Published in final edited form as:

J Org Chem. 2016 May 6; 81(9): 3744–3751. doi:10.1021/acs.joc.6b00394.

Discovery and Development of a Three-Component Oxidopyrylium [5+2] Cycloaddition

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Abstract

α -Hydroxy- γ -pyrone-based oxidopyrylium cycloaddition reactions are useful methods for accessing highly diverse range of oxabicyclo[3.2.1]octane products. Intermolecular variants of the reaction require the formation of a methyl triflate-based pre-ylide salt that upon treatment to base in the presence of alkenes or alkynes leads to α -methoxyenone-containing bicyclic product. Herein, we describe our discovery that the use of ethanol-stabilized chloroform as solvent leads to the generation of α -ethoxyenone-containing bicyclic byproducts. This 3-component process was further optimized by gently heating a mixture of a purified version of the oxidopyrylium dimer in the presence of the alcohol prior to addition of the dipolarophile. Using this convenient procedure, several new oxidopyrylium cycloaddition products can be generated in moderate yields. We also highlight the method in a tandem ring-opening/debenzylation method for the generation of α -hydroxytropolones.

Graphical Abstract

Introduction

Oxidopyrylium cycloaddition reactions are effective ways to generate bicyclic compounds,¹ and have found widespread use in chemical synthesis.² One particularly attractive method

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Supporting Information. Supporting information including ¹H and ¹³C NMR Spectra. These material are available free of charge via the Internet at <http://pubs.acs.org>.

leverages the facile tautomerization or rearrangement of α -hydrox- γ -pyrones to oxidopyrylium ylides that are capable of undergoing cycloaddition reactions (Scheme 1).³ While this is often effective for intramolecular reactions, the reaction is not efficient for intermolecular variants, likely in part due to the short lifetime of the active ylide. To overcome this limitation, a modified version of the reaction has been developed by Wender and coworkers that employs a methyl triflate-derived pre-ylide salt.⁴ While in principle it should be possible to employ alternative alkyl triflate-derived salts in the process, attempts by our lab at making other triflate-derived salts, namely benzyl and trifluoroethyl triflate salts, have been unsuccessful. As a result, all products derived from the Wender modification to date have α -methoxyenones present in the products. The following describes the discovery and optimization of a process that overcomes this limitation through the treatment of various alcohols to oxidopyrylium ylide dimers prior to the oxidopyrylium cycloaddition. The result is a 3-component oxidopyrylium cycloaddition for the generation of new oxabicyclic products.

Results and Discussion

Our work on the 3-component oxidopyrylium cycloaddition began with the observation that some slower oxidopyrylium cycloaddition reactions run using ethanol-stabilized chloroform as solvent produced minor amounts of ethanolincorporated cycloaddition products (ie **3a**, Table 1). For example, at typical stabilizer concentrations of 1%, which corresponded to 0.33 equivalents in our studies, the oxidopyrylium cycloaddition with phenylacetylene produced approximately 15% of **3a** (Table 1, entry 1). Intrigued by the results, we began to study the process and found that higher concentrations of ethanol in the reactions increased yields of **3a** with no diminishment in overall bicycle yields (entries 2,3). Longer reaction times of the oxidopyrylium cycloaddition reaction did not increase formation of **3a**, and resubjecting the bicycle **2a** to the reaction conditions with ethanol did not lead to any noticeable incorporation. On the other hand, when the reaction was run for a period of time prior to addition of alkyne, increases of **3a** were observed (entries 4–10), although higher temperatures and reaction times decreased overall yields. Finally, similar reaction yields were observed between reactions run using microwave irradiation and conventional heating (entry 7 vs 11).

Given these early optimization results, our current mechanistic hypothesis is that the incorporation is taking place through nucleophilic aromatic substitution on the oxidopyrylium ylide. While the oxidopyrylium ylide rapidly forms a dimer,⁵ and no ylide is ever observed in solution, the presumably reversible nature of this transformation, as has been hypothesized in our lab previously,⁶ could allow for this possibility (Scheme 2). Direct exchange with the dimer seems unlikely given the necessity for SN1 substitution on a bridgehead carbon and/or ready exchange of an α -alkoxy position of the enone. On the other hand, a mechanism involving exchange at an intermediate between the dimer and the ylide still remains a reasonable possibility. Mechanistic studies are currently underway.

While yields approaching 50% for **3a** were deemed practical for a 3-component process, a major obstacle faced early on in our work was the significantly lower yields for other substrates (ie Table 2, method A). In order to increase the reaction yields, we leveraged the

reversible dimerization of oxidopyrylium dimer **4**. The purified dimer is readily available and in high yields by adding triethylamine to the oxidopyrylium salt and then performing an aqueous ammonium chloride wash. We hypothesized that eliminating residual base and stoichiometric conjugate acid formed during the deprotonation of the oxidopyrylium triflate salt might allow for longer reaction times without decomposition, and indeed total yields were higher (Table 2, Total Yield) with increases in yields of **3b** approaching 20%. However, lower amounts of **2b** were also observed, suggesting that the incorporation might also be accelerated. Studies aimed at understanding these phenomena are ongoing that may help glean information to further optimize the process. Optimal reaction times were approximately 12 hours, and reaction times beyond that led to comparable yields of **3b**, although lower overall yields due to less **2b**. These times were convenient since they allowed for the first step of the reaction to take place overnight.

