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Triflic Acid-Mediated Rearrangements of 3-Methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones: Synthesis of Methoxytropolones and Furans

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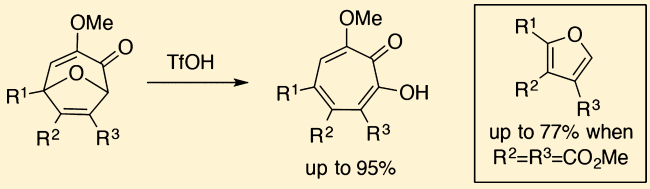
Supporting Information

ABSTRACT: Methoxytropolones are useful scaffolds for therapeutic development because of their known biological activity and established value in the synthesis of α-hydroxytropolones. Upon treatment with triflic acid, a series of 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones rearrange rapidly and cleanly to form methoxytropolones. Interestingly, bicycles that are derived from dimethyl acetylenedicarboxylate ($R^2 = R^3 = CO_2Me$) instead form furans as the major product.



INTRODUCTION

MY3-469 (Figure 1) is a methoxytropolone inhibitor of platelet-type 12-lipoxygenase, an enzyme that has been implicated in cardiovascular and renal diseases as well as cancer and inflammatory responses.[1] In addition, the methoxytropolone-containing natural product pareirubrine A has demonstrated potent antileukemic properties.[2] Our lab's interest in methoxytropolones stem from their demonstrated value as intermediates in the synthesis of α-hydroxytropolones, which have a broad range of bioactivity.[3] For example, α-hydroxytropolones are the most potent known inhibitors of ANT(2″),[4] a major enzyme associated with bacterial resistance to aminoglycoside antibiotics,[5] and are among the most potent inhibitors of HIV RT RNase H,[6] which is a promising target for HIV treatment.[7] Crystal structures of α-hydroxytropolones bound to the binuclear active site of RNase H reveal an ordered three oxygen, two metal binding pattern that likely provides this potency.[8] Similar binding is thought to be responsible for α-hydroxytropolone inhibition of other binuclear metalloenzymes such as inositol monophosphatase, alkaline phosphatase,[9] and phospholipase C,[10] and it is possible that this binding mode may lead to the pharmacophore having privilege for many other similar metalloenzymes.

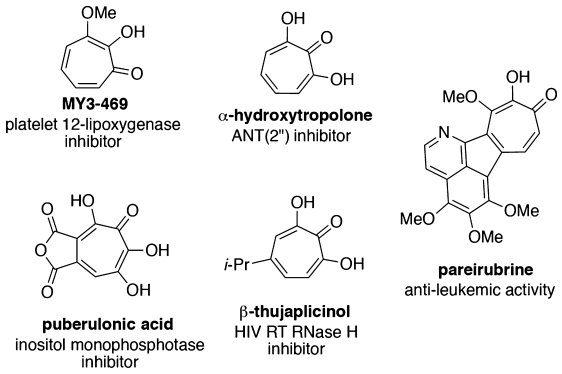


Figure 1. Methoxytropolones and hydroxytropolones and examples of their bioactivity.

Despite the potential of hydroxytropolones and methoxytropolones as therapeutic leads, very few synthetic-chemistry-driven structure–function studies have been conducted on them,[11] perhaps because of the scarcity of synthetic methods available to access them.[12] Early strategies to access this class of molecules focused on tropone oxidation (Scheme 1A), which can be an efficient method for generating the parent α-hydroxytropolone but can make introduction of functionality with control challenging.[13] This has led to efforts to generate the α-hydroxytropolones through other, more controlled, strategies. One method that could be particularly useful in structure–function studies is a cyclopropanation/ring-opening strategy used extensively by the Banwell group for tropone and tropolone synthesis.[14] In one representative example of this work, the group leveraged a bromine handle to perform cross-coupling chemistry to synthesize different α-hydroxytropolones (Scheme 1B).[14a] More recently, Föhlisch and co-workers showed a very efficient route to α-hydroxytropolones starting with furans that they then converted to dialkoxy-8-oxabicyclo[3.2.1]oct-6-en-3-ones (Scheme 1C).[15] These bicyclic substrates were then opened with the aid of base and heat

