JOC The Journal of Organic Chemistry

Article

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

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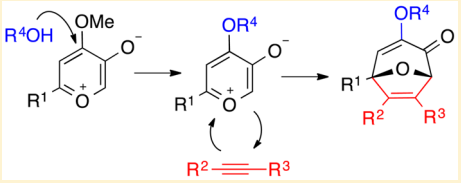
Supporting Information

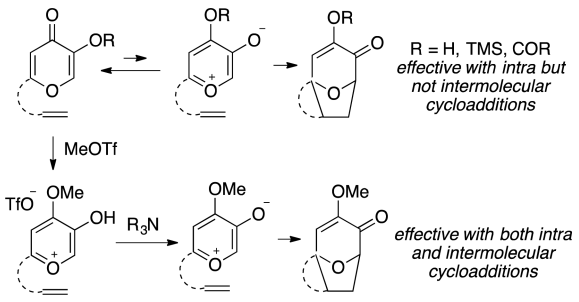
ABSTRACT: α-Hydroxy-γ-pyrone-based oxidopyrylium cycloaddition reactions are useful methods for accessing a highly diverse range of oxabicyclo[3.2.1]octane products. Intermolecular variants of the reaction require the formation of a methyl triflate-based pre-ylide salt that upon treatment with base in the presence of alkenes or alkynes leads to α-methoxyenone-containing bicyclic products. 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 three-component process was further optimized by gently heating a mixture of a purified version of the oxidopyrylium dimer in the presence of an alcohol prior to addition of a 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.



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 leverages the facile tautomerization or rearrangement of α-hydroxy-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 co-workers 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 laboratory 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 with oxidopyrylium ylide dimers prior to the oxidopyrylium cycloaddition. The result is a three-component oxidopyrylium cycloaddition for the generation of new oxabicyclic products.

Scheme 1. Overview of α-Hydroxy-γ-pyrone Oxidopyrylium Cycloaddition Reactions



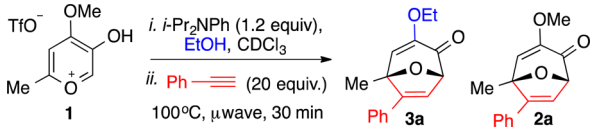
RESULTS AND DISCUSSION

Our work on the three-component oxidopyrylium cycloaddition began with the observation that some slower oxidopyrylium cycloaddition reactions run using ethanol-stabilized chloroform as solvent produced minor amounts of ethanol-incorporated cycloaddition products (i.e. **3a**; Table 1). For example, at typical stabilizer concentrations of 1%, which corresponded to 0.33 equiv in our studies, the oxidopyrylium cycloaddition with phenylacetylene produced approximately 15% of **3a** (Table 1, entry 1). Intrigued by these results, we began to study the process and found that higher concentrations of ethanol in the reactions increased the yields of **3a** with no diminishment in overall bicycle yields (entries 2 and 3). Longer reaction times of the oxidopyrylium cycloaddition reaction did not increase the 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

Received: February 23, 2016
Published: March 28, 2016

DOI: 10.1021/acs.joc.6b00394
J. Org. Chem. 2016, 81, 3744−3751

Table 1. Select Optimization Results for Formation of 3a from Methyl Triflate Salt 1



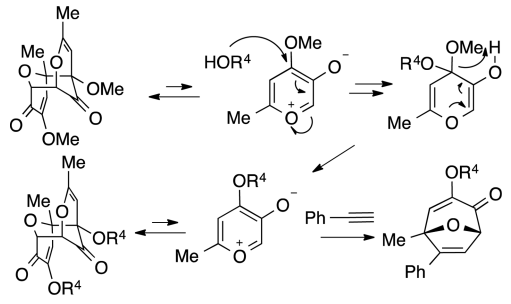
entry	amt of EtOH, equiv	temp, °C[a]	time[a]	yield, % (3a:2a)[b]
1	0.33			62 (1:5.2)
2	1			62 (1:2.7)
3	5			65 (1.2:1)
4	5	25	12 h	65 (1.2:1)
5	5	25	1 wk	64 (3.9:1)
6	5	60[c]	1 h	63 (1.4:1)
7	5	60[c]	2 h	63 (2:1)
8	5	60[c]	4 h	63 (2.6:1)
9	5	80[c]	1 h	58 (1.6:1)
10	5	80[c]	4 h	30 (6.2:1)
11[d]	5	60	2 h	56 (2.3:1)