Employing alternative alkynes to the benzyl alcohol/oxidopyrylium dimer reaction provided a series of new bicyclic products in 40–65% yield (**3b** – **3f**, Table 3). Electronically rich and poor substituted benzyl alcohol can also be used with comparable yields (**3g** and **3h**), with electronically poor benzyl alcohol derivatives requiring lower incorporation times. In addition, a methylene methyl ether-containing dimer can also be employed without any competitive transesterification (**3i**). Primary alcohols with adjacent sterics (**3j**, **3k**) or base-sensitive functionality (**3l**) can also be employed. On the other hands, steric limitations do apply as illustrated by the secondary alcohol *iso*-propanol requiring longer reaction times and providing lower reaction yields of **3m**. Furthermore, attempts at using the tertiary alcohol *tert*-butanol did not lead to any product formation. Allyl alcohol also provided significantly lower overall yields of **3n**, which we suspect may be due to competing Claisen-rearrangement-type decomposition pathways. In most cases, the cost of alkynes was low, and thus 20 equivalents were used to maximize product yields. However, 1,4-diethynylbenzene represented an alkyne in which cases higher equivalents were prohibitive. In these cases, 10 equivalents of alkyne could be used and provide comparable results (**3o** vs **3f**), and furthermore 80% of the alkyne was recovered, at a net consumption of 2 equivalents. Thus, alkyne equivalents can be lowered and unreacted alkyne should be recoverable in many cases.

Our main interest in the cycloaddition has been in the synthesis of α -hydroxytropolones,⁶ which have been identified as therapeutic leads for a variety of different diseases due to their ability to bind to and inhibit several therapeutically important dinuclear metalloenzymes.⁷ We have been leveraging an oxidopyrylium cycloaddition/ring-opening strategy toward their synthesis and usage in a number of different medicinal chemistry studies such as the development of antivirals against HIV,⁸ Hepatitis B,⁹ and herpes simplex virus,¹⁰ and as inhibitors of the aminoglycoside resistance enzyme ANT(2'')-Ia.¹¹ To date, our method has relied upon a final demethylation using refluxing HBr/AcOH conditions.¹²

With access to the new benzyl-containing bicycles, we have found that sulfonic acid conditions used for ring-opening are capable of promoting direct conversion of several of the new benzyl-containing bicycles to α -hydroxytropolones, negating the need for the demethylative conditions. For example, both methanesulfonic acid and Amberlyst®15 were capable of converting bicycle **3f** directly to **5**,¹³ with the former leading to higher yields with trace

impurities, while the latter led to cleaner reactions although lower yields and longer reaction times (Scheme 3). While the overall reaction mechanism for the process are still unknown, with shorter reaction times benzyloxytropolones are observed along with the hydroxytropolones, suggesting that ring-opening is taking place prior to debenzoylation. Current efforts are underway to understand the advantages and limitations of this method while also identifying new applications.

Conclusion

In summary, we have discovered that α -hydroxy- γ -pyrone-based oxidopyrylium dimers can undergo ex-change in the presence of alcohols to generate new oxidopyrylium species capable of intermolecular cycloaddition chemistry. The net result is a 3 component process for the generation of a broad range of oxabicyclic compounds from oxidopyrylium ylides, alcohols, and alkynes. We anticipate these results having high value in our ongoing work on the synthesis of α -hydroxytropolones.

Experimental

I. General Information

All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of CH_2Cl_2 , which was purified on a solvent purification system prior to reactions.¹⁴ ^1H NMR shifts are measured using the solvent residual peak as the internal standard (CHCl_3 δ 7.26), and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet), coupling constant (Hz), integration. ^{13}C NMR shifts are measured using the solvent residual peak as the internal standard (CDCl_3 δ 77.16), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by electrospray ionization (ESI) technique and time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage® Initiator (External IR Temperature Sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP 10g cartridges, in a solvent system of ethyl acetate in hexane.

II. Synthesis of Oxidopyrylium Dimers

($\pm$)-(1*R*,2*S*,6*S*,7*R*)-6,9-Dimethoxy-4,7-dimethyl-3,11-dioxatricyclo[5.3.1.1^{2,6}]dodeca-4,8-diene-10,12-dione (4**)**—To a solution of 5-hydroxy-4-methoxy-2-methylpyrylium trifluoromethanesulfonate (**1**) (5 g, 17.2 mmol) in CH_2Cl_2 (43 ml) was added triethylamine (2.89 mL, 20.7 mmol, 1.2 eq). After stirring for 10 min at rt, the reaction mixture was washed with aqueous NH_4Cl (5×50 mL). The organic layer was dried with Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **4** as a pale yellow solid (2.21 g, 92% yield), with ^1H NMR data consistent with previously reported data.^{6a} ^1H NMR (400 MHz, CDCl_3) δ 5.89 (s, 1H), 4.74 (d, $J = 2.7$ Hz, 1H), 4.69 (s, 1H), 4.42 (d, $J = 2.7$ Hz, 1H), 3.59 (s, 3H), 3.40 (s, 3H), 1.95 (s, 3H), 1.42 (s, 3H).

