularly for the simultaneous cyclization of stable acyclic enediyne into a 10-membered ring and the induction of acetylene–allene isomerization.

RESULTS AND DISCUSSION

Synthesis of α-diazo-β-ketoester 10

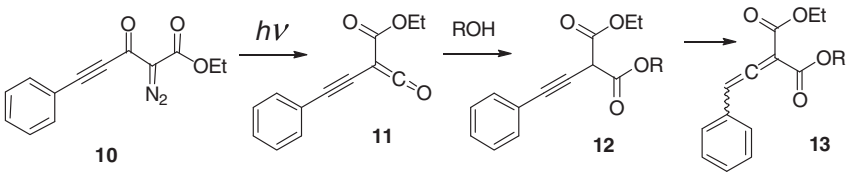
Phenylpropynal was prepared by the carbonylation of lithium salt of phenylacetylene with dimethylformamide. Condensation of the aldehyde with ethyl diazoacetate catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced α-diazo-β-hydroxyester **14**. The use of sodium hydride as a base for this aldol-type reaction, as recommended in the literature,[34] results in significantly lower yields of the product. 2-Iodoxybenzoic acid (IBX) oxidation[35,36] of hydroxy group in **14** gave the target α-diazo-β-ketoester **10** in excellent yield. It is important to note that pyridinium chlorochromate (PCC) oxidation of **14** led to rapid decomposition of the diazo compound (Scheme 3).

Synthesis of enediyne 20

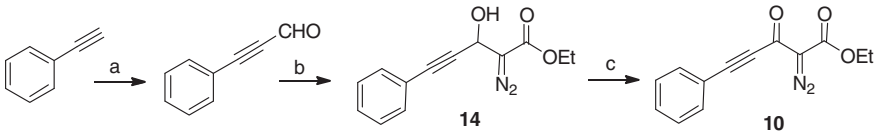
Sonogashira coupling of *o*-diiodobenzene with two-fold excess of propargyl alcohol produced quantitative yield of diol **15**. Mono-acylation of the latter, followed by a PCC oxidation, gave aldehyde **17**. DBU-catalyzed coupling of **17** with ethyl diazoacetate resulted in the formation of α-diazo-β-hydroxyester **18**. IBX oxidation of the hydroxy group in **18**, followed by saponification of an acetate protection, produced the target acyclic enediyne **20** (Scheme 4).

Photochemical reactivity of α-diazo-β-ketoester 10

The UV spectrum of **10** shows an intense absorbance band at 303 nm (log $\varepsilon = 4.3$), which can be assigned to the diazodicarbonyl fragment (solid line in Fig. 1). Irradiation of the ~0.1-mM methanol solution of α-diazo-β-ketoester **10** with 300-nm light for 1 min resulted in the bleaching of this band (dashed line in Fig. 1).



Scheme 2. Photo-Wolff reaction and subsequent isomerization of α-diazo-β-ketoester **10**.



Scheme 3. Synthesis of α-diazo-β-ketoester **10**. Reagents and conditions: (a) (i) *n*-BuLi, DMF, THF −78 °C; (ii) KH_2PO_4 0 °C; (b) N_2CHCO_2Et, DBU, CH_3CN; (c) IBX, DMSO

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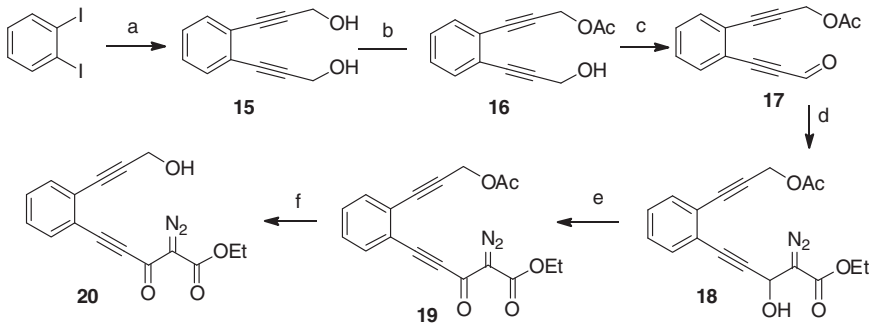