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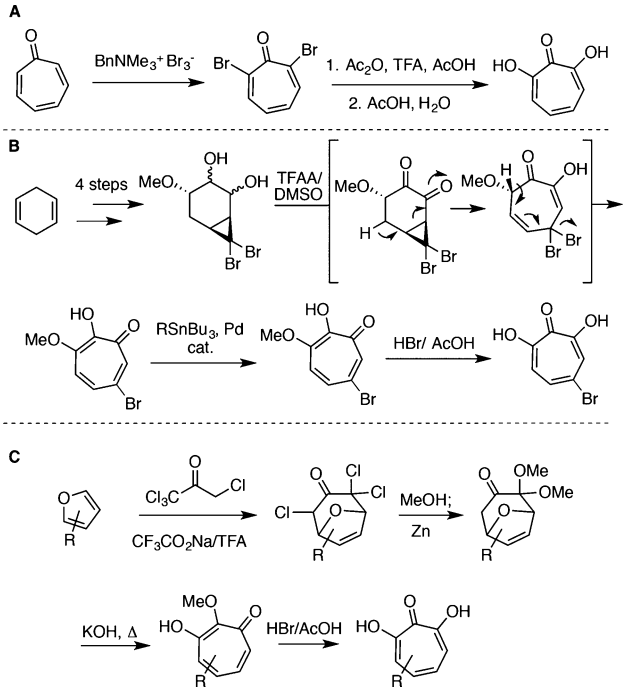
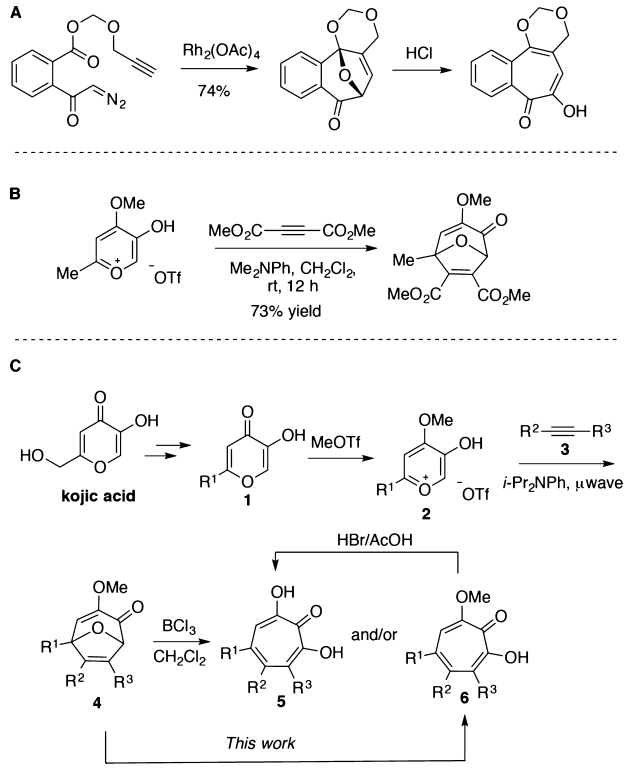
Scheme 1. Representative Examples Illustrating Established Strategies for the Synthesis of α-Hydroxytropolones



to produce methoxytropolones, which could be converted to α-hydroxytropolones through standard demethylation reaction conditions.

Inspired by literature examples where oxidopyrylium cycloaddition chemistry and ring-opening methods were used in tropolone synthesis (Scheme 2A), we have been studying similar strategies toward α-hydroxytropolones.[16] Adapting this approach required an α-hydroxy-γ-pyrone oxidopyrylium cycloaddition reaction[17] that was modified for intermolecular reactions by Wender and Mascareñas (Scheme 2B).[18] Using an optimized version of the Wender−Mascareñas oxidopyrylium cycloaddition procedure along with a demethylative boron trichloride ring-opening, we demonstrated that α-hydroxytropolones can be synthesized from kojic acid through a two-step sequence (Scheme 2C).[19] Among the benefits of this route are the low cost of the kojic acid starting material (10 kg can be purchased for $850 through Chem Impex), the scalability of the synthesis of **2**, which can be made on a gram scale within a few days without any need for chromatography, and the ability to quickly generate di- and polysubstituted α-hydroxytropolones.[20] Among the limitations to the process are the need for electronically stabilizing groups in conjugation with the alkynes (i.e., aryl acetylenes, propiolates, or ynones). The synthesis of various hydroxytropolones can be achieved in two to three steps from a common, scalable intermediate, making the route very appealing for SAR studies. Moreover, the boron trichloride method that we have reported led directly to α-hydroxytropolones for several substrates tested. However, in some instances, methoxytropolones were also generated, either as byproducts or, in once instance, the only product formed. In addition, a phenylacetylene-derived bicycle led to a mixture of at least three compounds that were inseparable. During the course of medicinal-chemistry-driven pursuits on these molecules, the unpredictable nature of the boron trichloride chemistry became an apparent barrier and thus we became interested in developing a more robust and predictable method

Scheme 2. Precedence (A and B) for Oxidopyrylium Cycloaddition/Ring-Opening Strategy toward Substituted α-Hydroxytropolones (C)

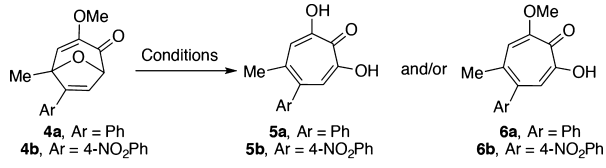


for this ring-opening. The following outlines our studies on triflic acid-mediated ring-openings of 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2ones to generate methoxytropolones.

RESULTS AND DISCUSSION

Early studies focused on phenyl acetylene-derived 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **4a** because of its problematic nature under the previously described conditions,[19] and deuterated chloroform was used to readily monitor reaction progress by ^{1}H NMR (Scheme 3). Although milder acids, including trifluoroacetic acid and toluenesulfonic acid, were not capable of mediating the ring-opening, sulfuric acid and triflic acid both led to methoxytropolone **6a** within a half of an hour

Scheme 3. Prior Results from Aryl-Substituted Bicycles 4a and 4b with Boron Trichloride (A) and under Triflic Acid Conditions (B and C)



Conditions A. BCl_3 (7 equiv), CH_2Cl_2, 0°C, 10 min:
4a = complex mixture;
4b = 81% (1:1 **5b/6b**)
Conditions B. TfOH (0.5 equiv), $CDCl_3$, rt, 30 min:
4a = 95% (**6a**);
4b = incomplete conversion/ decomposition
Conditions C. TfOH (4 equiv), $CDCl_3$, rt, 30 min:
4a = 95% (**6a**);
4b = 95% (**6b**)