(±)-(1*R*,2*S*,6*S*,7*S*)-6,9-Dimethoxy-4,7-bis(methoxymethyl)-3,11-dioxatricyclo[5.3.1.1^{2,6}]dodeca-4,8-diene-10,12-dione (S1)—To a solution of 5-hydroxy-4-methoxy-2-(methoxymethyl)pyrylium trifluoromethanesulfonate (1.64 g, 5.12 mmol) in CH₂Cl₂ (13 mL) was added triethylamine (857 μL, 6.15 mmol, 1.2 eq). After stirring for 10 min at rt, the reaction mixture was washed with aqueous NH₄Cl (5 × 20 mL). The organic layer was dried with Na₂SO₄, filtered, and concentrated under reduced pressure to yield **S1** as a brown solid (683.4 mg, 78% yield). Melting Point (MP) = 140–143°C. R_f = 0.25 in 50% EtOAc in hexanes. **IR** (thin film, KBr) 3074 (w), 2938 (m), 2839 (m), 1748 (s), 1705 (s), 1669 (m), 1621 (s), 1455 (m), 1369 (m), 1282 (m), 1194 (s), 1105 (s), 992 (m), 901 (m), 834 (m), 729 (m) cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 6.00 (s, 1H), 5.00 (s, 1H), 4.91 (d, *J* = 2.7 Hz, 1H), 4.54 (d, *J* = 2.7 Hz, 1H), 4.03 (d, *J* = 13.5 Hz, 1H), 3.96 (d, *J* = 13.6 Hz, 1H), 3.88 (d, *J* = 10.4 Hz, 1H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 3H), 3.43 (s, 3H), 3.43 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 197.4, 185.1, 157.2, 151.2, 115.7, 95.7, 87.3, 86.6, 85.2, 82.1, 73.5, 70.6, 59.9, 58.7, 55.4, 54.4. **HRMS** (ESI+) *m/z* calc'd for C₁₆H₂₁O₈⁺: 341.1231. Found: 341.1233.

III. Procedures for Alcohol Incorporation

3-Ethoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3a)

Representative Procedure for Synthesis of 3a: Triflate salt **1** (50 mg, 0.172 mmol), N,N-diisopropyl aniline (41 μL, 0.208 mmol, 1.2 eq), and CDCl₃ (0.5 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and stirred until no solid was observed. Ethanol (50 μL, 0.860 mmol, 5 eq) was then added and the reaction was heated to 60 °C in silicon bath oil for 2 hr. After the reaction was allowed to cool to room temperature, phenyl acetylene (378 μL, 3.44 mmol, 20 eq) was added to the reaction and the seal tube was heated to 100 °C for 30 min. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18 cm × 1.8 cm, solvent gradient: hexanes (50 mL); 5% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (150 mL)). Product fractions were concentrated to yield **3a** as a yellowish oil (17 mg, 38% yield) and **2a** as a yellow solid (8 mg, 19% yield). **2a** was consistent by ¹H NMR to previously reported spectra.^{6a} Characterization of **3a**: R_f = 0.21 in 15% EtOAc in hexanes. **IR** (thin film, KBr) 3057 (w), 2981 (m), 2936 (w), 1713 (s), 1603 (s), 1493 (m), 1446 (m), 1381 (w), 1339 (m), 1264 (m), 1130 (s), 1058 (m), 898 (m), 864 (m), 755 (s), 697 (m) cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.41 – 7.30 (m, 3H), 7.30 – 7.25 (m, 2H), 6.27 (d, *J* = 2.5 Hz, 1H), 6.18 (s, 1H), 4.98 (d, *J* = 2.5 Hz, 1H), 3.85 – 3.67 (m, 2H), 1.66 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H). **¹³C NMR** (50 MHz, CDCl₃) δ 190.2, 158.8, 145.2, 133.2, 128.82, 128.77, 126.1, 123.2, 119.7, 86.5, 86.0, 63.3, 22.2, 14.3. **HRMS** (ESI+) *m/z* calc'd for C₁₆H₁₇O₃⁺: 257.1172. Found: 257.1173.

tert-Butyl 3-(benzyloxy)-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (3b)

Representative Procedure Employing Method A: Triflate salt **1** (50 mg, 0.172 mmol), N,N-diisopropyl aniline (41 μL, 0.208 mmol, 1.2 eq), and CH₂Cl₂ (0.5 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and stirred until no solid was observed. Benzyl alcohol (89 μL, 0.860 mmol, 5 eq) was then added and

the reaction was heated to 60°C in silicon bath oil for 12 hr. After the reaction was allowed to cool to room temperature, *t*-butyl propiolate (472 μ L, 3.44 mmol, 20 eq) was added to the reaction and the seal tube was subjected to microwave irradiation at 100°C for 15 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 30 column volumes), yielding **3b** as a white solid (21.6 mg, 37% yield) and **2b** as a white solid (8.3 mg, 18%).

Representative Procedure Employing Method B: Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH₂Cl₂ (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. *t*-Butyl propiolate (472 μ L, 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 15 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 25 column volumes), yielding **3b** as a white solid (30.8 mg, 52% yield) and **2b** as a white solid (10.8 mg, 24%).

Characterization of 3b: MP = 99–102°C. R_f = 0.22 in 10% EtOAc in hexanes. **IR (thin film, KBr)** 3065 (w), 3034 (w), 2978 (w), 2936 (w), 1706 (s), 1614 (m), 1602 (m), 1455 (m), 1369 (m), 1327 (s), 1160 (s), 1122 (s), 1072 (s), 874 (m), 751 (m), 698 (m) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 7.38–7.27 (m, 5H), 6.98 (d, J = 2.5 Hz, 1H), 6.13 (s, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.80 (d, J = 11.9 Hz, 1H), 4.73 (d, J = 11.9 Hz, 1H), 1.72 (s, 3H), 1.48 (s, 9H). **¹³C NMR (100 MHz, CDCl₃)** δ 189.0, 162.2, 151.1, 144.0, 137.8, 135.6, 128.7, 128.3, 127.6, 121.6, 86.0, 85.5, 82.3, 69.6, 28.2, 21.5. **HRMS (ESI+)** m/z calc'd for C₂₀H₂₃O₅⁺: 343.1540. Found: 343.1545.