Scheme 4. Synthesis of enediyne **20**. Reagents and conditions: (a) propargyl alcohol, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, THF; (b) AcCl, DMAP, CH_2Cl_2; (c) PCC, CH_2Cl_2; (d) N_2CHCO_2Et, DBU, CH_3CN; (e) IBX, DMSO; (f) K_2CO_3, MeOH

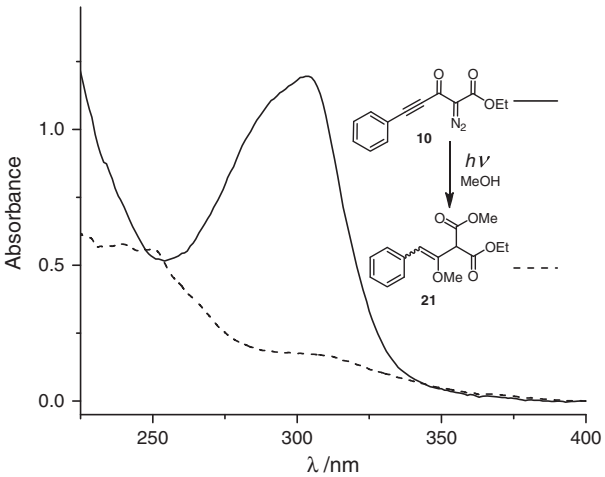


Figure 1. UV spectra of ~6×10^{-5} M solutions of the α-diazo-β-ketoester **10** (solid line) and the photoproduct **21a** (dashed line) in methanol

High-performance liquid chromatography (HPLC) analysis of the photolysate confirmed complete conversion of the diazocompound **10** into a single product. The same result was obtained in the photolysis using 350-nm lamps; only the full conversion required longer time (~20 min). The mass spectrum of the photolysis product, however, did not correspond to the expected **13a** or **12a** (Scheme 2, R = Me) but indicated that loss of nitrogen was accompanied by the addition of two solvent molecules (MW = 278). Preparative photolysis of **10** allowed us to isolate 1-ethyl 3-methyl 2-(1-methoxy-2-phenylvinyl)malonate (**21a**) in 82% yield. High stability of starting α-diazo-β-ketoester **10** in methanol solutions in the dark and the rearranged skeleton of the adduct **21a** indicate that it is formed upon the Wolff rearrangement of **10**. Formation of **21a** is a facile process, which is complete in less than a minute after photolysis. There are no changes observed in the UV spectrum recorded right after the photolysis (Fig. 1), and HPLC analysis of the photolysate shows no changes in the composition of the reaction mixture with time.

α-Oxoketene **11** formed upon loss of nitrogen and migration of alkynyl group is expected to react very rapidly with the solvent (10^4–10^5 s^{-1})[37–39] producing enol **22**. Such α-oxoenol compounds usually ketonize to β-dicarbonyl tautomer at somewhat slower pace (10^0–10^2 s^{-1}).[37–39] Diester **12a** undergoes tautomerization to allene **13a**, which then apparently reacts with methanol to yield the final product **21a** (Scheme 5).

The formation of 2-phenylethynylmalonate **12a** can be bypassed altogether if proton transfer to γ-(acetylenic) carbon is faster than protonation of β-(vinyl) position in **22**a.

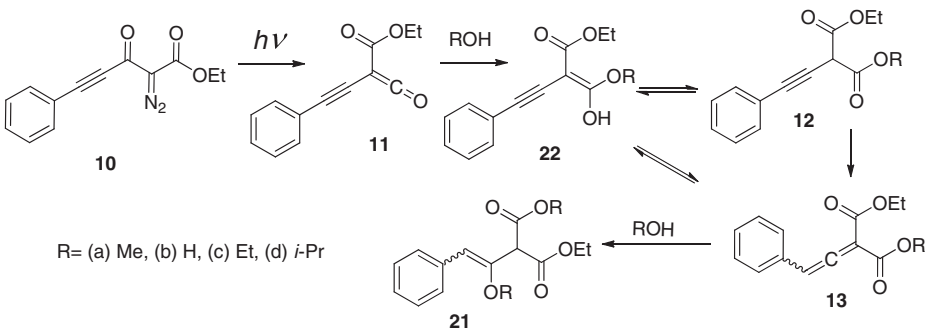
The second molecule of the solvent can, in principle, add across the triple bond of **12a** to give **21a** directly. We believe that this is highly unlikely. First of all, the inductive effect of two carbonyl groups in propargylic position is not strong enough to make the triple bond susceptible to nucleophilic attack. On the other hand, electrophilic addition of methanol across the triple bond should produce a different regioisomer. Secondly, analogous β-oxoacid **12b** and ethyl 4-phenyl-3-butynoate **23** do not react with hydroxylic solvents. The latter even withstands aqueous acid.[40] We also do not think that addition of alcohol occurs at the enol **22a** stage because electronically analogous enol **6a** does not add solvent in aqueous, methanol, or 2-propanol solutions.[25] Similar products are formed when photolyses of **10** is conducted in ethanol (**21c**) and 2-propanol (**21d**, Scheme 5).