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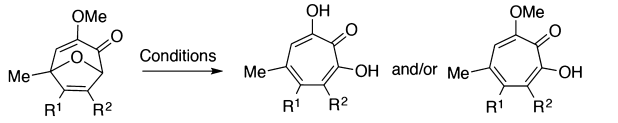
under ambient temperature and atmosphere, with triflic acid promoting a considerably cleaner reaction. During these studies, substoichiometric amounts of triflic acid (0.5 equiv) were found to be capable of leading to quantitative yields of **6a** (Scheme 3, conditions B).[21] When similar conditions were attempted on nitroaryl **4b**, incomplete conversion and other byproducts were observed. Fortunately, increasing the amount of acid to 4 equiv led to a near quantitative reaction (conditions C). This was in contrast to our previous studies with BCl_3 in which a 1:1 mixture of hydroxytropolone and methoxytropolone was obtained (conditions A).[19] Higher concentrations of triflic acid were also found to work well on **4a**. Thus, 4 equiv were identified as an optimal amount to use for our substrate scope studies.

Our attention was next turned toward cycloadducts arising from alkynyl caboxylates because some of these provided yield and selectivity issues under our previous conditions (Scheme 4,

Scheme 4. Prior Results from Bicycles Derived from Alkynyl Carboxylates (4c–e) with Boron Trichloride (A) and under New and Methoxytropolone-Selective Triflic Acid Conditions (C)



4c, R^1 = CO_2Et, R^2 = H
4d, R^1 = COPh, R^2 = H
4e, R^1 = CO_2Et, R^2 = Me

5c, R^1= CO_2Et, R^2 = H
5d, R^1 = COPh, R^2 = H
5e, R^1 = CO_2Et, R^2 = Me

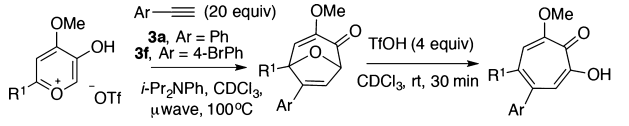
6c, R^1= CO_2Et, R^2 = H
6d, R^1= COPh, R^2 = H
6e, R^1= CO_2Et, R^2 = Me

Conditions A. BCl_3 (7 equiv), CH_2Cl_2, 0°C, 10 min
4c = 39% (7:1 **5c/6c**)
4d = >95% (1:1 **5d/6d**)
4e = 77% (**6e**)
Conditions C. TfOH (4 equiv), $CDCl_3$, rt, 30 min
4c = 89% (**6c**)
4d = >95% (**6d**)
4e = >95% (**6e**)

conditions A).[19] Ethyl ester bicycle **4c** had previously been found to lead to low yields, which we suspect may be due to hydrolysis of an exposed ester during the longer quench used in the boron trichloride reaction workup. Gratifyingly, we found that using the new triflic acid conditions (conditions C) methoxytropolone **6c** was formed in excellent yields. Another substrate, phenyl ketone bicycle **4d**, had previously led to a completely unselective 1:1 ratio of hydroxy- and methoxytropolone. Under the new conditions, methoxytropolone was formed exclusively in near quantitative yields. Finally, the compound bearing a methyl substituent at R^2 previously led to **6e** in 77% yield, which was satisfactory. However, under the new conditions, this reaction was again near quantitative, representing a significant improvement.

Cross-coupling of methoxytropolones have been widely precedented by the work of Banwell (Scheme 1B) and thus we also wanted to synthesize methoxytropolones with halogen handles that may be useful for structure–function studies. Two halogen-containing bicycles were synthesized through the optimized oxidopyrylium cycloaddition reaction previously described. One of these, **4f**, contained a bromide on the phenyl appendage, whereas the other, **4g**, had an alkyl chloride (Scheme 5). Of note was the sluggish reaction toward **4g** that employed a chloromethyl triflate salt **2b** and phenylacetylene (**3a**). In this instance, 4 h under microwave irradiation at 100 °C was necessary to obtain respectable yields of the bicycle.

Scheme 5. Synthesis of Halogen-Containing Bicycles 4f and 4g and Ring-Expansion Using Triflic Acid



2a, R^1= Me
2b, R^1= CH_2Cl

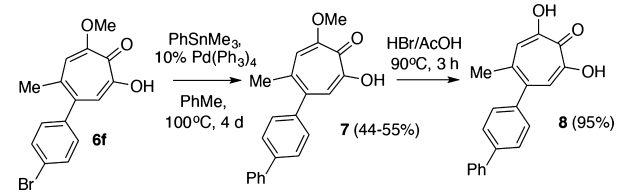
4f, Ar = 4-BrPh, R^1= Me (30 min, 61%)
4g, Ar = Ph, R^1= CH_2Cl (4 hr, 67%)

6f, Ar = 4-BrPh, R^1= Me (>95%)
6g, Ar = Ph, R^1= CH_2Cl (92%)

Gratifyingly, both bicycles rearranged cleanly to afford the anticipated products in excellent yields.