Characterization of 2b: MP = 82–85°C. R_f = 0.26 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3092 (w), 2979 (w), 2937 (w), 1708 (s), 1615 (m), 1605 (m), 1456 (w), 1369 (m), 1328 (m), 1272 (m), 1161 (m), 1128 (m), 1073 (m), 1024 (m), 873 (w), 760 (w) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 6.96 (d, J = 2.5 Hz, 1H), 6.06 (s, 1H), 4.97 (d, J = 2.5 Hz, 1H), 3.55 (s, 3H), 1.74 (s, 3H), 1.50 (s, 9H). **¹³C NMR (50 MHz, CDCl₃)** δ 189.2, 162.3, 151.1, 145.1, 137.6, 119.7, 85.8, 85.6, 82.4, 54.8, 28.3, 21.5. **HRMS (ESI+)** m/z calc'd for C₁₄H₁₉O₅⁺: 267.1227. Found: 267.1229.

Ethyl 3-(benzyloxy)-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (3c)—Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH₂Cl₂ (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Ethyl propiolate (349 μ L, 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 15 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 33 column volumes), yielding **3c** as a yellow oil (29.6 mg, 55%) and **2c** as a yellow oil (4 mg, 10% yield). **2c** was consistent by ¹H NMR to previously reported spectra.^{6a} **Characterization of 3c:** R_f = 0.25 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3065 (w), 2982 (w), 2937 (w), 1711 (s), 1615 (m), 1602 (m), 1455 (m), 1370 (m), 1317 (s), 1221 (m), 1123 (s), 1073 (s), 1037 (m), 875 (m), 750 (m), 698 (m) cm⁻¹. **¹H**

NMR (400 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 7.09 (d, J = 2.5 Hz, 1H), 6.16 (s, 1H), 5.03 (d, J = 2.5 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.30 – 4.17 (m, 2H), 1.75 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 188.7, 162.9, 149.6, 144.1, 138.8, 135.4, 128.7, 128.3, 127.7, 121.4, 86.2, 85.6, 69.7, 61.3, 21.4, 14.3. **HRMS (ESI+)** m/z calc'd for C₁₈H₁₉O₅⁺: 315.1227. Found: 315.1228.

6-Acetyl-3-(benzyloxy)-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3d)—Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH₂Cl₂ (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. 3-Butyne-2-one (269 μ L, 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 15 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 25% EtOAc/hexane gradient over 60 column volumes), yielding **3d** as a pale yellow solid (32 mg, 65% yield) and **2d** as a yellow solid (5.8 mg, 16%). Compound **2d** was consistent by ¹H NMR to previously reported data.^{6a} Characterization of **3d**: MP = 84–87°C. R_f = 0.32 in 25% EtOAc in hexanes. **IR (thin film, KBr)** 3066 (w), 3034 (w), 2981 (w), 2936 (w), 1712 (s), 1672 (s), 1608 (s), 1455 (m), 1365 (m), 1311 (s), 1269 (m), 1121 (s), 1065 (m), 872 (s), 739 (m), 699 (m) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 7.37 – 7.26 (m, 5H), 7.04 (d, J = 2.5 Hz, 1H), 6.18 (s, 1H), 5.06 (d, J = 2.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 2.36 (s, 3H), 1.71 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 194.3, 188.7, 156.4, 144.1, 139.1, 135.4, 128.7, 128.4, 127.8, 121.5, 86.1, 86.0, 69.7, 27.8, 21.3. **HRMS (ESI+)** m/z calc'd for C₁₇H₁₇O₄⁺: 285.1121. Found: 285.1122.

Dimethyl 3-(benzyloxy)-1-methyl-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (3e)—Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH₂Cl₂ (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Dimethyl acetylene-dicarboxylate (422 μ L, 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 10 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 35% EtOAc/hexane gradient over 45 column volumes), yielding **3e** as a pale yellow solid (29.8 mg, 48% yield) and **2e** as a yellow solid (5.2 mg, 11%). Compound **2e** was consistent by ¹H NMR to previously reported data.^{6a} Characterization of **3e**: MP = 104–107°C. R_f = 0.26 in 25% EtOAc in hexanes. **IR (thin film, KBr)** 3066 (w), 3034 (w), 2954 (w), 1721 (s), 1652 (w), 1605 (m), 1455 (w), 1437 (m), 1323 (m), 1287 (s), 1124 (m), 1073 (m), 1031 (m), 868 (w), 747 (m), 698 (w) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 7.39 – 7.28 (m, 5H), 6.09 (s, 1H), 5.26 (s, 1H), 4.78 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 1.64 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 186.8, 163.8, 161.5, 153.5, 144.3, 136.0, 135.2, 128.7, 128.4, 127.8, 119.9, 87.9, 86.8, 69.9, 52.9, 52.8, 20.9. **HRMS (ESI+)** m/z calc'd for C₁₉H₁₉O₇⁺: 359.1125. Found: 359.1130.

3-(Benzyloxy)-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3f)—Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH₂Cl₂ (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial,

0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Phenyl acetylene (378 μ L, 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 30 min. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18cm $\times$ 1.8cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 5% EtOAc in hexanes (100 mL); 7% EtOAc in hexanes (200 mL); 10% EtOAc in hexanes (100 mL)). Product fractions concentrated to yield **3f** as a white solid (21.9 mg, 40% yield). MP = 112–114°C. R_f = 0.24 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3061 (w), 3033 (w), 2979 (w), 2933 (w), 1709 (s), 1604 (s), 1491 (m), 1454 (m), 1339 (m), 1263 (m), 1125 (s), 1106 (m), 1058 (m), 866 (m), 754 (s), 697 (s) cm^{-1} . **^1H NMR (400 MHz, CDCl_3)** δ 7.40–7.27 (m, 8H), 7.18–7.12 (m, 2H), 6.27 (d, J = 2.4 Hz, 1H), 6.24 (s, 1H), 5.01 (d, J = 2.5 Hz, 1H), 4.92 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 1.62 (s, 3H). **^{13}C NMR (50 MHz, CDCl_3)** δ 189.9, 158.9, 144.7, 135.6, 133.1, 128.8, 128.7, 128.3, 127.5, 126.0, 123.2, 121.6, 86.5, 86.1, 69.7, 22.0. **HRMS (ESI+)** m/z calc'd for $\text{C}_{21}\text{H}_{19}\text{O}_3^+$: 319.1329. Found: 319.1332.