Irradiation of diazo compound **10** in aqueous acetonitrile unexpectedly produced ethyl 4-phenyl-3-butynoate **23** as a major product (Scheme 6). The same ester was obtained in the presence of 0.1 M of benzyl azide and in aqueous dimethyl sulfoxide (DMSO). No traces of allene **13b** or allene-derived products were detected in the photolysates. Unisomerized ester **23** is apparently formed by the decarboxylation of β-oxoacid **12b** (Scheme 6). The thermal or photochemical decarboxylation of **12b** is a facile process: HPLC analysis of the reaction mixture right after the photolysis shows only the presence of ester **23** in addition to two minor products, which are stable under ambient conditions.

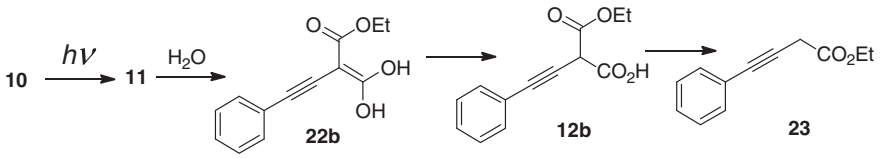
Exclusive formation of **12b** in the presence of water apparently suggests that α-alkynyl-β-dicarbonyl compounds **12** are kinetic products in tautomerization of **22**. α-Alkynyl-β-oxoester **12a** isomerizes into a thermodynamically more stable **13a**, whereas the decarboxylation of **12b** prevents its isomerization.

Photolyses of enediyne 20

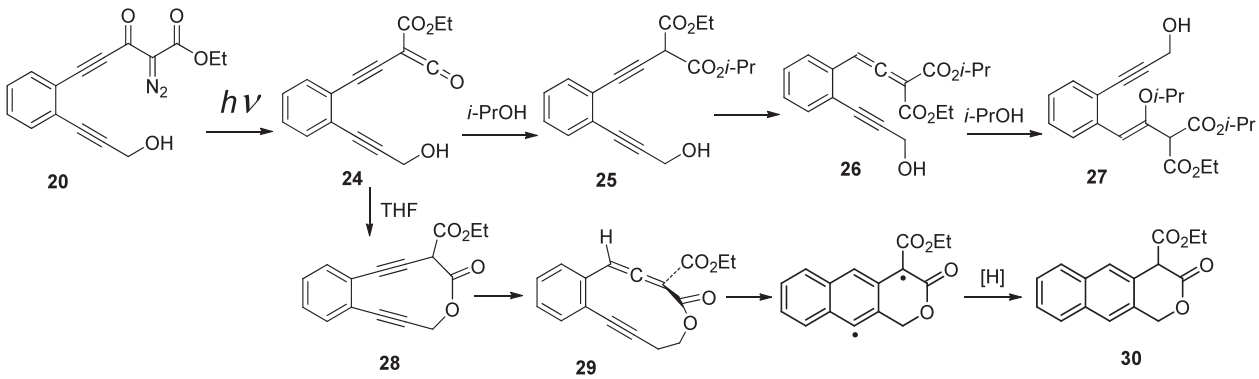
Efficient isomerization of α-alkynyl-β-oxoesters **12** into allenes **13** permits the use of photo-Wolff reaction for the generation of enyne–allenes. The photochemically triggered acetylene–allene isomerization can be coupled with intramolecular addition of alcohol to ketene moiety in the intermediate **24** to provide a strategy for simultaneous ring closure and tautomerization producing very reactive cyclic enyne–allenes, such as **29** (Scheme 7).