[a]Reaction temperatures and times correspond to the first step. [b]Yields were calculated on the basis of combined **2a** and **3a**, and ratios were determined by ^{1}H NMR integration. [c]Heated with microwave irradiation. [d]Conventional heating throughout reaction.

were observed between reactions run using microwave irradiation and those run using 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 laboratory previously,[6] could allow for this possibility (Scheme 2). Direct exchange with the dimer seems

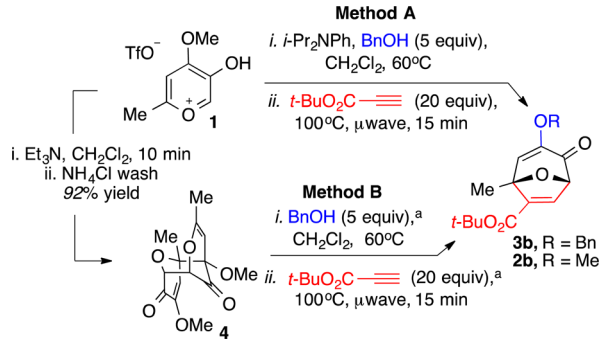
Scheme 2. Proposed Mechanism for Incorporation of Alcohols into Oxidopyrylium Ylide



unlikely, given the necessity for S_N1 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 three-component process, a major obstacle faced early on in our work was the significantly lower yields for other substrates (i.e. 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 in high yields by adding triethylamine to the oxidopyrylium salt

Table 2. Representative Result Comparing Reactions Carried out from Salt/Base to Those from Purified Oxidopyrylium Dimer



			yield, %[c]		
entry	method	time, h[b]	3b[c]	2b[d]	total
1	A	2	12	60	72
2	**B**	**2**	**25**	**56**	**81**
3	A	6	25	35	60
4	**B**	**6**	**47**	**24**	**71**
5	A	8	30	28	58
6	**B**	**8**	**47**	**24**	**71**
7	A	12	37	18	55
8	**B**	**12**	**52**	**24**	**76**
9	**B**	**18**	**51**	**10**	**61**
10	**B**	**24**	**55**	**7**	**62**

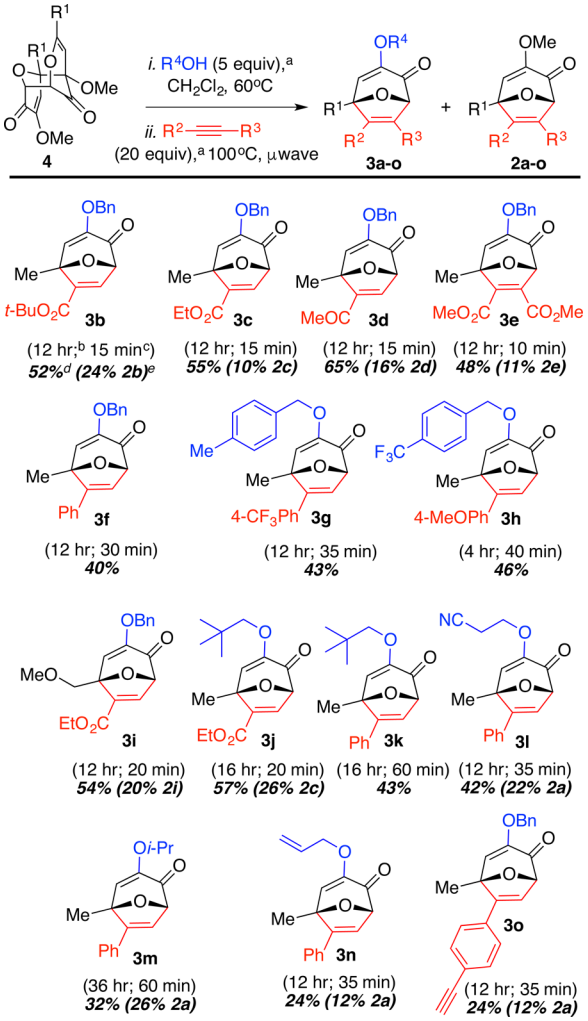
[a]Equivalents are calculated on the basis of monomeric ylide for consistency. [b]Time for first step, with conventional heating. [c]Isolated yields following silica gel chromatography. [d]Product **2b** was isolated along with benzyl alcohol, and yields were approximated on the basis of the ^{1}H NMR integration ratio of signature peaks of **2b** and benzyl alcohol.