5-Methyl-3-((4-methylbenzyl)oxy)-6-(4-(trifluoromethyl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3g)—Dimer **4** (25 mg, 0.0892 mmol), 4-methylbenzyl alcohol (105 mg, 0.860 mmol, 9.6 eq), and CH_2Cl_2 (0.26 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. 4-Ethynyl- α , α , α -trifluorotoluene (561 μ L, 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 35 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 25 column volumes), yielding **3g** as a yellow solid (30.2 mg, 42% yield). MP = 115–119°C. R_f = 0.31 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3054 (w), 2982 (w), 2936 (w), 1712 (m), 1615 (m), 1603 (m), 1455 (w), 1326 (s), 1165 (m), 1125 (s), 1069 (s), 1016 (w), 869 (m), 835 (w), 804 (w), 740 (w) cm^{-1} . **^1H NMR (400 MHz, CDCl_3)** δ 7.57 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 6.36 (d, J = 2.4 Hz, 1H), 6.18 (s, 1H), 5.02 (d, J = 2.5 Hz, 1H), 4.93 (d, J = 12.1 Hz, 1H), 4.76 (d, J = 12.1 Hz, 1H), 2.32 (s, 3H), 1.59 (s, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 189.6 (s), 157.8 (s), 144.5 (s), 138.1 (s), 136.8 (d, J = 1.2 Hz), 132.5 (s), 130.6 (q, J = 32.7 Hz), 129.5 (s), 127.5 (s), 126.3 (s), 125.7 (q, J = 3.8 Hz), 125.6 (s), 124.0 (q, J = 272.1 Hz), 121.4 (s), 86.5 (s), 86.3 (s), 69.7 (s), 21.9 (s), 21.2 (s). **HRMS (ESI+)** m/z calc'd for $\text{C}_{23}\text{H}_{19}\text{F}_3\text{O}_3\text{Na}^+$: 423.1179. Found: 423.1182.

6-(4-Methoxyphenyl)-5-methyl-3-((4-(trifluoromethyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3h)—Dimer **4** (25 mg, 0.0892 mmol), 4-(trifluoromethyl)benzyl alcohol (118 μ L, 0.860 mmol, 9.6 eq), and CH_2Cl_2 (0.26 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 4 hr. 4-Ethynylanisole (446 μ L, 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 40 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 20% EtOAc/hexane gradient over 30 column volumes), yielding a crude product. After vacuum distillation of the crude material, **3h** was obtained as a yellow oil (34.1 mg, 46% yield). R_f = 0.23 in 20% EtOAc in hexanes.

IR (thin film, KBr) 3055 (w), 2977 (w), 2937 (w), 1711 (s), 1607 (m), 1510 (s), 1457 (w), 1326 (s), 1253 (s), 1164 (m), 1125 (s), 1067 (s), 1020 (m), 867 (m), 828 (m), 725 (w) cm^{-1} . **^1H NMR (400 MHz, CDCl_3)** δ 7.60 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.19 (s, 1H), 6.16 (d, J = 1.8 Hz, 1H), 4.99 (d, J = 2.1 Hz, 1H), 4.97 (d, J = 13.5 Hz, 1H), 4.83 (d, J = 12.7 Hz, 1H), 3.82 (s, 3H), 1.62 (s, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 189.7 (s), 160.2 (s), 158.5 (s), 144.5 (s), 139.8 (q, J = 1.1 Hz), 130.5 (q, J = 32.5 Hz), 127.5 (s), 127.3 (s), 125.8 (q, J = 3.7 Hz), 125.4 (s), 124.1 (q, J = 272.1 Hz), 122.1 (s), 121.0 (s), 114.3 (s), 86.4 (s), 86.0 (s), 68.8 (s), 55.5 (s), 22.1 (s). **HRMS (ESI+)** m/z calc'd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{O}_4^+$: 417.1308. Found: 417.1310.

Ethyl 3-(benzyloxy)-5-(methoxymethyl)-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (3i)—Dimer **S1** (29 mg, 0.0860 mmol), benzyl alcohol (89 μL , 0.860 mmol, 10 eq), and CH_2Cl_2 (0.25 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Ethyl propiolate (349 μL , 3.44 mmol, 40 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 20 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 30% EtOAc/hexane gradient over 35 column volumes), yielding **3i** as a white solid (31.8 mg, 54% yield) and **2i** as a yellow oil (9 mg, 20%).

Characterization of 3i: MP = 80–84°C. R_f = 0.30 in 30% EtOAc in hexanes. **IR (thin film, KBr)** 3065 (w), 2983 (w), 2931 (w), 1712 (s), 1617 (w), 1604 (m), 1455 (w), 1370 (w), 1320 (m), 1278 (w), 1217 (m), 1114 (m), 1097 (m), 1032 (w), 869 (w), 749 (w) cm^{-1} . **^1H NMR (400 MHz, CDCl_3)** δ 7.37–7.27 (m, 5H), 7.12 (d, J = 2.4 Hz, 1H), 6.09 (s, 1H), 5.12 (d, J = 2.4 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.30–4.18 (m, 2H), 3.97 (d, J = 10.9 Hz, 1H), 3.93 (d, J = 11.0 Hz, 1H), 3.44 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 188.4, 162.7, 147.5, 145.2, 139.0, 135.3, 128.7, 128.4, 127.8, 116.8, 88.4, 86.4, 72.2, 69.8, 61.4, 59.8, 14.3. **HRMS (ESI+)** m/z calc'd for $\text{C}_{19}\text{H}_{21}\text{O}_6^+$: 345.1333. Found: 345.1334.