An example of the utility can be seen in the synthesis of biphenyl methoxytropolone **7** from bromophenyl **6f** (Scheme 6). Although the $(PPh_3)_2Pd(II)Cl_2$/ dioxane Stille conditions

Scheme 6. Stille Cross-Coupling of 6f to Afford 7 and Demethylation to Afford 8

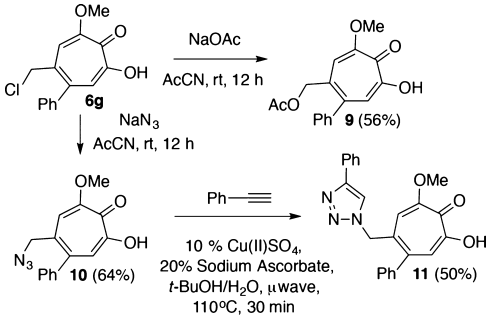


6f
7 (44-55%)
8 (95%)

previously described by Banwell did not work in this case, we found that the use of $Pd(PPh_3)_4$ in refluxing toluene provided the anticipated cross-coupling product in yields ranging from 44 to 55%. These compounds can also be demethylated under known conditions to provide α-hydroxytropolone **8**.

Attempts at similar cross-coupling reactions with chloromethyl-containing compound **6g** were unsuccessful. However, **6g** does react with nucleophiles such as sodium acetate and sodium azide to generate new methoxytropolones **9** and **10**, the latter of which will undergo copper-catalyzed Huisgen [3 + 2] dipolar cycloaddition coupling with phenyl acetylene to generate triazole **11** (Scheme 7).[22]

Scheme 7. Modifications of Methoxytropolone 6g



6g
9 (56%)
10 (64%)
11 (50%)

When bicycle **4h** was subjected to the triflate reaction conditions, we noticed a surprising change in reactivity. In this instance, the anticipated methoxytropolone was only a minor component (<20%), and the major isolated compound was instead furan **12h**,[23] as confirmed by comparison to known ^1H NMR spectral data (Scheme 8A). Given the surprising nature of this discovery and our initial skepticism, we synthesized **4i**, which would lead to another known furan that had symmetry and would thus confirm this discovery. The oxidopyrylium

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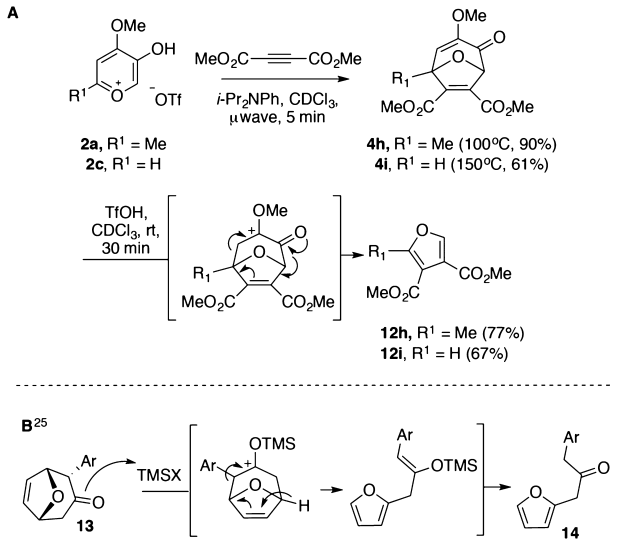
Scheme 8. Unanticipated Furan Rearrangement of Dimethylacetylene Dicarboxylate-Derived Bicycles 4h and 4i (A) and Mechanistically Similar Rearrangement Reported by Mann and Co-workers (B)



cycloaddition chemistry with triflate salt **2c** did not react at all at 100 °C and had to be heated at 150 °C to promote the conversion to **4i**. With **4i** in hand, treatment of the molecule under these reaction conditions led to the known, symmetric furan **12i**,[24] which helped confirm this rearrangement.

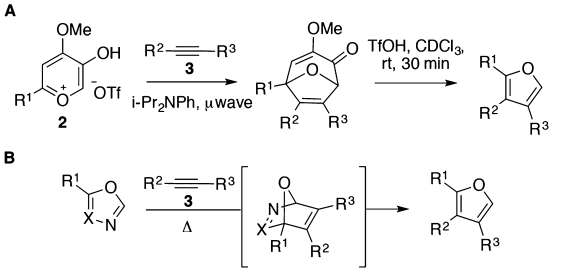
Our current hypothesis is that furan formation is favored when the two ethyl esters destabilize the allylic carbocation character necessary for ring-opening. This may allow for protonation of the enol ether, which may initiate a cation-mediated cycloreversion reaction (as is illustrated in Scheme 8A). Mann and co-workers disclosed a mechanistically related fragmentation that supports this proposal (Scheme 8B).[25] This could happen either through sp hybridized oxonium formation (as shown) or through a hemiacetal or hydrate intermediate. However, no noticeable differences in reactivity were observed when the reaction was run over molecular sieves. Another possibility is that protonation of one or multiple carbonyls may promote a cycloreversion reaction, generating cyclopropenone byproducts. Unfortunately, we have been unable to identify any byproducts that could provide insight into the reaction, which may be the result of polymerization of acrylate-like byproducts. Mechanistic studies are currently underway.

Although the synthesis of furan and furan-containing compounds were described as early as the 19th century,[26] polysubstituted furan synthesis remains a significant challenge and one of high interest to chemists.[27] This serendipitous finding reveals a two-step oxidopyrylium cycloaddition/fragmentation strategy to furans that is reminiscent of widely used thermal processes involving oxazole or 1,3,4-oxadiazole-based Diels–Alder/retro-Diels–Alder processes (Scheme 9)[28] and could find complementary use. The development of conditions for this fragmentation that would work for a broader range of substrates is clearly needed to meet this potential.