Scheme 5. Photolysis of α-diazo-β-ketoester **10** in alcohols



Scheme 6. Photolysis of α-diazo-β-ketoester **10** in aqueous solutions



Scheme 7. Photolysis of enediyne **20** in 2-propanol and aqueous solutions

The UV spectrum and photochemical reactivity of enediyne **20** are very similar to that of **10**. One minute of 300-nm irradiation of ~0.1-mM 2-propanol solution of diazo compound **20** results in complete consumption of the starting material. Only a single product **27** can be detected in the reaction mixture by chromatographic analysis. This compound is apparently formed by the sequential addition of two molecules of 2-propanol to ketene **24** (Scheme 7). This observation indicates that intramolecular addition of propargylic alcohol to ketene moiety is slower than the nucleophilic attack of the solvent molecules. Results of the photolyses in non-hydroxylic solvents support this conclusion. After 1 min exposure of a tetrahydrofuran (THF or THF/hexane) solution of **20** to 300-nm light, analysis of the reaction mixture confirms the formation of naphthalene derivative **30** as the major product (~65–70%). Lactone **30** is an apparent product of the Myers–Saito cyclization of the intermediate enyne–allene **29**.

CONCLUSIONS

We have demonstrated that photochemical reaction of β-alkynyl-α-diazo-β-ketoesters is regioselective, producing only the product of the migration of alkynyl group in the Wolff rearrangement. Addition of alcohols to the resulting α-oxoketenes gives α-alkynyl-β-diesters, which undergo rapid isomerization to 1,1-dicarbalkoxyallene. Intramolecular version of this reaction allowed us to achieve two goals in one step: cyclization of acyclic enediyne, which is accomplished by the reaction between hydroxy and ketene groups, and isomerization of relatively stable enediyne into very reactive enyne–allene. Although this strategy works well in non-polar solvents, in hydroxylic solvents, the nucleophilic addition of solvent molecules outcompetes the intramolecular ketene reaction. We are currently exploring two approaches to the solution of this problem: replacement of the hydroxy group with more nucleophilic thiol or/and using steric compression to enhance the rate of intramolecular reaction.

EXPERIMENTAL SECTION

General methods

All organic solvents were dried and freshly distilled before use. All oxygen-sensitive and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for moisture-sensitive reactions were distilled prior to usage. Flash chromatography was performed using 40–63-μm silica gel. All NMR spectra were recorded in $CDCl_3$

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and referenced to tetramethylsilane unless otherwise noted. Photolyses of diazo compounds **10** and **20** were conducted at ambient temperatures using mini-Rayonet photochemical reactor equipped with eight fluorescent UV lamps (4 W, 300 or 350 nm) in quartz cuvettes (for HPLC/gas chromatography–mass spectrometry (GC/MS) analyses) or tubular flow system (preparative irradiation). Reaction mixtures after photolysis were analyzed by HPLC and GC/MS using pure substrates as references. In the case of preparative photolyses, reaction mixtures were separated on a silica gel; pure compounds were characterized by NMR, GC/MS, and high-resolution mass spectrometry (HRMS) analyses.

Materials

All commercially available materials were purchased from VWR or Sigma-Aldrich and used as received unless otherwise stated.

*Ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (**14**)*

n-Butyllithium (1.13 mL, 1.8 mmol, 1.6 M in hexane) was added to a stirred solution of phenylacetylene (186 mg, 1.8 mmol) in 5 mL of THF at −78 °C under nitrogen atmosphere, followed by a dropwise addition of dimethylformamide (263 mg, 3.6 mmol, 0.28 mL) over 10 min. The reaction mixture was warmed to room temperature (r.t.), stirred for 30 min at the temperature, and then poured into a mixture of 5 mL of diethyl ether and 10 mL of 10% aqueous KH_2PO_4 pre-cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 min, warmed up to r.t., organic layers were separated, and aqueous phase was washed with ether. The combined organic layers were dried over magnesium sulfate, and solvents were evaporated under reduced pressure to give 234 mg of crude 3-phenylpropiolaldehyde, which was used in the next reaction without further purification because of its instability.