Characterization of 2i: R_f = 0.27 in 35% EtOAc in hexanes. **IR (thin film, KBr)** 3067 (w), 2982 (w), 2935 (w), 1712 (s), 1618 (m), 1607 (m), 1455 (w), 1319 (m), 1218 (m), 1120 (s), 1098 (s), 1033 (m), 986 (w), 868 (w), 828 (w), 769 (w) cm^{-1} . **^1H NMR (400 MHz, CDCl_3)** δ 7.11 (d, J = 2.5 Hz, 1H), 6.01 (s, 1H), 5.10 (d, J = 2.5 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.00 (d, J = 10.9 Hz, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.57 (s, 3H), 3.45 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 188.7, 162.8, 147.7, 146.3, 138.9, 115.0, 88.4, 86.2, 72.3, 61.4, 59.9, 54.9, 14.3. **HRMS (ESI+)** m/z calc'd for $\text{C}_{13}\text{H}_{17}\text{O}_6^+$: 269.1020. Found: 269.1024.

Ethyl 5-methyl-3-(neopentyloxy)-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (3j)—Dimer **4** (25 mg, 0.0892 mmol), neopentyl alcohol (76 mg, 0.860 mmol, 9.6 eq), and CDCl_3 (0.26 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Ethyl Propiolate (349 μL , 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 20 min. The reaction was then

immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 25% EtOAc/hexane gradient over 25 column volumes), yielding **3j** as a yellow solid (29.8 mg, 57% yield) and **2c** as a yellow solid (10.9 mg, 26% yield). Compound **2c** was consistent by ^1H NMR to previously reported data.^{6a} Characterization of **3j**: MP = 69–73°C. R_f = 0.31 in 10% EtOAc in hexanes. **IR** (thin film, KBr) 3066 (w), 2958 (m), 2870 (w), 1712 (s), 1616 (m), 1602 (m), 1478 (w), 1367 (m), 1316 (s), 1220 (m), 1125 (s), 1074 (s), 994 (w), 874 (m), 752 (m), 677 (w) cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.09 (d, J = 2.5 Hz, 1H), 6.02 (s, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.26 (d, J = 8.9 Hz, 1H), 3.21 (d, J = 8.9 Hz, 1H), 1.75 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H). **^{13}C NMR** (100 MHz, CDCl_3) δ 188.7, 163.1, 149.6, 144.8, 138.9, 119.7, 86.2, 85.6, 77.2, 61.2, 31.8, 26.7, 21.5, 14.3. **HRMS** (ESI+) m/z calc'd for $\text{C}_{16}\text{H}_{23}\text{O}_5^+$: 295.1540. Found: 295.1542.

5-Methyl-3-(neopentyloxy)-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3k)—Dimer **4** (25 mg, 0.0892 mmol), neopentyl alcohol (76 mg, 0.860 mmol, 9.6 eq), and CDCl_3 (0.26 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Phenyl acetylene (378 μL , 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 1 hr. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18cm $\times$ 1.8cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 3% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL)). Product fractions were concentrated to yield **3k** as a yellow solid (22.9 mg, 43% yield) and **2a** as a yellow solid (3.2 mg, 7% yield). MP = 114–117°C. R_f = 0.33 in 10% EtOAc in hexanes. **IR** (thin film, KBr) 3057 (w), 2957 (m), 2869 (w), 1714 (s), 1603 (m), 1478 (w), 1446 (w), 1365 (w), 1338 (w), 1260 (w), 1130 (m), 1059 (w), 995 (w), 865 (m), 755 (m), 697 (w) cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.42 – 7.27 (m, 5H), 6.29 (d, J = 2.4 Hz, 1H), 6.14 (s, 1H), 4.97 (d, J = 2.5 Hz, 1H), 3.34 (d, J = 8.8 Hz, 1H), 3.25 (d, J = 8.8 Hz, 1H), 1.67 (s, 3H), 0.99 (s, 9H). **^{13}C NMR** (100 MHz, CDCl_3) δ 189.7, 158.7, 145.7, 133.3, 128.8, 128.7, 126.1, 123.3, 119.4, 86.5, 86.1, 77.3, 31.8, 26.7, 22.2. **HRMS** (ESI+) m/z calc'd for $\text{C}_{19}\text{H}_{23}\text{O}_3^+$: 299.1642. Found: 299.1645.