■ CONCLUSIONS

We have demonstrated that several methoxytropolones can be readily synthesized through acid-mediated ring-openings of 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones. The high-yielding nature of the chemistry along with the ease of

Scheme 9. Oxidopyrylium Cycloaddition/Ring-Opening (A) and Oxazole/Oxadiazole Diels–Alder/retro-Diels–Alder (B) Strategy for Furan Synthesis[a]



[a]R^1, R^2, and R^3 are labeled as such for comparative purposes.

synthesis (ambient atmosphere and temperature) and rapid conversion (30 min) makes it an excellent method for quickly generating methoxytropolones, and it should have value in structure–function studies on methoxy and hydroxytropolones.

■ EXPERIMENTAL SECTION

General Experiments Methods. All starting materials and reagents were purchased from commercially available sources and used without further purification with the exception of dichloromethane, which was purified on a solvent-purification system prior to the reaction. Microwave reactions were carried out in a Biotage Initiator (External IR Temperature Sensor). ^{1}H NMR shifts are measured using the solvent residual peak as the internal standard ($CDCl_3$ δ 7.26) and are 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 77.20) and are reported as chemical shifts. Infrared (FTIR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w).

General Procedure for Oxidopyrylium Cycloaddition. Known 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones **4a–e** and **4h** were synthesized as previously described. New 3-methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones **4f**, **4g**, and **4i** were synthesized under previously described conditions.[19] In short, into a microwave reactor vial was added triflate salt (**2a–c**), alkyne (20 equiv), and $CHCl_3$ (0.2 M). *N*,*N*-Diisopropylaniline (1.2 or 2.0 equiv) was added, and the reaction vessel was sealed and heated under microwave irradiation at 100 °C (controlled temperature). The reaction was monitored periodically by ^{1}H NMR and was deemed complete when the oxidopyrylium dimer was no longer observable.

6-(4-Bromophenyl)-3-methoxy-5-methyl-8-oxabicyclo-[3.2.1]octa-3,6-dien-2-one (4f). 5-Hydroxy-4-methoxy-2-methylpyrylium **2a** (100 mg, 0.34 mmol) and 1-ethynyl-4-bromobenzene (1.0 g, 6.9 mmol) were suspended in $CHCl_3$ (2 mL). *N*,*N*-Diisopropylaniline (81 μL, 0.41 mmol) was added to the reaction, the reaction vessel was sealed, and the reaction mixture was heated under microwave irradiation at 100 °C (controlled temperature) for 30 min. The reaction mixture was then concentrated and purified by chromatography (silica gel, 18 × 1.8 cm, 50 mL of hexanes, 200 mL of 2% EtOAc in hexanes, 100 mL of 10% EtOAc in hexanes, 200 mL of 15% EtOAc in hexanes) to lead to **4f** as a light-yellow solid (68 mg, 61% yield). mp 192–200 °C. R_f = 0.17 in 16% EtOAc/hexanes. FTIR (KBr, thin film): 525 (m), 714 (m), 1057 (w), 1132 (m), 1606 (s), 1708 (s), 1905 (w), 2978 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.29 (d, J = 2.5 Hz, 1H), 6.14 (s, 1H), 4.96 (d, J = 2.5 Hz, 1H), 3.58 (s, 3H), 1.64 (s, J = 3H). ^{13}C NMR (100 MHz, $CD_3CN/CDCl_3$): δ 189.43, 157.75, 145.66, 132.19, 131.73, 127.99, 124.04, 122.10, 119.73, 86.16, 85.77, 54.47, 21.35. HRMS m/z m/z (ESI+): calcd for $C_{15}H_{14}BrO_3$ (M + H), 321.0121; found, 321.0114.

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5-(Chloromethyl)-3-methoxy-6-phenyl-8-oxabicyclo[3.2.1]-octa-3,6-dien-2-one (4g). 2-(Chloromethyl)-5-hydroxy-4-methoxypyrylium **2b** (200 mg, 0.616 mmol) and phenylacetylene (1.35 mL, 12.3 mmol) were dissolved in $CHCl_3$ (3.08 mL). *N*,*N*-Diisopropylaniline (240 μL, 1.23 mmol) was added to the reaction, the reaction vessel was sealed, and the reaction mixture was heated under microwave irradiation at 100 °C (controlled temperature) for 4 h. The reaction mixture was then concentrated and purified by chromatography (silica gel, 18 × 1.8 cm, 50 mL of hexanes, 200 mL of 2% EtOAc in hexanes, 100 mL of 10% EtOAc in hexanes, 200 mL of 15% EtOAc in hexanes) to lead to **4g** as a highly viscous yellow oil (114 mg, 67% yield). R_f = 0.14 in 20% EtOAc in hexanes. FTIR (KBr, thin film): 656 (w), 798 (s), 1078 (m), 1261 (s), 1607 (b), 1709 (b) 1960 (w), 2254 (w), 2838 (w), 2962 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.09 (m, 5H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.11 (s, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 3.94 (d, *J* = 12.4 Hz, 1H), 3.77 (d, *J* = 12.4 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 156.3, 146.9, 132.7, 129.4, 129.2, 125.9, 124.9, 114.8, 88.7, 86.4, 55.2, 45.9. HRMS *m*/*z* (ESI+): calcd for $C_{15}H_{13}ClO_3$ (M + H), 276.0553; found, 276.0552.