1,8-Diazabicyclo[5.4.0]undec-7-ene (54 µL, 0.36 mmol) and a solution of 3-phenylpropioaldehyde (234 g, 1.8 mmol) in anhydrous CH_3CN (3 mL) were added to a solution of ethyl diazoacetate (0.23 mL, 2.16 mmol) in anhydrous CH_3CN (7 mL). The reaction mixture was stirred overnight at r.t. and then concentrated in vacuum. The residue was purified chromatography (10% to 30% of ethyl acetate in hexanes) to give 200 mg (46% over two steps) of ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (**14**) as yellow oil. ^{1}H NMR: 7.46–7.44 (m, 2H), 7.33–7.31 (m, 3H), 5.76 (s, 1H), 4.32–4.26 (q, $J = 7$ Hz, 2H), 1.68 (br s, 1H), 1.33–1.30 (t, $J = 7$ Hz, 3H). IR spectrum: 3412, 2981, 2098, 1668, 1490. DIP/MS: 216 (M^+–N_2, 18), 200 (6), 188 (9), 171 (16), 151 (36), 137 (15), 129 (100), 114 (32), 102 (34).

*Ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (**10**)*

A solution of **14** (200 mg, 0.82 mmol) in DMSO (3 mL) was added to a solution of IBX (344 mg, 1.23 mmol) in DMSO (5 mL), and the mixture was stirred for 3 h at r.t. The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (15% to 20% of ethyl acetate in hexanes) yielding 163 mg (82%) of pure ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (**10**) as yellow crystals. ^{1}H NMR: 7.65–7.64 (d, $J = 7.2$ Hz, 2H), 7.49–7.45 (m, 1H), 7.42–7.38 (t, $J = 7.2$ Hz, 2H), 4.40–4.34 (q, $J = 7$ Hz, 2H), 1.38–1.34 (t, $J = 7$ Hz, 3H). ^{13}C NMR: 180.7, 160.02, 133.07, 130.96, 128.64, 128.35, 120.00, 85.52, 76.72, 61.80, 14.41. DIP/MS: 242 (M+, 25), 214 (3), 142 (25), 129 (100), 114 (37), 101 (13). High res. EI-HRMS: Found 242.0693, Calc. 242.0691.

*o-Bis(3-hydroxy-1-propynyl)benzene (**15**)*

Bis(triphenylphosphine)palladium dichloride (1 g, 1.4 mmol) was added to a stirred solution of *o*-diiodobenzene (5 g, 15.2 mmol) in dry degassed THF (100 mL) under inert atmosphere. The solution was degassed with a flow of argon, and powdered copper(I) iodide (6 mol%, 17.3 mg, 0.91 mmol) was added to the mixture. After 5 min of stirring, propargyl alcohol (3.4 g, 60.6 mmol, 3.5 mL) was added to the mixture, followed by diethyl amine (10 mL). The reaction vessel was purged with argon, sealed, and left with overnight stirring at r.t. Another two equivalents of propargyl alcohol and 5 mL of diethyl amine were added to the reaction mixture. After two more days of stirring, the reaction mixture was filtered through a 3-cm layer of silica gel (5% ethyl acetate in hexanes); fractions containing the desired product were combined, and solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (30% to 50% of ethyl acetate in hexanes to 30% of ethyl acetate in dichloromethane) yielding 2.82 g (quant.) of **15**[41] as yellowish oil. ^{1}H NMR: 7.40–7.38 (dd, $J_1 = 3.4$ Hz, $J_2 = 5.6$ Hz, 2H), 7.25–7.23 (dd, $J_1 = 3.4$ Hz, $J_2 = 5.6$ Hz, 2H), 4.54 (s, 4H), 4.05 (br s, 2H). ^{13}C NMR: 131.59, 128.28, 125.59, 92.01, 84.43, 51.65. DIP/MS: 186 (M+, 9), 168 (10), 139 (100), 128 (34), 115 (24), 102 (6), 89 (11).

*1-(3-Acetoxypropynyl)-2-(3-hydroxypropynyl)benzene (**16**)*

Acetyl chloride (1.07 µL, 15.1 mmol) was added to a solution of **15** (2.8 g, 15.1 mmol) in dichloromethane (100 mL), followed by 4-dimethylaminopyridine (310 mg). The reaction mixture was left with stirring at r.t., the solvent was evaporated, and the residue purified by column chromatography (10% to 30% of ethyl acetate in hexanes) to give 1.57 g (46%) of **16** as brownish oil and 1.28 g of the diacetate by-product. ^{1}H NMR: 7.45–7.41 (m, 2H), 7.31–7.25 (m, 2H), 4.93 (s, 2H), 4.54 (s, 2H), 2.96 (br s, 1H), 2.15 (s, 3H). ^{13}C NMR: 171.25, 132.22, 131.81, 128.84, 128.28, 126.19, 124.93, 92.32, 87.07, 85.01, 83.95, 53.29, 51.77, 21.15. MS: 228 (M+, 2), 210 (6), 195 (8), 168 (36), 139 (100), 127 (10), 115 (21), 91 (40).