3-((1-Methyl-4-oxo-7-phenyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)oxy)propanenitrile (3l)—Dimer **4** (25 mg, 0.0892 mmol), 3-hydroxypropionitrile (59 μL , 0.860 mmol, 9.6 eq), and CDCl_3 (0.26 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Phenyl acetylene (378 μL , 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 35 min. The reaction was then immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 40% EtOAc/hexane gradient over 30 column volumes), yielding **3l** as an orange oil (21.1 mg, 42% yield) and **2a** as a yellow solid (9.6 mg, 22%). Compound **2a** was consistent by ^1H NMR to previously reported data.^{6a} Characterization of **3l**: R_f = 0.24 in 35% EtOAc in hexanes. **IR** (thin film, KBr) 3058 (w), 2979 (w), 2937 (w), 2253 (w), 1710 (s), 1606 (m), 1492 (w), 1446 (w), 1342 (w), 1264 (w), 1132 (s), 1057 (m), 878 (m), 864 (m), 755 (m), 698 (m) cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.43 – 7.33 (m, 3H), 7.30 – 7.23 (m, 2H), 6.32 (s, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.00 (d, J = 2.5 Hz, 1H), 4.05 – 3.87 (m, 2H), 2.81 (t, J =

6.8 Hz, 2H), 1.68 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 189.2, 158.5, 144.3, 132.9, 129.0, 128.9, 126.1, 123.2, 122.7, 116.7, 86.4, 86.0, 62.7, 22.0, 18.2. **HRMS (ESI+)** *m/z* calc'd for C₁₇H₁₅NO₃Na⁺: 304.0944. Found: 304.0948.

3-Isopropoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3m)—

Dimer **4** (25 mg, 0.0892 mmol), isopropyl alcohol (66 μL, 0.860 mmol, 9.6 eq), and CDCl₃ (0.26 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 36 hr. Phenyl acetylene (378 μL, 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 1 hr. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18cm × 1.8cm, solvent gradient: hexanes (50 mL); 5% EtOAc in hexanes (100 mL); 8% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (100 mL), 15% EtOAc in hexanes (100 mL)). Product fractions were concentrated to yield **3m** as a yellowish oil (15.3 mg, 32% yield) and **2a** as a yellowish solid (11.3 mg, 26% yield). Compound **2a** was consistent by ¹H NMR to previously reported data.^{6a} Characterization of **3m**: R_f = 0.27 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3057 (w), 2979 (m), 2935 (w) 1710 (s), 1600 (s), 1596 (s), 1493 (w), 1447 (w), 1384 (w), 1375 (w), 1263 (w), 1125 (s), 1058 (w), 865 (m), 754 (m), 697 (w) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 7.42 – 7.31 (m, 3H), 7.30 – 7.25 (m, 2H), 6.28 (d, *J* = 2.4 Hz, 1H), 6.19 (s, 1H), 4.98 (d, *J* = 2.5 Hz, 1H), 4.24 (sept, *J* = 6.1 Hz, 1H), 1.66 (s, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H). **¹³C NMR (50 MHz, CDCl₃)** δ 190.7, 158.8, 143.8, 133.3, 128.9, 128.7, 126.1, 123.4, 121.1, 86.5, 86.1, 69.9, 22.2, 21.5. **HRMS (ESI+)** *m/z* calc'd for C₁₇H₁₉O₃⁺: 271.1329. Found: 271.1331.

3-(Allyloxy)-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3n)—

Dimer **4** (25 mg, 0.0892 mmol), allyl alcohol (58 μL, 0.860 mmol, 9.6 eq), and CDCl₃ (0.26 M, 344 μL) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 12 hr. Phenyl acetylene (378 μL, 3.44 mmol, 39 eq) was added to the seal tube and the reaction was subjected to microwave irradiation at 100°C for 30 min. The reaction was then immediately purified by column chromatography (silica gel, 6 inch height of silica gel, 18cm × 1.8cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL); 5% EtOAc in hexanes (100 mL); 7% EtOAc in hexanes (150 mL); 10% EtOAc in hexanes (50 mL); 15% EtOAc in hexanes (100 mL)). Product fractions were concentrated to yield **3n** as yellowish oil (11.5 mg, 24% yield) and **2a** as yellowish solid (5.2 mg, 12% yield). Compound **2a** was consistent by ¹H NMR to previously reported data.^{6a} Characterization of **3n**: R_f = 0.24 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3081 (w), 3057 (w), 2981 (w), 2935 (w), 1710 (s), 1603 (s), 1491 (w), 1447 (w), 1338 (w), 1264 (w), 1125 (m), 1106 (m), 1058 (m), 865 (m), 755 (s), 697 (m) cm⁻¹. **¹H NMR (400 MHz, CDCl₃)** δ 7.41 – 7.32 (m, 3H), 7.29 – 7.25 (m, 2H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.21 (s, 1H), 6.02–5.91 (m, 1H), 5.35 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H), 4.34 (ddt, *J* = 12.6, 5.4, 1.4 Hz, 1H), 4.26 (ddt, *J* = 12.7, 5.6, 1.3 Hz, 1H), 1.66 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 190.0, 158.8, 144.7, 133.2, 132.1, 128.84, 128.80, 126.1, 123.3, 120.8, 118.7, 86.5, 86.1, 68.6, 22.2. **HRMS (ESI+)** *m/z* calc'd for C₁₇H₁₆O₃Na⁺: 291.0992. Found: 291.0997.