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 h, and reaction times beyond that led to comparable yields of **3b**, although yields were lower overall 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−f**; Table 3). Electronically rich and poorly substituted benzyl alcohol can also be used with comparable yields (**3g,h**), 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,k**) or base-sensitive functionality (**3l**) can also be employed. On the other hand, steric limitations do apply, as illustrated by the secondary alcohol isopropyl alcohol requiring longer reaction times and providing lower reaction yields of **3m**. Furthermore, attempts at

DOI: 10.1021/acs.joc.6b00394
J. Org. Chem. 2016, 81, 3744−3751

Table 3. Optimized Three-Component Cycloaddition among Oxidopyrylium Dimer, Benzyl Alcohol, and Various Alkynes



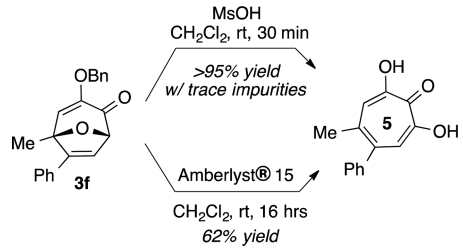
[a]Equivalents are calculated based upon monomeric ylide. [b]Time for step 1. [c]Time for step 2. [d]Isolated yields following silica gel chromatography. [e]In cases where methyl enol ethers (**2a**–**n**) appeared substantial and isolatable, they were isolated and the yields are provided in parentheses. [f]10 equiv of alkyne was used, 80% of which was recovered during chromatography.

using the tertiary alcohol *tert*-butyl alcohol 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 equiv was used to maximize product yields. However, 1,4-diethynylbenzene represented the case of an alkyne for which higher amounts were prohibitive. In these cases, 10 equiv 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 equiv. 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 Amberlyst15 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

Scheme 3. Tandem Ring-Opening/Debenzylation of 3f



the process is still unknown, with shorter reaction times benzyloxytropolones are observed along with the hydroxytropolones, suggesting that ring opening is taking place prior to debenzylation. 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 exchange in the presence of alcohols to generate new oxidopyrylium species capable of intermolecular cycloaddition chemistry. The net result is a three-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 SECTION

General Information. All starting materials and reagents were purchased from commercially available sources and used without further purification, with the exception of CH_2Cl_2, which was purified on a solvent purification system prior to reactions.[14] ^{1}H NMR shifts were 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 doublets, q = quartet, m = multiplet), coupling constant (Hz), integration. ^{13}C NMR shifts were 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 the electrospray ionization (ESI) technique with a 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

DOI: 10.1021/acs.joc.6b00394
J. Org. Chem. 2016, 81, 3744–3751

silica gel chromatography using a Biotage Isolera Prime, with Biotage SNAP 10 g cartridges, in a solvent system of ethyl acetate in hexane.

Synthesis of Oxidopyrylium Dimers. *(±)-(1R,2S,6S,7R)-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 equiv). After it was stirred for 10 min at room temperature, 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 give **4** as a pale yellow solid (2.21 g, 92% yield), with ^{1}H NMR data consistent with previously reported data.[6a] ^{1}H 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).