Dimethyl 3-Methoxy-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6,7-dicarboxylate (4i). 3-Hydroxy-4-methoxypyrylium[29] **2c** (108 mg, 0.391 mmol) and dimethylacetylene dicarboxylate (1.11 mg, 7.82 mmol) were dissolved in $CHCl_3$ (780 μL). *N*,*N*-Diisopropylaniline (91 μL, 0.47 mmol) was added to the reaction, the reaction vessel was sealed, and the reaction mixture was heated under microwave irradiation at 150 °C (controlled temperature) for 5 min. The reaction mixture was then concentrated and purified by chromatography (silica gel, 18 × 1.8 cm, 50 mL of hexanes, 75 mL of 10% EtOAc in hexanes, 100 mL of 20% EtOAc in hexanes, 200 mL of 30% EtOAc in hexanes) to lead to **4i** as a white solid (64 mg, 61% yield). mp 113−116 °C. R_f = 0.15 in 25% EtOAc/hexanes. FTIR (KBr, thin film): 688 (m), 794 (w), 1000 (b), 1129 (s), 1611 (s), 1654 (m), 1716 (b), 2838 (m), 2956 (s), 3019 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.17 (d, *J* = 4.8 Hz, 1H), 5.46 (d, *J* = 4.8 Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 162.7, 161.9, 149.5, 146.9, 138.5, 114.2, 88.9, 80.9, 55.2, 53.2, 53.1. HRMS *m*/*z* (ESI+): calcd for $C_{12}H_{13}O_7$ (M + H), 269.0656; found, 269.0652.

General Procedure for Methoxytropolone Synthesis. 3-Methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones (**4a**−**g**) were dissolved in $CHCl_3$ (0.1 M), and trifluoromethanesulfonic acid (4 equiv) was added to the reaction. The reaction was stirred for 30 min, at which time it was quenched with phosphate buffer (1.6 M, pH 7), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to yield methoxytropolones (**6a**−**g**).

2-Hydroxy-7-methoxy-5-methyl-4-phenylcyclohepta-2,4,6-trienone (6a). 3-Methoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **4a** (10 mg, 0.041 mmol) was dissolved in $CDCl_3$ (410 μL), and trifluoromethanesulfonic acid (15 μL, 0.165 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 20 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6a** as a yellow solid (9.5 mg, 95% yield) that decomposes at 175 °C . FTIR (KBr, thin film): 799 (s), 1095 (s), 1260 (s), 1451 (w), 1726 (b), 2923 (w), 2962 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.24 (m, 5H), 7.23 (s, 1H), 7.18 (s, 1H), 4.04 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 158.9, 158.4, 143.9, 143.6, 135.4, 128.9, 128.6, 128.0, 122.7, 122.4, 56.8, 27.0. HRMS *m*/*z* (ESI+): calcd for $C_{15}H_{15}O_3$ (M + H), 243.1016; found, 243.1019.

2-Hydroxy-7-methoxy-5-methyl-4-(4-nitrophenyl)-cyclohepta-2,4,6-trienone (6b). 3-Methoxy-5-methyl-6-(4-nitrophenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **4b** (29 mg, 0.10 mmol) was dissolved in $CDCl_3$ (1.0 mL), and trifluoromethanesulfonic acid (61 μL, 0.41 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 20 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6b** as a fine, powdery yellow solid (30 mg, >95% yield). ^1H NMR matched previously reported data.[20] ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.29 (s, 1H), 7.14 (s, 1H), 4.05 (s, 3H), 2.26 (s, 3H).

Ethyl 6-Hydroxy-4-methoxy-2-methyl-5-oxocyclohepta-1,3,6-trienecarboxylate (6c). Ethyl 3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate **4c** (40 mg, 0.168 mmol) was dissolved in $CDCl_3$ (1.68 mL), and trifluoromethanesulfonic acid (59 μL, 0.672 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 50 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6c** as an orange solid (35.7 mg, 89% yield). mp 99−106 °C. FTIR (KBr, thin film): 750 (s), 1056 (w), 1457 (s), 1561 (s), 1717 (s), 2927 (w), 3252 (b) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.03 (s, 1H), 4.46−4.29 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 3H), 2.56 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 168.9, 159.8, 137.4, 132.4, 121.9, 117.8, 62.3, 56.8, 26.2, 14.5. HRMS *m*/*z* (ESI+): calcd for $C_{12}H_{15}O_5$ (M + H), 239.0914; found, 239.0913.

4-Benzoyl-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (6d). 6-Benzoyl-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]-octa-3,6-dien-2-one **4d** (20 mg, 0.074 mmol) was dissolved in $CDCl_3$ (0.74 mL), and trifluoromethanesulfonic acid (26.2 uL, 0.30 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 25 mL), extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6d** as a dark yellow solid (19.7 mg, >95% yield). ^1H NMR matched previously reported.[20] ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 29.1 Hz, 1H), 7.10 (s, 1H), 4.05 (s, 3H), 2.33 (s, 3H).