3-(Benzyloxy)-6-(4-ethynylphenyl)-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (3o)—Dimer **4** (24 mg, 0.0860 mmol), benzyl alcohol (89 μ L, 0.860 mmol, 10 eq), and CH_2Cl_2 (0.25 M, 344 μ L) were added to a sealed tube reactor (Biotage[®] microwave reaction vial, 0.5–2 mL) and the reaction was heated to 60°C in silicon bath oil for 14 hr. 1,4-Diethynylbenzene (217 mg, 1.72 mmol, 20 eq) and CH_2Cl_2 (344 μ L) were added to the seal tube and the reaction was stirred until no solid was observed. The reaction was then subjected to microwave irradiation at 100°C for 35 min, and immediately purified by column chromatography (silica [10g], 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 30 column volumes). Product fractions were concentrated to yield **3o** as an orange oil (25.7 mg, 44% yield). Due to high value of 1,4-diethynylbenzene, fractions containing it were also concentrated (174 mg, 89% recovery (195 mg would be 100% theoretical yield of un-reacted product)). $R_f = 0.28$ in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3287 (m), 3035 (w), 2981 (w), 2935 (w), 2106 (w), 1709 (s), 1600 (m), 1498 (m), 1455 (m), 1339 (m), 1264 (m), 1124 (s), 1058 (m), 867 (m), 734 (m), 697 (m) cm^{-1} . **¹H NMR (400 MHz, CDCl_3)** δ 7.45 (d, $J = 8.4$ Hz, 2H), 7.35 – 7.27 (m, 5H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.30 (d, $J = 2.5$ Hz, 1H), 6.19 (s, 1H), 5.01 (d, $J = 2.5$ Hz, 1H), 4.93 (d, $J = 12.1$ Hz, 1H), 4.78 (d, $J = 12.1$ Hz, 1H), 3.15 (s, 1H), 1.60 (s, 3H). **¹³C NMR (100 MHz, CDCl_3)** δ 189.7, 158.2, 144.7, 135.6, 133.6, 132.5, 128.8, 128.3, 127.5, 126.0, 124.3, 122.5, 121.4, 86.4, 86.2, 83.2, 78.6, 69.7, 22.0. **HRMS (ESI+)** m/z calc'd for $\text{C}_{23}\text{H}_{18}\text{O}_3\text{Na}^+$: 365.1148. Found: 365.1150.

IV. Synthesis of α -Hydroxytropolones via Acid-Mediated Debenzylation

Procedure A—To a solution of **3f** (25.6 mg, 0.0804 mmol) in CH_2Cl_2 (500 μ L) was added methanesulfonic acid (210 μ L, 3.22 mmol, 40 eq). The reaction was stirred for 1 hr, at which time it was quenched with phosphate buffer (pH 7, 15 mL), extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **5** as a reddish brown oil (19.0 mg, >95% crude yield). Compound **5** was consistent by ¹H NMR to previously reported data.¹²

Procedure B—To a solution of **3f** (25 mg, 0.0785 mmol) in CH_2Cl_2 (1 mL) was added Amberlyst-15 (4.7 mmol/g, 671 mg, 3.14 mmol, 40 eq). The reaction was stirred for 16 hr, at which time the Amberlyst was washed with CH_2Cl_2 (5×2 mL). The Amberlyst was then stirred in phosphate buffer (pH 7, 15 mL) for 10 min, and the aqueous layer was extracted with EtOAc (5×10 mL). Combined organics were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **5** as a light brown oil (11.6 mg, 65% yield). Compound **5** was consistent by ¹H NMR to previously reported data.¹²

Acknowledgments

MD, CM, and RM are grateful for support from The National Instituted of Health (SC1GM111158), and the Alfred P. Sloan Foundation. We are also thankful to John A. Beutler and Stuart F. J. Le Grice (NCI Frederick) for helpful discussions and support associated with our work on the manuscript.

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Scheme 1. Overview of α -hydroxy- γ -pyrone oxidopyrylium cycloaddition reactions

Scheme 2.

Proposed Mechanism for Incorporation of Alcohols into Oxidopyrylium Ylide

Scheme 3.
Tandem ring-opening/debenzylation of **3f**

Table 1Select optimization results for formation of **3a** from methyl triflate salt **1**

Entry	EtOH equiv.	Temp ^a	Time ^a	Yield (3a:2a) ^b
1	0.33	-	-	62% (1:5.2)
2	1	-	-	62% (1:2.7)
3	5	-	-	65% (1.2:1)
4	5	25°C	12 hr	65% (1.2:1)
5	5	25°C	1 wk	64% (3.9:1)
6	5	60°C ^c	1 hr	63% (1.4:1)
7	5	60°C ^c	2 hr	63% (2:1)
8	5	60°C ^c	4 hr	63% (2.6:1)
9	5	80°C ^c	1 hr	58% (1.6:1)
10	5	80°C ^c	4 hr	30% (6.2:1)
11 ^d	5	60°C	2 hr	56% (2.3:1)

^aReaction temperatures and times correspond to first step.^bYields were calculated based upon combined **2a** and **3a** and ratios determined by ^1H NMR integration.^cHeated with microwave irradiation.^dConventional heating throughout reaction.

Table 2

Representative result comparing reactions carried out from salt/base to those from purified oxidopyrylium dimer.

Entry	Method	Time ^b	% Yield ^c		
			3b ^c	2b ^d	Total
1	A	2 hr	12	60	72
2	B	2 hr	25	56	81
3	A	6 hr	25	35	60
4	B	6 hr	47	24	71
5	A	8 hr	30	28	58
6	B	8 hr	47	24	71
7	A	12 hr	37	18	55
8	B	12 hr	52	24	76
9	B	18 hr	51	10	61
10	B	24 hr	55	7	62

^aEquivalents are calculated based upon monomeric ylide for consistency.

^bTime for first step, with conventional heating.

^cIsolated yields following silica gel chromatography.

^dProduct **2b** was isolated along with benzyl alcohol, and yields were approximated based upon ¹H NMR integration ratio of signature peaks of **2b** and benzyl alcohol.

Table 3

Optimized 3-component cycloaddition between oxidopyrylium dimer, benzyl alcohol, and various alkynes

^aEquivalents are calculated based upon monomeric ylide^bTime for step 1.

^cTime for step 2.

^dIsolated yields following silica gel chromatography.

^eIn cases where methyl enol ether (**2a–n**) appeared substantial and isolatable, they were isolated and the yields are provided in brackets.

^f10 equivalents of alkyne were used, 80% of which was recovered during chromatography.