*(±)-(1R,2S,6S,7S)-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 CH_2Cl_2 (13 mL) was added triethylamine (857 μL, 6.15 mmol, 1.2 equiv). After it was stirred for 10 min at room temperature, the reaction mixture was washed with aqueous NH_4Cl (5 × 20 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give **S1** as a brown solid (683.4 mg, 78% yield). 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{16}H_{21}O_8^+$, 341.1231; found, 341.1233.

Procedures for Alcohol Incorporation/Cycloaddition Sequence. *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*-diisopropylaniline (41 μL, 0.208 mmol, 1.2 equiv), and $CDCl_3$ (0.5 M, 344 μL) were placed in 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 equiv) was then added, and the reaction mixture was heated to 60 °C in a silicon oil bath for 2 h. After the reaction mixture was cooled to room temperature, phenylacetylene (378 μL, 3.44 mmol, 20 equiv) was added and the sealed tube was heated to 100 °C for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. 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 give **3a** as a yellowish oil (17 mg, 38% yield) and **2a** as a yellow solid (8 mg, 19% yield). **2a** was consistent by ^{1}H NMR with previously reported spectra.[6a] Characterization data for **3a** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 calcd for $C_{16}H_{17}O_3^+$, 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*-diisopropylaniline (41 μL, 0.208 mmol, 1.2 equiv), and CH_2Cl_2 (0.5 M, 344 μL) were placed in 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 equiv) was then added, and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. After the reaction mixture was cooled to room temperature, *tert*-butyl propiolate (472 μL, 3.44 mmol, 20 equiv) was added to the reaction mixture and the sealed tube was subjected to microwave irradiation at 100 °C for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 30 column volumes), giving **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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL) and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. *tert*-Butyl propiolate (472 μL, 3.44 mmol, 40 equiv) was placed the sealed tube and the reaction mixture was subjected to microwave irradiation at 100 °C for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 25 column volumes), giving **3b** as a white solid (30.8 mg, 52% yield) and **2b** as a white solid (10.8 mg, 24%).

*Characterization Data 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{20}H_{23}O_5^+$, 343.1540; found, 343.1545.

*Characterization Data 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 calcd for $C_{14}H_{19}O_5^+$, 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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Ethyl propiolate (349 μL, 3.44 mmol, 40 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 33 column volumes), giving **3c** as a yellow oil (29.6 mg, 55%) and **2c** as a yellow oil (4 mg, 10% yield). **2c** was consistent by ^{1}H NMR with previously reported spectra.[6a] Characterization data of **3c** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{18}H_{19}O_5^+$, 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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. 3-Butyn-2-one (269 μL, 3.44 mmol, 40 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 15 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0%

DOI: 10.1021/acs.joc.6b00394
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EtOAc/hexane to 25% EtOAc/hexane gradient over 60 column volumes), giving **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 ^{1}H NMR with previously reported data.[6a] Characterization data of **3d** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{17}O_4^+$, 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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Dimethyl acetylenedicarboxylate (422 μL, 3.44 mmol, 40 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 10 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 35% EtOAc/hexane gradient over 45 column volumes), giving **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 ^{1}H NMR with previously reported data.[6a] Charaterization data of **3e** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{19}H_{19}O_7^+$, 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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Phenylacetylene (378 μL, 3.44 mmol, 40 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. height of silica gel, 18 cm × 1.8 cm, 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 were concentrated to give **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}. ^{1}H 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 calcd for $C_{21}H_{19}O_3^+$, 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 equiv), and CH_2Cl_2 (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. 4-Ethynyl-α,α,α-trifluorotoluene (561 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 35 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 25 column volumes), giving **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}. ^{1}H 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 calcd for $C_{23}H_{19}F_3O_3Na^+$, 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 μL, 0.860 mmol, 9.6 equiv), and CH_2Cl_2 (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 4 h. 4-Ethynylanisole (446 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 40 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 20% EtOAc/hexane gradient over 30 column volumes), giving product contaminated with aryl alcohol. The aryl alcohol could be removed by vacuum distillation, leaving **3h** 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}. ^{1}H 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 calcd for $C_{23}H_{20}F_3O_4^+$, 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 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Ethyl propiolate (349 μL, 3.44 mmol, 40 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 20 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 30% EtOAc/hexane gradient over 35 column volumes), giving **3i** as a white solid (31.8 mg, 54% yield) and **2i** as a yellow oil (9 mg, 20%).