Ethyl 6-Hydroxy-4-methoxy-2,7-dimethyl-5-oxocyclohepta-1,3,6 trienecarboxylate (6e). Ethyl 3-methoxy-5,7-dimethyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate **4e** (19 mg, 0.075 mmol) was dissolved in $CDCl_3$ (750 μL), and trifluoromethanesulfonic acid (26 μL, 0.30 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 30 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6e** as a red solid (18.5 mg, >95% yield). ^1H NMR matched previously reported data.[20] ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

4-(4-Bromophenyl)-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (6f). 6-(4-Bromophenyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **4f** (70.1 mg, 0.22 mmol) was dissolved in $CDCl_3$ (2.2 mL) and trifluoromethanesulfonic acid (77 μL, 0.87 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with phosphate buffer (1.6 M, pH 7, 50 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6f** as a yellow solid (70 mg, >95% yield). mp 110−115 °C. FTIR (KBr, thin film): 815.4 (w), 1211.4 (s), 1264.2 (s), 1713.9 (w), 2939.4 (w), 3259.2 (b) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.32 (s, 1H), 7.14 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 4.02 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 158.8, 158.5, 142.7, 141.8, 135.1, 132.1, 130.4, 122.4, 122.2, 121.7, 56.7, 26.9. HRMS *m*/*z* (ESI+): calcd for $C_{15}H_{14}BrO_3$ (M + H), 321.0121; found, 321.0128.

4-(Chloromethyl)-7-hydroxy-2-methoxy-5-phenylcyclohepta-2,4,6-trienone (6g). 5-(Chloromethyl)-3-methoxy-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **4g** (37 mg, 0.13 mmol) was dissolved in $CDCl_3$ (1.34 mL), and trifluoromethanesulfonic acid (47 μL, 0.54 mmol) was added to the reaction. The reaction was stirred for 20 min and was quenched with phosphate buffer (1.6 M, pH 7, 25 mL), extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated to yield **6g** as a brownish solid (34 mg, 92% yield). mp 159−167 °C. FTIR (KBr, thin film): 702 (s), 735 (m), 762 (w), 1157 (w), 1261 (s), 1559 (b), 1713 (b), 2927 (b), 3247 (b) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.14 (m, 7H), 4.31 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.49, 159.48, 158.96, 144.55, 141.92, 134.06, 129.04, 128.72, 128.57, 122.05, 121.37, 56.97, 49.01. HRMS *m*/*z* (ESI+): calcd for $C_{15}H_{14}ClO_3$ (M + H), 277.0626; found, 277.0627.

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4-([1,1′-Biphenyl]-4-yl)-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (7). 4-(4-Bromophenyl)-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (**6f**) (28 mg, 0.087 mmol) was suspended in toluene (1.75 mL), and trimethyl(phenyl)tin (47.6 uL, 62 mg, 0.25 mmol) and tetrakis(triphenylphosphine)palladium(0) (10.02 mg, 0.0088 mmol) were added. The reaction was stirred vigorously for 4 days at reflux under argon. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (2 mL). The solution was then treated with aqueous NaOH (1 M, 25 mL) and aqueous KF (saturated, 25 mL) and stirred vigorously for 30 min. The solution was acidified with aqueous HCl (2M, 25 mL) to a pH of 3. The solution was extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated. Chromatography (C18 column [10 g], 35% MeCN/H_2O [0.05% TFA] to 100% MeCN [0.05% TFA] gradient over 20 column volumes) followed by concentration of product peaks yielded **7** as a light-yellow solid (15 mg, 55% yield). mp 174−180 °C. FTIR (KBr, thin film): 1113 (s), 1132 (w), 1211 (s), 1554 (s), 1774 (w), 2933 (w), 2986 (w), 3018 (w), 3257 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.21 (m, 11H), 4.04 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.79, 158.77, 158.24, 143.03, 142.66, 140.69, 140.57, 135.29, 129.06, 128.97, 127.77, 127.40, 127.26, 122.54, 122.18, 56.61, 26.89. HRMS *m*/*z* (ESI+): calcd for $C_{21}H_{18}O_3$ (M + H), 318.1251; found, 318.1256.

4-([1,1′-Biphenyl]-4-yl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (8). **4**-([1,1′-Biphenyl]-4-yl)-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (**7**) (16.5 mg, 0.052 mmol) was dissolved in 33%HBr/AcOH (0.52 mL). The reaction was heated to reflux for 3 h with constant stirring. The solution was cooled to room temperature, quenched with phosphate buffer (pH 7), extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to yield **8** as a light-yellow solid (16.1 mg, >95% yield). mp 170−175 °C. FTIR (KBr, thin film): 1525 (s), 2923 (w), 3246 (br), cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79−7.20 (m, 11H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.35, 158.12, 156.87, 143.80, 142.84, 140.92, 140.70, 139.41, 129.24, 129.13, 127.96, 127.58, 127.44, 126.51, 124.79, 26.86. HRMS *m*/*z* (ESI+): calcd for $C_{20}H_{16}O_3$ (M + H), 304.1099; found, 304.1105.