*Ethyl 5-(2-(3-acetoxyprop-1-ynyl)phenyl)-2-diazo-3-hydoxypent-4-ynoate (**18**)*

Pyridinium chlorochromate (1.6 g, 7.2 mmol) was added to a stirred suspension of celite in a solution of **16** (1.1 g, 4.8 mmol) in dichloromethane (60 mL) at r.t. Three hours later, the reaction mixture was filtered through a 3-cm layer of silica gel with 1:1 ethyl acetate/hexanes as eluant. The solvents were evaporated under reduced pressure producing 1.08 g of crude 3-(2-(3-acetoxyprop-1-ynyl)phenylpropiolaldehyde) (**17**), which was not further purified but immediately introduced into the next reaction.

A solution of DBU (143 µL, 0.96 mmol) and **17** (1.08 g, 4.8 mmol) in anhydrous CH_3CN (10 mL) were added to a solution of ethyl diazoacetate (0.608 mL, 5.76 mmol) in anhydrous CH_3CN (40 mL). The reaction mixture was stirred overnight at r.t. and then concentrated in vacuum. The residue was purified by column chromatography (20% to 40% of ethyl acetate in hexanes) producing 0.78 g (46% over two steps) of **18** as yellowish oil.

^{1}H NMR: 7.47–7.43 (m, 2H), 7.32–7.27 (m, 2H), 5.76–5.74 (d, J = 6.4 Hz, 1H), 4.97–4.89 (m, 2H), 4.32–4.26 (m, 2H), 3.91 (br s, 1H), 2.14 (s, 3H), 1.33–1.30 (t, J = 7 Hz, 3H). ^{13}C NMR: 171.30, 165.41, 132.39, 132.20, 128.85, 125.14, 125.08, 88.72, 87.44, 85.18, 84.79, 61.55, 58.85, 53.34, 21.05, 14.68. DIP/MS: 312 (M^+-N_2, 13), 270 (22), 241 (35), 224 (32), 197 (16), 181 (45), 167 (23), 155 (37), 139 (47), 127 (58), 115 (37), 86 (40), 61 (69), 45 (100). IR (neat, cm^{-1}): 3447, 2984, 2359, 2342, 2099, 1744, 1689, 1558, 1481, 1442.

*Ethyl 5-(2-(3-acetoxyprop-1-ynyl)phenyl)-2-diazo-3-oxopent-4-ynoate (**19**)*

A solution of **18** (0.78 g, 2.3 mmol) in DMSO (3 mL) was added to a solution of IBX (966 mg, 3.45 mmol) in DMSO (7 mL) and stirred for 5 h. The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (2 × 20 mL). Combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (20% of ethyl acetate in hexanes) to yield 718 mg (93%) of **19** as yellowish oil. ^{1}H NMR: 7.66–7.64 (d, J = 7.8, 1H), 7.53–7.51 (d, J = 7.8, 1H), 7.43–7.34 (m, 2H), 4.99 (s, 2H), 4.38–4.33 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.37–1.33 (t, J = 7.2 Hz, 2H). ^{13}C NMR: 180.67, 170.50, 160.11, 133.88, 132.74, 130.70, 128.83, 126.25, 122.94, 88.80, 88.52, 84.11, 62.02, 53.08, 20.97, 14.56. DIP/MS: 338 (M+, 5), 281 (53), 240 (34), 222 (18), 211 (30), 194 (20), 183 (46), 150 (100), 139 (91), 127 (48), 115 (15). IR (neat, cm^{-1}):2984, 2207, 2133, 1724, 1669, 1600, 1481, 1442.