*Characterization Data 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}. ^{1}H 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 calcd for $C_{19}H_{21}O_6^+$, 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}. ^{1}H 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,

DOI: 10.1021/acs.joc.6b00394
J. Org. Chem. 2016, 81, 3744−3751

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 calcd for $C_{13}H_{17}O_6^+$, 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 equiv), and $CDCl_3$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Ethyl propiolate (349 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 20 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 25% EtOAc/hexane gradient over 25 column volumes), giving **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 ^{1}H NMR with previously reported data.[6a] Characterization data of **3j** are as follows. 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}. ^{1}H 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 calcd for $C_{16}H_{23}O_5^+$, 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 equiv), and $CDCl_3$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Phenylacetylene (378 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. height of silica gel, 18 cm × 1.8 cm, 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 give **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}. ^{1}H 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 calcd for $C_{19}H_{23}O_3^+$, 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 equiv), and $CDCl_3$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Phenylacetylene (378 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 35 min. The reaction mixture was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 40% EtOAc/hexane gradient over 30 column volumes), giving **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 ^{1}H NMR with previously reported data.[6a] Characterization data of **3l** are as follows. 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}. ^{1}H 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{15}NO_3Na^+$, 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 equiv), and $CDCl_3$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 36 h. Phenylacetylene (378 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. height of silica gel, 18 cm × 1.8 cm, 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 ^{1}H NMR with previously reported data.[6a] Characterization data of **3m** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{19}O_3^+$, 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 equiv), and $CDCl_3$ (0.26 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 12 h. Phenyl acetylene (378 μL, 3.44 mmol, 39 equiv) was placed in the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was then immediately purified by column chromatography (silica gel, 6 in. height of silica gel, 18 cm × 1.8 cm, 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 a yellowish oil (11.5 mg, 24% yield) and **2a** as a yellowish solid (5.2 mg, 12% yield). Compound **2a** was consistent by ^{1}H NMR with previously reported data.[6a] Characterization data of **3n** are as follows. 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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{16}O_3Na^+$, 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 μL, 0.860 mmol, 10 equiv), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage microwave reaction vial, 0.5−2 mL), and the reaction mixture was heated to 60 °C in a silicon oil bath for 14 h. 1,4-Diethynylbenzene (217 mg, 1.72 mmol, 20 equiv) and CH_2Cl_2 (344 μL) were placed the sealed tube, and the reaction mixture was stirred until no solid was observed. The reaction mixture was then subjected to microwave irradiation at 100 °C for 35 min and immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 30 column volumes). Product fractions were concentrated to give **3o** as an orange

DOI: 10.1021/acs.joc.6b00394
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oil (25.7 mg, 44% yield). Due to the high cost of 1,4-diethynylbenzene, fractions containing it were also concentrated (174 mg, 89% recovery (195 mg would be 100% theoretical yield of unreacted 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). ^{13}C 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 calcd for $C_{23}H_{18}O_3Na^+$, 365.1148; found, 365.1150.

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 μL) was added methanesulfonic acid (210 μL, 3.22 mmol, 40 equiv). The reaction mixture was stirred for 1 h, 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 give **5** as a reddish brown oil (19.0 mg, >95% crude yield). Compound **5** was consistent by ^1H NMR with previously reported data.[11]

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 equiv). The reaction mixture was stirred for 16 h, 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). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **5** as a light brown oil (11.6 mg, 65% yield). Compound **5** was consistent by ^1H NMR with previously reported data.[11]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00394.

^1H and ^{13}C NMR spectra (PDF)

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Notes

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■ ACKNOWLEDGMENTS

M.P.D., C.M., and R.P.M> are grateful for support from The National Institutes 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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