(4-Hydroxy-6-methoxy-5-oxo-2-phenylcyclohepta-1,3,6-trien-1-yl)methyl acetate (9). To a solution of chloromethoxytropolone **6g** (33 mg, 0.1191 mmol) in acetonitrile (11.9 mL) was added sodium acetate (195 mg, 2.38 mmol). The reaction was stirred for 12 h at ambient temperature and atmosphere, and phosphate buffer (pH 6) was added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **7** as a light-yellow solid (20 mg, 56% yield). mp 159−161 °C. FTIR (KBr, thin film): 3243 (s), 1743 (s), 1579 (s), 1478 (s), 1264 (s), 1103 (s), 704 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.72−6.96 (m, 7H), 4.88 (s, 2H), 4.04 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.70, 159.53, 158.55, 144.72, 141.82, 131.75, 128.74, 128.57, 128.39, 121.45, 120.33, 67.72, 56.63, 21.16. ^{13}C NMR (50 MHz, $CDCl_3$/CD_3CN): δ 169.82, 169.73, 158.64, 157.85, 143.49, 141.20, 131.33, 127.95, 127.86, 127.54, 120.40, 119.76, 66.76, 55.89, 20.08. HRMS *m*/*z* (ESI+) *m*/*z* calcd for $C_{17}H_{17}O_5$ (M + H), 301.1071; found, 301.1071.

4-(Azidomethyl)-7-hydroxy-2-methoxy-5-phenylcyclohepta-2,4,6-trien-1-one (10). To a solution of chloromethoxytropolone **6g** (62 mg, 0.22 mmol) in acetonitrile (22 mL) was added sodium azide (285 mg, 4.39 mmol). The reaction was stirred for 12 h under ambient temperature and atmosphere, and phosphate buffer (pH 6) was added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **10** as a brown solid (40 mg, 64% yield). mp 115−119 °C. FTIR (KBr, thin film): 3228 (s), 2102 (s), 1524 (s), 1463 (s), 1228 (s), 1128 (s), 703 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71−7.37 (m, 7H), 4.22 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.57, 159.18, 158.56, 143.64, 141.67, 131.40, 128.81, 128.42, 128.30, 121.13, 119.56, 56.54, 56.16. HRMS *m*/*z* (ESI+) *m*/*z* calcd for $C_{15}H_{14}N_3O_3$ (M + H), 284.1030; found, 284.1024.

2-Hydroxy-7-methoxy-4-phenyl-5-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)cyclohepta-2,4,6-trien-1-one (11). To a suspension of azidomethoxytropolone **10** (21 mg, 0.074 mmol) in water (800 mL) and *tert*-butanol (800 mL) were added phenylacetylene (20 mL, 0.18 mmol), copper sulfate pentahydrate (2 mg, 0.008 mmol), and sodium ascorbate (3 mg, 0.015 mmol). The reaction mixture was heated under microwave irradiation at 110 °C (controlled temperature) for 30 min. The *t*-BuOH/H_2O was evaporated, and the reaction was then resuspended in NaCl(aq) (1 mL), extracted with CH_2Cl_2 (3 × 1 mL), dried over Na_2SO_4, filtered, and concentrated to yield **11** as a brown solid (14 mg, 50% yield). mp 171−173 °C. FTIR (KBr, thin film): 3221 (s), 2939 (s), 1568 (s), 1467 (s), 1229 (s), 1121 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.63−7.29 (m, 10H), 7.23 (s, 1H), 5.42 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): δ 170.33, 159.35, 158.48, 147.62, 143.59, 141.20, 130.17, 129.42, 128.56, 128.40, 128.02, 128.00, 127.87, 125.16, 121.44, 120.40, 118.95, 55.62, 54.72. HRMS *m*/*z* (ESI+) *m*/*z* calcd for $C_{23}H_{20}N_3O_3$ (M + H), 386.1499; found, 386.1492.

General Procedure for Furan Synthesis. 3-Methoxy-8-oxabicyclo[3.2.1]octa-3,6-dien-2-ones (**4h**, **4i**) were dissolved in $CHCl_3$ (0.1 M), and trifluoromethanesulfonic acid (4 equiv) was added to the reaction. The reaction stirred for 30 min, at which time the reaction was quenched with triethylamine, concentrated, and purified by silica gel chromatography.

Dimethyl 2-Methylfuran-3,4-dicarboxylate (12h). Dimethyl 3-methoxy-1-methyl-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate **4h** (20 mg, 0.071 mmol) was dissolved in $CHCl_3$ (0.71 mL), and trifluoromethanesulfonic acid (25 μL, 0.283 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with triethylamine (50 μL). The reaction mixture was then concentrated and purified by chromatography (silica gel, 18 × 1.8 cm, 50 mL of hexanes, 100 mL of 5% EtOAc in hexanes, 100 mL of 10% EtOAc in hexanes, 200 mL of 20% EtOAc in hexanes) to lead to **12h** as a light-yellow solid (10.9 mg, 78% yield). ^1H NMR matched previously reported data.[22] ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.50 (s, 3H).

Dimethyl Furan-3,4-dicarboxylate (12i). Dimethyl 3-methoxy-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6,7-dicarboxylate **4i** (20 mg, 0.074 mmol) was dissolved in $CHCl_3$ (0.746 mL), and trifluoromethanesulfonic acid (0.026 mL, 0.289 mmol) was added to the reaction. The reaction was stirred for 30 min and was quenched with triethylamine (50 μL). The reaction mixture was then concentrated and purified by chromatography (silica gel, 18 × 1.8 cm, 50 mL of hexanes, 100 mL of 2% EtOAc in hexanes, 100 mL of 5% EtOAc in hexanes, 100 mL of 8% EtOAc in hexanes) to lead to **12i** as a light-yellow solid (8.6 mg, 63% yield). ^1H NMR matched that previously reported.[23] ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 3.86 (s, 6H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds and ^1H NMR data of all known compounds with new experimental procedures. HMBC and HSQC spectra of **6f** with assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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