*Ethyl 2-diazo-5-(2-(3-hydroxyprop-1-ynyl)phenyl)-3-oxopent-4-ynoate (**20**)*

Potassium carbonate (15.2 mg, 0.11 mmol) was added to a solution of **19** (37.7 mg, 0.11 mmol), in aqueous methanol (5 mL), stirred for 5 min, and poured into a mixture of 10% of aqueous KH_2PO_4 and diethyl ether. After 15 min of vigorous stirring, layers were separated, and the aqueous layer was extracted with ether. Combined organic layers were dried over sodium sulfate, solvents were removed under reduced pressure, and the residue was purified by column chromatography (10% to 30% of ethyl acetate in hexanes) to give 17 mg (76%) of pure **20** and 12 mg (31%) of starting acetate **19**. ^{1}H NMR: 7.67 (d, J = 7.2 Hz, 1H), 7.48–7.40 (m, 2H), 7.36–7.32 (m, 1H), 4.54 (s, 2H), 4.38–4.33 (q, J = 7.2 Hz, 2H), 1.76 (br s, 1H), 1.39–1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR: 160.64, 154.92, 133.04, 131.95, 130.28, 128.36, 127.92, 122.76, 93.97, 89.09, 85.82, 83.51, 62.29, 53.17, 14.46. DIP/MS: 296 (M+, 1), 268 (1), 239 (12), 211 (16), 196 (10), 183 (23), 168 (21), 150 (30), 139 (100), 127 (67), 115 (20).

Preparative photolyses of ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (10)

In methanol: A solution of diazo compound **10** (20 mg, 0.082 mmol) in 200 mL of methanol was irradiated with two 300-nm fluorescent lamps until the complete bleaching of the diazo compound **10**, absorbance at 303 nm (~18 min). The solvent was removed under reduced pressure, and the residue was separated by column chromatography (10% to 20% of acetone in hexanes) to give 18 mg (82%) of 1-ethyl 3-methyl 2-(1-methoxy-2-phenylvinyl)malonate (**21a**) as colorless oil. ^{1}H NMR: 7.34–7.30 (t, J = 7.6 Hz, 2H), 7.24–7.21 (m, 1H), 7.16–7.14 (d, J = 7.6 Hz, 1H), 5.93 (s, 1H), 4.62 (s, 1H), 4.26–4.21 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 1.29–1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR: 167.48, 166.92, 151.00, 135.78, 129.12, 128.87, 128.53, 127.53, 126.48, 104.30, 61.82, 55.64, 53.86, 52.79, 14.02. MS: 278 (M+, 53), 219 (7), 205 (9), 174 (37), 159 (12), 145 (100), 131 (39), 115 (34), 103 (45). ESI-HRMS: Found 279.1233, Calc.(M + H$^+$) 279.1227.

In CH_3CN: A solution of diazo compound **10** (20 mg, 0.083 mmol) in 200 mL of aqueous acetonitrile was irradiated as described earlier. The solvent was evaporated under reduced pressure, and the residue was separated by column chromatography (10% to 30% of ethyl acetate in hexanes) affording 9.4 mg (61%) of ethyl 4-phenylbut-3-ynoate (**23**).[42] ^{1}H NMR: 7.46–7.43 (m, 2H), 7.31–7.29 (m, 3H), 4.25–4.21 (q, J = 7.2 Hz, 2H), 3.51 (s, 2H), 1.33–1.29 (t, J = 7.2 Hz, 3H). MS: 188 (M+, 21), 160 (7), 144 (5), 115 (100), 89 (12). EI-HRMS: Found 188.0833, Calc. 188.0837.

Photolysis of ethyl 2-diazo-5-(2-(3-hydroxyprop-1-yn-1-yl) phenyl)-3-oxopent-4-ynoate (20)

Approximately 0.1-mM solution of **20** was irradiated for 1 min using 300-nm lamps. UV spectrum of photolysate and HPLC analysis showed the complete consumption of the starting material. The composition of the reaction mixture was analyzed using HPLC and GC/MS.

*1-Ethyl 3-isopropyl 2-(2-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-1-isopropoxyvinyl) malonate (**27**)*

MS: 388 (M+, 16), 346 (13), 328 (25), 286 (7), 279 (24), 241 (15), 223 (26), 197 (20), 169 (45), 149 (89), 141 (39), 115 (73), 70 (67), 57 (58), 45 (100).

*Ethyl 3-oxo-3,4-dihydro-1 H-benzo[g]isochromene-4-carboxylate (**30**)*

MS: 270 (M+, 7), 243 (20), 229 (12), 213 (11), 197 (41), 169 (44), 157 (32), 141 (36), 128 (37), 115 (10), 71 (100).

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